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Epidemiology and Treatment of Kaposi's Sarcoma in HIV-1 Infected Individuals in a Poor Resource Setting

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1. Introduction

Kaposi's sarcoma was first described in 1872 by Moritz Kaposi, a Vienna-based Hungarian dermatologist, as a rare multifocal angioproliferative tumour involving blood and lymphatic vessels in elderly men of Jewish origin (Kaposi, 1872). Before the AIDS epidemic three clinico-epidemiological forms with similar histological features have been described. The classic Kaposi's sarcoma (KS) originally described by Kaposi is primarily a skin disease with a chronic indolent course that can sometimes regress spontaneously (Kaposi, 1872). Most of the cases occurred in elderly men of Mediterranean and Jewish origin. The African-endemic KS is seen in the indigenous population of sub-Saharan Africa (Franceschi & Geddes, 1995). It is also seen more commonly among male patients, but differs from the classic form in that it may affect a younger population and is more likely to spread to visceral organs and lymphatics. In addition, it has a variable clinical presentation ranging from a benign disease with few skin lesions to a widely disseminated disease associated with high morbidity and mortality (Franceschi & Geddes, 1995; Taylor et al 1971). Kaposi's sarcoma seen in patients as a result of immunosuppression complicating organ transplantation may have chronic or progressive course and spontaneous remission after discontinuation of immunosuppressive therapy is observed in the majority of patients (Penn, 1979).

The first description of AIDS-associated Kaposi's sarcoma (AAKS) was in 1981, when Friedman-Kien et al (1981) reported some previously healthy young homosexual men with Kaposi's sarcoma involving lymph nodes, viscera, and mucosa as well as skin. This was associated with life-threatening opportunistic infections and a profound defect in cell-mediated immunity. This aggressive and frequently fatal form of Kaposi's sarcoma is the most common cancer in patients with HIV infection (Schwartz, 2004). Before the discovery and widespread use of highly active antiretroviral therapy (HAART) KS was over 20,000 times more common in AIDS patients than the general population (Engels et al 2006). However, several studies showed that HAART reduced the incidence of KS in high income countries (.Franceschi et al, 2008; Pipkin et al, 2011; Simard et al, 2011). The cumulative incidence of Kaposi sarcoma declined from 14.3% during 1980 to 1989, to 6.7% during 1990

to 1995, and to 1.8% during 1996 to 2006 (Simard et al, 2011). In a Swiss HIV cohort study, the overall KS incidence was 33.3 per 1000 person year (py) in 1984–1986 and did not change significantly in the subsequent periods until 1996–1998, when it fell to 5.1 (95% CI, 3.9–6.5) . The incidence further decreased to 1.4 per 1000 py in 1999–2001 and remained constant thereafter (Franceschi et al, 2008). In another recent pan-European multi-centre study, there was a decrease in the incidence rate of KS from 24.7 cases (95% CI 17.2–32.2) per 1000 py in 1994 to 4.7 (95% CI 2.7–6.7) per 1000 py in 1997 and 1.7 (95% CI 0.7–3.4) per 1000 in recent years among HIV-infected individuals (Pipkin et al, 2011). In a report from Sao Paulo Brazil, a low income country, 17% of a cohort of patients on HAART was seropositive for human herpesvirus-8 of which only 2% developed AAKS in 5 years compared to 20% prevalence of AAKS detected in the same region before the HAART era (Yoshioka et al, 2004). In contrast, the incidence of KS has been steadily increasing in parallel with the AIDS epidemic in sub-Saharan Africa (Bassett et al, 1995; Parkin et al, 2008; Sasco et al, 2010). In 2002, of 66,200 estimated KS cases worldwide, 58,800 ware estimated to be in Africa (Parkin et al, 2008). Of these, about 39,500 cases in males and 17,100 cases in females occurred in sub-Saharan Africa compared to 102 males and 17 females in Northern Africa (Parkin et al, 2008). In areas such as Malawi, Uganda and Zimbabwe where Kaposi's sarcoma was common before the AIDS epidemic, the incidence of this cancer has increased by about 20-times and it is now the most common cancer in males and second most common cancer in females (Sasco et al, 2010). In Zimbabwe, the age-adjusted incidence of KS per 100,000 population was 2.3 in men and 0.3 in women before the AIDS epidemic, compared to 48 and 18, respectively, during the AIDS epidemic (Bassett et al, 1995). Recent studies conducted in South Africa and Rwanda found a clear association between HIV infection and KS with odd ratio ranging from 21.9 (95% CI 12.5–38.6) to 47.1 (95% CI 31.9–69.8) (Newton et al, 1995; Stein et al, 2008). Similarly, Newton et al (2001)in a study carried out in Kampala, Uganda found a higher risk of KS among HIV- infected compared to HIV-negative children with an odd ratio of 94.9 (95% CI 28.5–315.3).

Although the course of AAKS is variable most patients would eventually develop progressive and disseminated disease requiring active therapy. The choice of treatment is determined by the stage of KS, its rate of progression, the degree of immune competence and HIV associated diseases. Several therapeutic options are available for AAKS but the optimal therapy is still unclear. Highly active antiretroviral therapy including protease inhibitors may be the first treatment step for indolent slowly progressive disease (Martellotta et al, 2009). Following treatment with HAART, there may be complete remission in patients with good immunological response and limited disease (Martellotta et al, 2009). However, recent studies indicate that there is no significant regression when patients with advanced, symptomatic AAKS are treated with HAART without simultaneous chemotherapy (Krown, 2004; Martin-Carbonero 2004). A wide variety of chemotherapeutic agents, individually and in combination, have been evaluated for the treatment of AAKS. In high income countries, combination of vincristine, doxorubicin and bleomycin (VAB) that was considered the standard chemotherapy regimen for AAKS has been supplanted by liposomal anthracylines due to their higher efficacy and reduced toxicity (Ashish et al 2007; Cooley, 2007). In addition, the angiogenic nature of KS makes it particularly suitable for therapies based on targeted agents such as metalloproteinase inhibitors, angiogenesis inhibitors and tyrosine kinase inhibitors (Koon et al, 2011; Sullivan et al, 2009). In low income countries, the choice of therapeutic agents is limited to the combination of VAB or even more toxic drugs such as therlidomide because liposomal anthracyclines are not available or affordable (Makombe et al, 2009).

1.1 Aetiology and pathogenesis

For a long time, the aetiology and pathogenesis of KS remained unclear. The discovery in 1994 of KS-associated herpes virus (KSHV), also known as human herpes virus-8 (HHV-8), in cells isolated from an AAKS lesion was followed by molecular and epidemiological data confirming an aetiological link between this virus and all clinical forms of KS (Chang et al, 1994; Hengge et al, 2002). Though infection with HHV-8 is not sufficient for tumour development, the virus has developed various mechanisms to manipulate host cell signal transduction, and thereby lead to the activation of numerous pro-growth and anti-apoptotic pathways. HIV-1 transactivation (Tat) protein is a short-term growth factor for KS (Guadalupe et al, 2011; Hassman et al, 2011). Tat protein through the mediation of IFN-γ, b-FGF and other cytokines has the capacity to induce endothelial cell proliferation and facilitate invasion of extracellular matrix (Hassman et al, 2011). In addition, it enhances HHV-8 infectivity for endothelial cells and increases its viral load by reactivating it from latent state (Guadalupe et al, 2011). On the other hand, HHV-8 activates nuclear receptors NF-kappa and NF-AT and this level of activation is synergistically increased by HIV-1 Tat protein (Guadalupe et al, 2011). Thus, infection with HHV-8 is associated with KS the risk for which correlates with HHV-8 viral load. However, for a given HHV-8 titre, the risk is greater in HIV-seropositive, as compared to HIV-seronegative individuals (Casper, 2011). Exceptions have been found in some parts of West Africa, South America and Australia where although the incidence of HHV-8 infection is high only few cases of KS are found (Ablashi et al 1999; Rezza et al, 2001). This indicates that other factors are important in the pathogenesis of KS.

In Nigeria, the incidence of HIV/AIDS was estimated at 4.1 million and is on the downward trend (National Action Committee on AIDS (NACA) 2010). KS has become the most common malignant skin tumour with the disease appearing in areas where it did not exit in the past (Asuquo & Ebughe, 2009; Iregbu & Elegba, 2006). A report from Calabar South Eastern Nigeria showed that KS is the most common malignant skin tumour accounting for 38.0% cases (Asuquo & Ebughe, 2009). Reports from Abuja and Benin both in Nigeria showed KS in 0.8% of newly diagnosed HIV infected patients compared to a prevalence of 0.5% a decade earlier (Akinsete et al, 1998; Iregbu & Elegba, 2006; Onunu et al, 2007). Most of our patients present with extensive and advanced disease that usually required a combination of HAART and chemotherapy. This together with limited therapeutic facilities resulted in poor outcome of treatment (Ahmed et al, 2001; Asuquo & Ebughe, 2009). With improved AIDS awareness and access to HAART more patients are likely to present earlier. Our institution is one of the Federal Government HIV/AIDS designated treatment centre and we see patients from various parts of Nigeria. There is little information on the treatment and outcome of KS in HIV-1infected patients who have been treated with HAART in Africa. The objective of this study was to review the clinical features, treatment and outcome of AIDS –associated Kaposi's sarcoma patients in our institution particularly in the context of increasing use of highly active antiretroviral therapy. We shall also highlight the difficulties in the evaluation and treatment of these patients.

2. Patients and method

This prospective study was carried out at Ahmadu Bello University Teaching Hospital Zaria, the premier referral and teaching hospital in Northern Nigeria. Patients with concurrent diagnosis of HIV infection and Kaposi's sarcoma seen between January 2007 and

December 2010 were included. Only patients 18 years or more were included. Consent was obtained from each patient after counselling and at the time of taking blood sample, tissue specimen or taking photographs of accessible lesions. Permission for the study was also obtained from the hospital ethical committee.

2.1 Patient's evaluation and treatment

Patients were assessed at the time of diagnosis of AAKS and at four to eight weekly intervals during follow-up. At each visit, weight, vital signs and Kaposi's sarcoma symptoms were recorded, and a physical examination was performed. During evaluation efforts were made to discover the probable mode of HIV transmission to the patient. The dimension, number, appearance and sites of involvement of KS lesions were recorded. Lesions causing disfigurement were photographed. Tumour size was defined as the sum of the greatest diameters of each measurable tumour. The Karnofsky score status of the patients was also recorded. The tumour was staged according to AIDS Clinical Trials Group (ACTG) classification using the tumour (T), immune system (I) and systemic illness (S) (Krown et al, 1997). Tumour was defined as T0 if disease was confined to the skin and lymph nodes or oral involvement was confined to the hard palate, or T1 if there was pulmonary or gastrointestinal involvement, tumour associated oedema or ulceration, or extensive oral involvement. Cutaneous KS lesions confined to one anatomical area were classified as local while lesions involving two or more sites as disseminated. Morphologically the lesions were classified as macular, nodular and ulcerative. Tumour response was assessed by comparing lesion characteristics to the baseline tumour evaluations. Treatment responses were assessed according to ACTG criteria. A complete response (CR) was defined as the absence of any detectable residual disease, including tumour-associated oedema, persisting for at least four weeks. Partial response (PR) was defined as ≥50% decrease in the number or size of previously existing evaluable lesions lasting for at least four weeks without the appearance of new lesions or tumour-associated oedema. Stable disease (SD) was defined as any response that did not meet the criteria for progression or PR. Overall response rate was defined as both complete and partial response rates. Progressive disease (PD) was defined as ≥25% increase in the size of previously existing lesions or the appearance of new ones or the development of new or increasing tumour-associated oedema or effusion. Relapse was defined as the development of progressive disease in the presence of a documented CR, or PR.

Screening test for HIV antibodies were performed by parallel testing using Enzyme-linked immunoabsorvent assay (ELISA) with Immunocomb II, HIV-1 and HIV-2 (M/S Orgenics, Israel) and Stat Pak (Trinity Biotech, Wicklow, Ireland). Positive test results from the two different kits were taken as confirmatory evidence of HIV antibodies. The CD4 cell counts were performed using the Dynabeads method (Dynal Biotech LLC, Milwaukee, WI, USA). Patients that presented from 2008 to 2010 were screened with Stat Pak (Trinity Biotech, Wicklow, Ireland) and Bundi HIV-1 and HIV-2 (Bundi International Diagnostics, Abia, Nigeria) and confirmed with Western blot method. Their CD4 count was performed with Partec flow cytometre (Partec GmbH, Munster, Germany). Plasma HIV-1 RNA levels were measured with Roche-Ampiclor HIV-1 monitor test, (version 1.5 (Roche-Ampiclor-Roche Diagnostics, Branchburg, USA). Viral load less than 400 copies/mL was considered undetectable. Diagnosis of Kaposi's sarcoma was based on histological examination of tissue specimens fixed in 10% formalin embedded in paraffin wax and stained with haematoxylin

and eosin. Special stains were employed in selected cases. Serum urea and electrolytes, liver function test and complete blood count with differential and platelet count were done at the time of diagnosis of AAKS and before administration of chemotherapy. Chest radiographs, ECG, abdominal ultrasound, faecal occult blood and gastrointestinal endoscopic examination were performed in appropriate cases.

Our protocol for the treatment of AAKS has been presented previously (Ahmed et al, 2001). Following evaluation, patients were resuscitated and started on HAART which we defined as therapy consisting of at least three antiretroviral drugs in accordance with national guidelines (NACA, 2007). Our protocol recommends that patients with AAKS are started on HAART irrespective of CD4 count. Stable patients that have KPS of ≥40 and adequate bone marrow, renal and hepatic functions were then commenced on specific anti-KS chemotherapy. This consisted of six courses of three weekly cycles of vincristine 1.5mg/m^2, doxorubicin 10mg/m^2 and bleomycin 15mg/m^2 by bolus intravenously. Treatments were delayed for up to two weeks for recovery from grade ≥3 neutropenia, thrombocytopenia or severe diarrhoea. Patients with relapse were treated with same course. Radiotherapy and surgical excision of localised lesions were performed in appropriate cases. Treatment complications and outcome were monitored. Patients were followed-up at four to eight weekly intervals until death or lost to follow-up.

2.2 Statistical analysis

We analysed data using SPSS statistical software (version 17.0, SPSS, Chicago IL). Data were reported as proportions, mean ± standard deviation (SD) or median (range). Categorical variables and proportions were compared by Fisher's exact test while continuous variables were compared by Wilcoxon two-sample test. In patients that responded to treatment, the duration of response was summarised using Kaplan Meier method. Fisher's exact test was used to test for agreement between the occurrence of clinical benefit and the presence of clinical response. Survival was calculated from the day of KS diagnosis until death or the date of last follow-up. Overall survival duration curves and duration of tumour response were plotted according to Kaplan-Meier method. Logistic regression modeling performed to identify independent determinants of survival and tumour response was done using the following clinicopathologic variables: age, sex, presence of comorbid condition, presence of systemic symptoms, KPS, stage of tumour, viral load and CD4 count at presentation. Risk factors were first analysed univariately, and the statistically significant variables were used to construct a multivariate model. Interactions were also analysed to confirm independence. We considered $p \leq 0.05$ to be statistically significant.

3. Results

3.1 Patient's characteristics

During the period of study 7,155 patients with HIV infection were seen of which 98 (1.4%) had associated Kaposi's sarcoma. The number of patients with AAKS increased steadily from 2007 to 2010 (table 1). Their ages ranged from 18 to 54 years (Figure 1), mean of 33.6 ± 3.8 SD. Nine (9.2%) patients were less than 21 years old while 44 (44.9%) were in the third decade. There were 56 males and 42 females, male to female ration of 1.3:1. The male to female ratio decreased from 1.5:1 in 2007 to 1:1 in 2010. Females were younger than males (mean age of 27years vs. males 34; $p < 0.04$). Comorbid conditions were seen in 43 (43.9%)

patients including 20 (20.4%) pulmonary tuberculosis, 17 (17.3%) oral candidiasis, 15(15.3%) hypertension and 2 diabetes mellitus. Duration of symptoms of AAKS ranged from 1 to 13 months, mean 5.7 ±1.2SD. Symptoms were present in 91 (92.9%) patients and included pain (62.2%), swelling of the limbs (figure 2) (52.6%) and cosmetic disability (31.6%). Seven (7.1%) patients had no symptoms of Kaposi's sarcoma and the diagnosis was made during routine clinical evaluation (figure 3) at antiretroviral therapy (ART) clinic. Kaposi's sarcoma was the AIDS defining disease in 64 (65.3%) patients while in the remaining 34 (34.7%) it was diagnosed between 1 and 15 months after the initial diagnosis of AIDS. Sixteen patients had used HAART for 1- 13 months at the time of diagnosis of AAKS. The KPS ranged from 20% to 100%, median of 60%. All the patients were heterosexual although 11 were men having sex with men (MSM). Patients on anti-retroviral therapy at the time of diagnosis had a mean CD4 count of 267± 65SD cell/mm^3. Overall, the mean CD4 count at presentation was 165 cells/mm^3 (range: 26 – 875; 95% CI: 97 - 425). The mean HIV-1 viral load (VL) assessed in 71 patients was 48,593 copies/mL (range: 200- 989,571; 95% CI: 28,593- 76,225).

3.2 Tumour characteristics

The anatomic distribution of AAKS lesions is shown in table 2. All patients had multiple lesions the lower limbs being most frequently involved (45.9%). In 20 (20.4%) patients, tumour was limited to extremities, with fungating and exophytic growth invading and destroying the subcutaneous and surrounding tissues including the underlying bones (Figure 4). Unusual sites including 7 conjunctiva, 9 penile and 12 vulva were also involved. Perineal involvement was more common in females. Visceral lesions included 3 rectal, 5 intestinal and 2 gastric tumours. Tumour size ranged from 2.0 to 58.0cm, mean 29± 15.7SD. The histological type was mixed cellularity in 63 (64.3%) patients and anaplastic in 9 (9.2%). KS stage at presentation was T1, I1, S1 in 47 (48.0%); T1, I1, S0 in 22 (22.4%); T0, I0, S1, in 8 (8.2%) and T0, I0, S0 in 21 (21.4%). Overall, 77 (78.6%) patients had poor prognosis stage comprising 38 (90.5%) females and 39 (69.6%) males (OR= 3.5, 95% CI 1.7–5.6, P < 0.01). Women also had more disseminated cutaneous AAKS lesions involving an increased number of lesions at multiple anatomical sites, compared to more localised lesions in males (OR =3.4, 95% CI = 1.7–5.5, P = 0.001). Despite the differences in age and disease severity between males and females, no gender-specific differences were observed in CD4 counts or plasma HIV-1 viral load. However, when males and females were analysed separately, there were significant correlations between the severity of KS and the degree of immune suppression as measured by CD4 count (χ^2 test, P= 0.001) and between poor disease prognosis and immune suppression (P= 0.001)

Year	HIV infected patients		AIDS associated Kaposi's sarcoma patients		
	No	%	No.	% of HIV patients	Male: Female
2007	1667	23.3	20	1.2	1.5:1
2008	1755	24.5	23	1.3	1.3:1
2009	1837	25.7	25	1.4	1.2:1
2010	1896	26.5	30	1.6	1:1
Total	7155	100	98	1.4	1.3:1

Table 1. Prevalence of HIV infection and AIDS-associated Kaposi's sarcoma

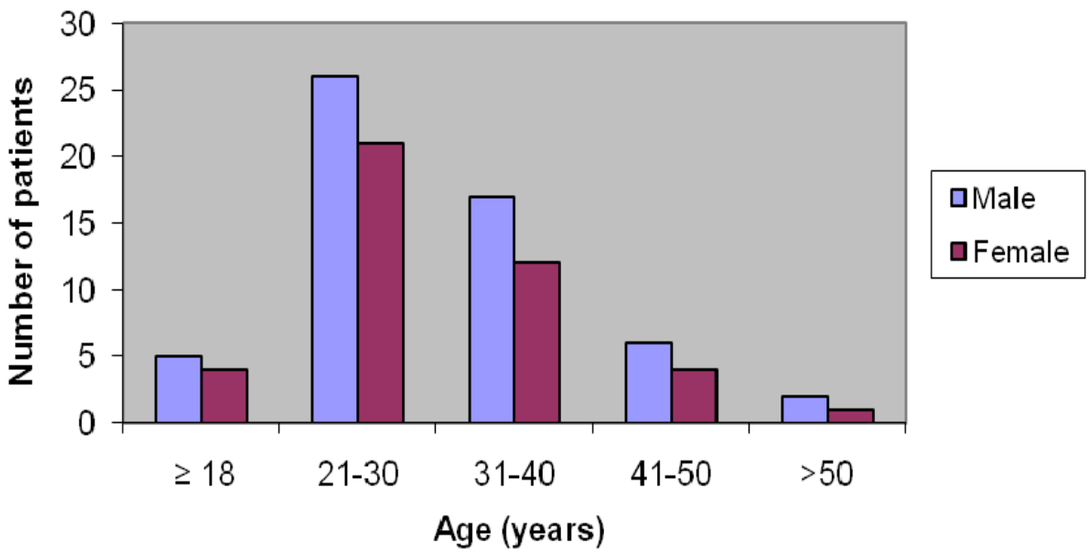


Fig. 1. Age and sex distribution of patients with AIDS-associated Kaposi's sarcoma



Fig. 2. Nodular Kaposi's sarcoma with swelling of the lower limb



Fig. 3. Asymptomatic Kaposi's sarcoma lesion discovered during routine clinical evaluation

Site	No.	%
Lower limb	45	45.9
Trunk	37	37.8
Lymph node	33	33.7
Perineum	19	19.4
Oropharynx	15	15.3
Upper limb	13	13.3
Visceral	9	9.2
Other	6	6.1

Table 2. Anatomical distribution of AIDS-associated Kaposi's sarcoma lesions



Fig. 4. Fungating Kaposi's sarcoma lesions of upper and lower limbs

Characteristics at presentation	HAART alone				HAART +VAB				P - value
	n	Mean	(SD)	Standard error of mean	n	Mean	(SD)	Standard error of mean	
Age (years)	19	32.5	(4.7)	4.21	67	31.8	(7.5)	2.94	0.29
Duration of symptom (months)	19	3.5	(1.7)	0.84	67	3.9	(1.3)	1.25	0.14
Viral load (x10^3 copies/mL)	10	503	(128.8)	17.50	41	512	(125.0)	15.9	0.15
CD4 count (cell/uL)	19	162	(56.4)	2.37	67	168	(55.8)	1.45	0.07
Sex									0.75
Male	12				42				
Female	7				25				
ACTG Stage									
Good prognosis	4	(21.1%)			16	(23.9%)			
Poor prognosis	15	(78.9%)			51	(76.1%)			
Time of diagnosis of KS									0.18
At diagnosis of AIDS	12	(63.2%)			43	(64.2%)			
After diagnosis of AIDS	7	(36.8%)			24	(35.8%)			

SD= standard deviation; ACTG = AIDS clinical trials group; KS= Kaposi's sarcoma
HAART= highly active antiretroviral therapy; VAB= combination of Vincristine, Doxorubicin and Bleomycin

Table 3. Characteristics of patients that were treated with HAART alone or HAART and VAB

3.3 Treatment and outcome

Overall, 67 (68.4%) patients were treated with both HAART and VAB of which 53 had completed six cycles. Of the 14 patients that did not complete anti-KS therapy, eight died in the course of treatment after two to five courses, treatment was stopped in two because of severe side effects and four were lost to follow-up (LTF). The median time to start chemotherapy after diagnosis of AAKS was three months (range 1 to 5months). Because of financial constraints, 19 (19.4%) patients had only antiretroviral therapy. The patients that had both HAART and VAB and those that had HAART alone had similar ACTG clinical stage, KPS and CD4 counts (table3). The remaining 12(12.2%) patients had only supportive care because of poor KPS (7) and refusal of consent (5). Two patients had limb amputation, five had excision of localised ulcerated lesions while 17(17.4%) had radiotherapy. Overall, 69 (70.4%) patients had improvement of AAKS symptoms that lasted a median duration of ten months (range 3 months to 4 years). The cumulative tumour response is shown in figure 5.

Fifty four (80.6%) patients treated with HAART and VAB had tumour response compared to 8 (42.1%) of those treated with HAART alone (p< 0.005). Patients treated with both HAART and VAB were more likely to have tumour response or stable disease (OR 2.7; CI: 1.8- 3.6) compared to those that had HAART alone (table 4). There was a positive correlation between symptoms control and tumour response (Pearson correlation coefficient, r = 0.35 and r = 0.28; p < 0.05 by two tailed Fisher exact test). While haematotoxicity was the most frequent toxicity in both treatment groups, neutropenia grades three and four was higher in patients treated with both HAART and VAB (22.4%) compared to HAART alone (10.5%)(P < 0.001). Digestive toxicity was frequently observed in both groups, with a higher rate of diarrhea in the HAART and VAB group. Five patients had peripheral neuropathy while two others had asymptomatic cardiomyopathy. These toxicities delayed chemotherapy by 1-2 weeks in 15 patients.

Patient's response	HAART alone (n=19)	HAART +VAB (n=67)	P -value
Symptom control			0.003
No. (%)	10 (52.6)	59 (88.1)	
Median duration of symptoms control, months (range)	5 (1- 13)	12 (5- 54)	0.001
Overall tumour response	8 (42.1)	54 (80.6)	0.005
Complete response	2 (10.5)	31 (46.3)	0.001
Partial response	6 (31.6)	23 (34.3)	0.075
Median duration of tumour response, months (range)	5 (1-17)	11 (2- 54)	0.001
Median time to relapse, months (range)	3 (2.5-15)	9 (5-26)	0.001
Treatment related complications			
No. (%)	7 (36.8)	38 (56.7)	0.015
Median KPS (range)			
At diagnosis of KS	60 (30-90)	60 (30-90)	
3 months after diagnosis of KS	60 (20-90)	60 (40-90)	0.017
Mortality at 6 months			
No. (%)	6 (31.5)	7 (10.4)	0.005

KS= Kaposi's sarcoma; KPS= Kernofsky performance score
HAART= highly active antiretroviral therapy; VAB= combination of Vincristine, Doxorubicin and Bleomycin

Table 4. Response of patients to treatment with HAART alone or HAART and VAB.

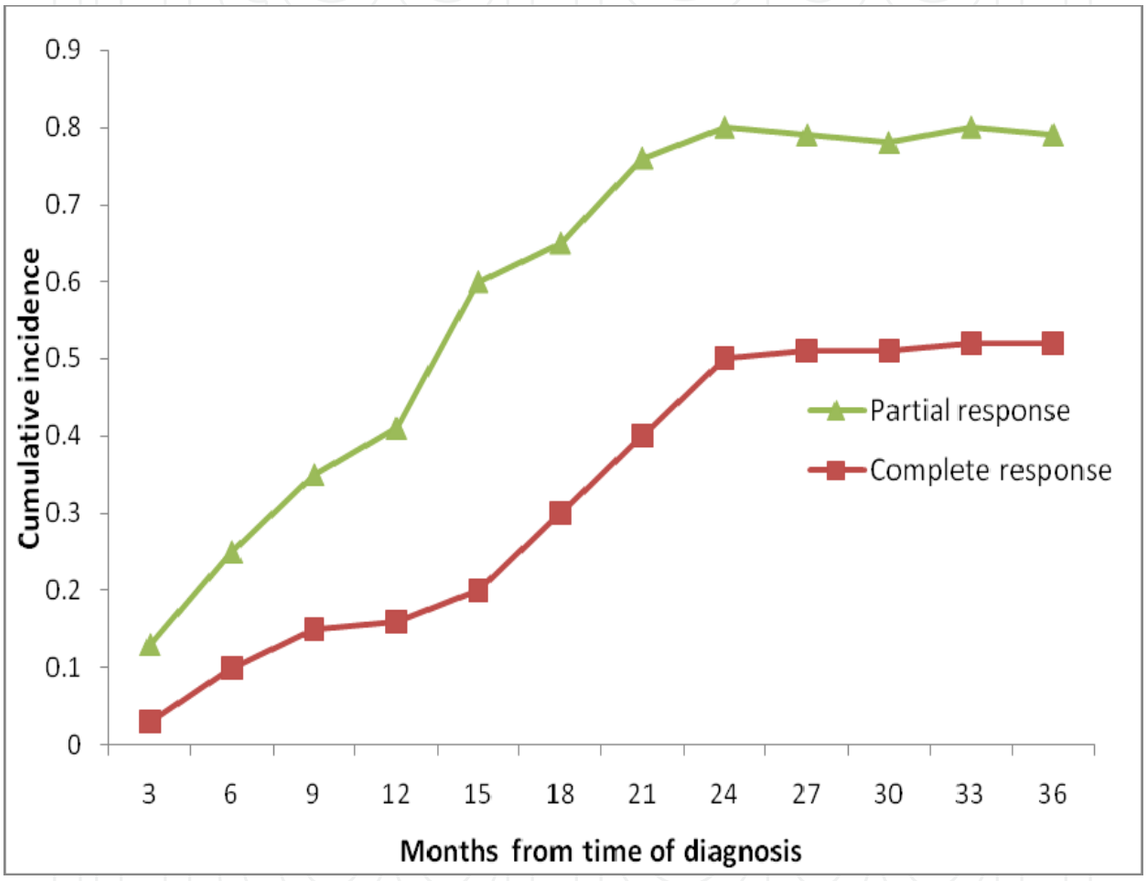


Fig. 5. Cumulative tumour response following treatment of AIDS-associated Kaposi's sarcoma

Overall, median survival was 14 months from the time of diagnosis of AAKS. The median survival was 12 months for patients treated with HAART compared to 18 months for those treated with both HAART and VAB (figure 6). Overall 56 (57.1%) patients had significant improvement in quality of life. Seven (7.1%) patients died during their first admission in the hospital while additional 7 were lost to follow-up. At one year 34 (34.7%) patients had died, comprising of 12 (100%) patients that had only supportive treatment, 9(47.4.0%) of those treated with HAART and 13 (19.4%) treated with HAART and VAB (figure 6). Univariate analysis showed that females, poor ACTG stage, CD4 count <200 cells/mm^3, viral load > 21,000 copies/mL, and not using antiretroviral therapy were significantly associated with poorer survival (table 5). When these factors were subjected to multiple regression analysis, poor ACTG stage (p=0.015), viral load > 21,000 copies/mL (p=0.001), not using antiretroviral (p=0.005) and not using anticancer chemotherapy (p=0.003) were the significant independent factors associated with poorer survival. Patient's follow-up ranged from one month to four years. Fifty two (53.1%) patients were followed-up for one year.

Variable	Number of patients	Death		OR	95% CI	P - value
		No	%			
Sex						
Male	56	21	37.5	1		
Female	42	20	47.6	1.4	1.2 – 2.9	0.049
Age (years)						
1-20	9	4	44.4	1		
21-40	76	32	42.1	1.5	1.4 – 3.5	
41-60	13	5	38.5	1.3	1.1 –2.7	0.175
Time of diagnosis of KS						
After diagnosis of AIDS	34	13	38.2	1		
As AIDS defining disease	64	27	42.2	1.7	1.5 – 4.9	0.075
ACTG stage						
Good prognosis	21	5	23.8	1		
Poor prognosis	77	35	45.5	4.8	3.7 – 12.4	0.005
CD4 count (cells/mm^3)						
>200	40	15	37.5	1		
≤200	58	25	43.1	2.4	1.6 – 3.9	0.016
Viral load (copies/mL)						
0-20,000	11	2	18.2	1		
≥ 21,000	40	19	47.5	2.9	2.7 – 6.5	0.003
Use of HAART						
Yes	86	28	32.5	1		
No	12	12	100.0	5.5	3.9 – 14.6	0.001
Use of VAB						
Yes	67	18	26.8	1		
No	31	22	71.0	3.2	2.1 – 5.7	0.001

OR= odd ratio; CI = confidence interval; ACTG = AIDS clinical trials group; KS= Kaposi's sarcoma
HAART= highly active antiretroviral therapy; VAB= combination of Vincristine, Doxorubicin and Bleomycin

Table 5. Univariate analysis of factors related to mortality in patients with AIDS-associated Kaposi's sarcoma

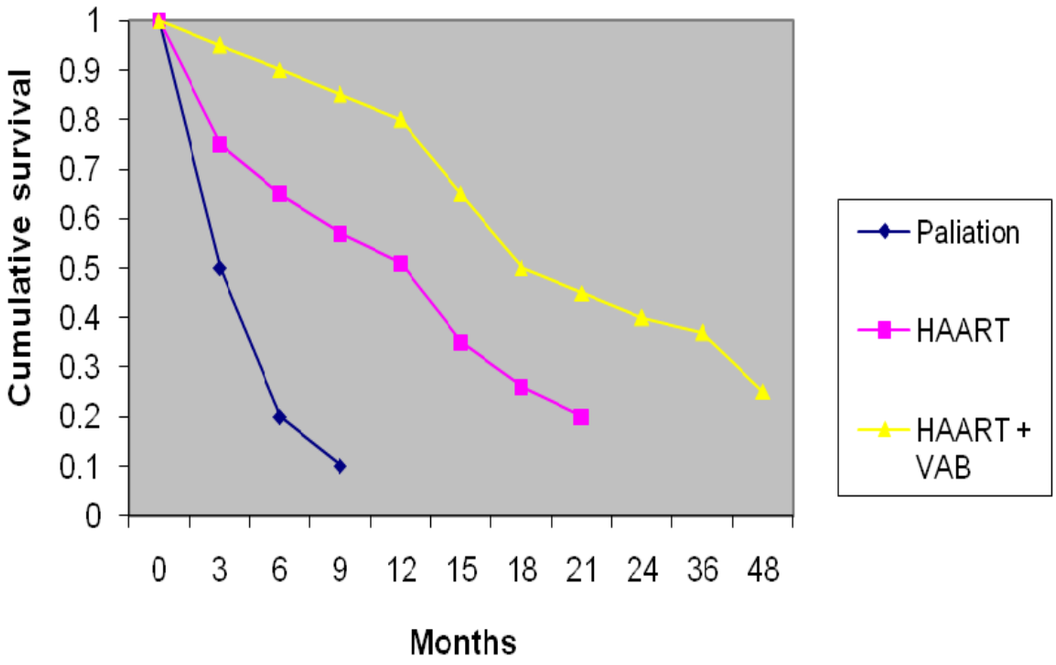


Fig. 6. Cumulative survival following treatment of patients with AIDS-associated Kaposi's sarcoma

4. Discussion

To our knowledge, this is the largest study to date on the treatment and outcome of patients with AIDS-associated Kaposi's sarcoma from Nigeria. The present study identified KS in 1.4% of HIV-1 infected patients. The patients are young with female patients being relatively younger than males. The male to female ratio decreased from 1.5:1 in 2007 to 1:1 four years later. Majority of the patients (78.6%) presented with high tumour burden that was categorised as poor prognosis disease, while 20 (20.4%) had pulmonary tuberculosis. Simultaneous treatment with HAART and combination chemotherapy was carried out on 67(68.4%) patients. This treatment was associated with significant morbidity but was the only chance for control of symptoms and prolonged survival.

In high income countries the incidence of AAKS has decreased significantly from mid 1990s (Franceschi et al, 2008; Pipkin et al, 2011). This reduced AAKS incidence is due to wide spread use of HAART which has the effect of immune reconstitution and direct inhibitory effects on angiogenesis. In addition, there are safer sex practices and other preventive and therapeutic measures against HIV infection. Recently, Phatak et al (2010) from India identified no case of KS among 46 AIDS-associated cancers reviewed over 5 years. In another report from Thailand, the incidence was 0.026 per 100,000 despite high incidence of HIV infection because HHV-8 infection is low at 4.0% (Sriplung & Parkin, 2004). In the present study, there was progressive increase in prevalence of AAKS over the study period (table 1). In a previous report from our institution, 15 AAKS patients were seen from 1991 to 1995 compared to 98 patients seen from 2007 to 2010 in the present study (Ahmed et al, 2001). Overall, the prevalence of AAKS in this study was 1.4% which is lower than 1.6% reported from Jos, Nigeria and 3.4% from South Africa, but higher than 0.8% reported from

other centres in Nigeria (Agaba et al, 2009; Iregbu & Elegba, 2006; Chu et al 2010). The high incidence of HHV-8 infection and limited access to HAART and other preventive measures explain in part the reason for increasing incidence of AAKS in sub-Saharan Africa.

Prior to the HIV epidemic KS was a disease of middle-aged men (Penn, 1979; Taylor et al, 1971). The mean age of 33.6 years in the present study is similar to that reported in other studies in our sub-region (Chu et al, 2010; Phipps et al, 2010). The lower age of these patients is probably due to the high risk behaviour and incidence of HIV infection is highest in the age group 20-40 years in sub-Saharan Africa. In addition, our female patients were younger than males. The finding that AAKS occurs at an earlier age in women when compared with men has been reported previously (Mosam et al, 2008; Phipps et al, 2010). In the present study, the proportion of KS patients was highest among women in their mid-20s who heterosexually acquired HIV-1 infection. This indicates that females acquire HIV-1 infection at an earlier age than males. Alternatively, immunosuppression from HIV infection and KS pathogenesis might progress more rapidly in females compared to males. Previous studies have shown that the age-specific distribution pattern for female KS was essentially similar to that previously reported for HIV-1 infection (Jombo et al, 2006). Therefore, the risk of developing AAKS is closely related to the epidemiology of HIV-1 infection in females.

Variable	Category	OR	95% CI	P-value
Sex	Female vs. Male	1.8	1.5- 2.9	0.075
ACTG stage	Poor vs. Good prognosis	5.3	2.2- 17.3	0.015
CD4 count (cells/mm^3)	≤ 200 vs. > 200	1.6	1.3- 3.8	0.075
Viral load (copies/mL)	≥ 21,000 vs. < 21,000	3.1	2.6- 9.5	0.001
Use of HAART	No vs. Yes	2.8	2.3- 6.9	0.005
Use of VAB	No vs. Yes	1.9	1.5- 3.8	0.003

OR= odd ratio; CI = confidence interval; ACTG = AIDS clinical trials group;
HAART= highly active antiretroviral therapy; VAB= combination of Vincristine, Doxorubicin and Bleomycin

Table 6. Multiple regression analysis of factors related to mortality in patients with AIDS-associated Kaposi's sarcoma

In Western countries all forms of KS are more common among men than women (Simard et al, 2011; Martellotta et al 2009). This is similar to the findings in Africa before the advent of HIV infection (Sasco et al, 2010; Taylor et al, 1971). Among HIV-infected individuals other than MSM, reported incidence rates of KS are still higher in men in other studies (Kagu et al, 2006; Sissolak & Mayaud, 2005). In a recent study from Brazil 94.4% of 107 AAKS patients were men, giving a male to female ratio of 18:1 (Yoshioka et al, 2004). The observations that a tumorigenic KS cell line could not be established in pregnant immunodeficient mice and that human chorionic gonadotropin (hCG) inhibited KS growth in-vitro suggested a possible biologic basis for the lower KS incidence among women (Lunardi-Iskandar et al, 1995;

Rabkin et al, 1995). However, therapeutic trials with hCG have been inconclusive while studies in women with HIV infection revealed that pregnancy afforded no protection from KS development or dissemination (Rabkin et al, 1995). In our patients, the male to female ratio was 1.3:1 which decreased progressively from 1.5:1 in 2007 to 1:1 four years later. This is similar to 1.4:1 recently reported from South Africa (Chu et al, 2010). A report from Jos Nigeria revealed a reversal of the gender ratio from a male to female ratio of 10:1 about four decades ago to 1:1.4 (Agaba et al, 2009). The reason for the near equivalent distribution of AAKS cases among men and women in recent studies may be a reflection of the high proportion of HIV infected females with >60% of person living with the virus in Africa being women. Additionally, women are more frequently subjected to HIV testing as routine counselling and testing has been applied to perinatal settings, and this may lead to higher number of AAKS cases being identified among women. Finally, unlike in Western countries where MSM constitute a high proportion of AAKS cases, the heterosexual mode of HIV transmission in our patients mean that HHV-8 would be equally distributed among men and women. Therefore, the trend in increasing proportion of female patients with AAKS may continue until when females predominate.

Patients in this study presented with extensive and disseminated disease with 78.6% having poor prognosis stage, a much higher proportion than reported from resource rich countries (Ashish et al, 2007; Krown 2004). Other reports from poor resource countries revealed that poor prognosis disease constitute 60-82% of cases (Agaba et al, 2009; Bassett et al, 1995; Phipps et al 2010). Cutaneous lesions were present in 64.7% of patients in this series followed in order of frequency by lymphadenopathy and visceral lesions. Moderate enlargement of peripheral lymph nodes is not uncommon in HIV infected patients. A biopsy of such nodes would often reveal a focus of KS, a finding that appears to have little clinical consequence (Krown 2004). However, 11 of our patients had massive generalised lympadenopathy in the absence of evidence of KS elsewhere. In sub-Saharan Africa lymphadenopathy is comparatively common and has various causes including tuberculosis, lymphoma, KS and HIV infection. There is a significant overlap in the clinical presentation of these diseases although each requires distinctly different treatment. Histology provides a reliable and cost effective definitive diagnosis since each disease can be distinctively diagnosed under the microscope. However, it has been suggested that co-existing lesions can be missed even in biopsy material if special stains for demonstration of microorganisms are not performed (Pantanowitz et al 2010). Involvement of the gastrointestinal tract (GIT) was seen in only nine of our patients. However, most patients with GIT KS are asymptomatic, and because the lesions are submucosal they are not visualized on contrast-enhanced radiographs (Kibria et al 2010). Previous studies showed that asymptomatic GIT lesions have little clinical consequences hence, endoscopy should be carried out only on symptomatic patients (Kibria et al, 2010; Sissolak & Mayaud, 2005). In our patients, KS involved multiple anatomical regions. The lower limbs were most frequently affected with an associated lymphoedema which may be extensive and disproportionate to the extent of cutaneous disease. This lymphoedema may result from tumour involvement of dermal lymphatics or from the production by KS cells of growth factors that increase vascular permeability (Feller et al, 2008). Additionally, HHV-8-induced exuberant proliferation of endothelial cells may lead to the occlusion of lymphatic vascular lumens leading to lymphoedema (Feller et al, 2008).

In this as in other reports, at the time of diagnosis women had more widespread and advanced AAKS compared to men (Chu et al 2010; Meditz et al, 2007). It is probable that the

reason for the increased severity of AAKS in women is not related to virological or immunological differences since both men and women in our study had similar mean VL and mean CD4 counts. This is in agreement with studies from Zimbabwe and South Africa (Meditz et al, 2007; Mosam et al, 2008). Of special interest is a small cohort of 14 patients who were on HAART for 6-13 months at the time of diagnosis of KS. These patients had a median CD4 count of 375 cells/mm^3 and undetectable HIV viral load. They required systemic therapy to control their KS but were more likely to have complete resolution of their tumours and demonstrated a trend towards better survival than patients having KS with lesser CD4 counts and detectable HIV viral loads. In the past, AAKS has been reported in African patients with CD4 counts of >350 cells /mm^3 indicating that severe immunosuppression is not necessary for development of KS (Morgan et al, 2000). Similarly, recent reports from high income countries have identified a group of patients that developed AAKS despite effective and sustained HIV suppression and good immune system function (Crum-Cianflone et al, 2010; Mani et al, 2009; Maurer et al, 2007). This raises questions about the integrity of the immune system and its ability to control certain viruses in patients with long-standing HIV infection. It has been suggested that with the ageing of HIV infected patients those who are co-infected with HHV-8 may develop KS despite good control of HIV infection (Crum-Cianflone et al, 2010). The impacts of AAKS on quality of life are varied. In our patients, extensive oedema of the lower limbs was associated with stiffness and pain that may interfere with walking while ulcerated tumours were infected and foul smelling. Lesions of the face and genitalia also have social and emotional consequences, including isolation because of obvious disfiguring lesions, and depression and anxiety from the constant visible reminder of illness.

The disability and suffering associated with AAKS means that treatment to reduce symptoms and improve quality of life should be carried out promptly and efficiently. HAART is an essential treatment for all AAKS patients (Krown, 2004; Tirelli & Bernardi, 2001). In patients with low tumour burden and slowly progressing disease, histological regression of existing KS lesions has been shown in response to HAART (Martellotta et al, 2009). However, HAART alone can not effectively control all cases of KS and there may be initial tumour progression as part of the immunoreconstitution syndrome (Bower et al, 2005). In addition, it is not possible to state with certainty what proportion of patients with AAKS will benefit from HAART alone, or what are the precise characteristics that can be use to identify such patients. In our patients as in others, HAART is an effective post-chemotherapy maintenance treatment in patients with advanced and extensive disease that has been reduced significantly as a result of conventional chemotherapy (Cooley et al, 2007; Martin-Carbonero, 2004). The effects of HAART on Kaposi's sarcoma are multifactorial and include inhibition of HIV replication, diminished production of HIV-1 transactivating protein Tat, reconstitution of immune response against HHV-8 and possibly direct antiangiogenic activity by inclusion of protease inhibitors (Tirelli & Bernardi, 2001). In the present study, decision to initiate systemic chemotherapy was based on the extent of Kaposi's sarcoma in addition to other considerations such as patient KPS, end organ function, degree of immunosuppression, and other HIV comorbidities.

Our patients were treated with a combination of vincristine, doxorubicin and bleomycin, similar to reports from other low income countries (Chu et al, 2010; Dedicoat et al, 2003). In high income countries liposomal anthracyclines and taxanes are being used for treatment of AAKS due to higher efficacy and reduced toxicity (Ashish et al, 2007; Cooley et al, 2007). In

a meta- analysis comparing pegylated doxorubicin (PLD) and VAB among 499 patients, Dedicoat et al (2003) found a better response among the PLD group although there was no survival advantage by either group. However, liposomal anthracyclines are unlikely to be available or affordable in low income countries where the majority of AAKS patients live. In a recent analysis from Brazil, PLD was found to be associated with improved efficacy and less toxicity but in terms of cost effectiveness, the VAB regimen is the most rational treatment option for AAKS patients in poor resource settings (Vanni et al, 2006). Our results showed that six cycles of this regimen could produce a significant and quick response in symptomatic patients with advanced AAKS. Overall response rate of 80.6% in our patients compares favourably to 50% to 88% reported in other studies (Dedicoat et al, 2003; Makombe et al, 2008; Phipps et al, 2010). Differences in response rates are largely attributable to differences in the patient populations evaluated, the lack of strictly defined response criteria and variations in the dosing schedules used. Of the 67 patients that had chemotherapy in this study, 52% had complete resolution of their disease within 36 months of diagnosis. This is similar to observed resolution rates of 44%-60% reported using similar regimen (Bihl et al, 2007; Nasti et al, 2000; Nguyen et al, 2008). However, we found the median time to complete resolution to be 9 months which is considerably longer than 5 months previously reported (Bihl et al, 2007). This is provably because chemotherapy was not immediately started in many of our patients due to financial constraints. In the present study, both HAART and VAB were independently associated with complete resolution of tumour suggesting that even in the HAART era, chemotherapy plays a significant role in the treatment of advanced AAKS patients. In addition, HIV viral load was significantly associated with resolution of KS. This finding is consistent with other reports of AAKS improvement or resolution associated with significant decrease or undetectable HIV viral load (Nguyen et al, 2008). Indeed, it seems that controlling HIV viral load is essential for clinical improvement, disease resolution of KS, and perhaps decreased risk of relapse. In this as in other studies there was no association between CD4 T-cell count and KS response, suggesting that suppression of HIV replication plays a more vital role in the resolution of KS than immune reconstitution (Mosam et al, 2008; Iregbu & Elegba, 2006). In our patients, there was positive correlation between tumour response and clinical response, and the response was maintained for a significant period of time after discontinuation of chemotherapy. Clinical response was associated with improved quality of life as evidenced by control of fungating and foul smelling ulcers and improvement of pain, cosmetic appearance and KPS. In the present study, median survival was 18 months following chemotherapy compared to 12 months following HAART alone. Both VAB and HAART are independently associated with improved survival, similar to the Multicenter AIDS Cohort Study which demonstrated an 81% reduced risk of death for KS patients treated with HAART (Tam et al, 2002). Whilst CD4 count <200 cells/mm^3 was associated with mortality on univariate analysis, it was not on multivariate analysis. This may be due to the effects of advanced KS disease (T1 and S1 stages) whose effects were stronger than CD4 count.

The toxicities observed following chemotherapy in our patients are similar to those reported in other studies using same regimen and are well tolerated (Dedicoat et al, 2003; Guadalupe et al, 2011). In the absence of haemopoetic growth factors, cytotoxic chemotherapy was used cautiously in our patients to minimise the risk of bone marrow suppression that may lead to infectious complications. Bacterial infections which resulted from severe neutropenia secondary to chemotherapy were observed in three of our patients. Doxorubicin causes

significant bone marrow suppression which is at its nadir on day 14 after administration. This bone marrow suppression recovers slowly over 7-10 days but in an HIV infected individual the magnitude and duration of the bone marrow suppression may be longer, hence the need to wait for three weeks to allow the bone marrow to recover before the next cycle of chemotherapy is given. The selection of therapy for KS must take into account the potential benefit and adverse effects of treatment, interactions with other medications, and potential impact on underlying immunosuppression.

When dealing with localised bulky or cosmetically disturbing lesions, radiotherapy is the most effective local therapy. In this as in other reports, irradiated lesions regress with treatment, but regrowth, after 6 months is common (Bih et al, 2007; Nguyen et al, 2008). In addition to providing effective palliation, radiotherapy is associated with minimal side effects. Although surgery is effective in excision of localised isolated lesions, heroic surgery is unjustified. Our study has several limitations. Among the patients that died, other risk factors for mortality such as tuberculosis were not independently considered hence the actual death due to KS were not isolated. In addition, some of our patients were lost to follow-up and a previous study indicates that about 40% of these patients were actually dead (Brinkhof et al, 2009). Similarly, because many patients lost to follow-up were treated with VAB, the beneficial effects of chemotherapy may be underestimated. Finally, follow-up of patients was difficult and inconsistent hence, it was not possible to monitor the timing of treatment outcome accurately.

5. Conclusion

In conclusion KS is not uncommon in patients with HIV-1 infection. The patients present with extensive and advanced disease that requires systemic treatment. All AAKS patients should receive HAART. In low income countries like ours, chemotherapy consisting of a combination of vincristine, doxorubicin and bleomycin should be given simultaneously with HAART to patients that can physiologically withstand such therapy. The usual number of cycles for effective therapy is six cycles. However, chemotherapy may continue for 1-2 cycles beyond complete remission to maximise the chance of attacking all microscopic KS cells. Following successful treatment chemotherapy can be restarted for recurrent tumour. If KS continues to grow in the presence of effective HAART regimen, chemotherapy with VAB should be stopped and alternative treatment modalities should be instituted if possible, or else palliative KS management should be started. Palliative care for KS may include adequate pain relief, reduction of the size of tumours with radiotherapy and reduction of the offensive smell of ulcerated lesions with appropriate dressing argent. Prevention and treatment of other opportunistic infections is necessary as uncontrolled infections may stimulate KS progression probably due to production of angiogenic cytokines. Using this approach we achieved quick and prolonged tumour response in addition to improved quality of life as evidenced by symptoms control and improved cosmetic appearance and KPS. High satisfaction and reduced toxicities as well as availability, affordability and ease of administration of the drugs led to good patient's compliance. This approach is recommended for treating AAKS patients in a poor resource setting. It is necessary to identify KS patients early in the disease when treatment is likely to provide significant benefits in terms of reducing the bulk of disease and improving long-term survival. However, early access to highly active antiretroviral therapy constitutes the best hope for the control of this stigmatizing and lethal disease in sub-Saharan Africa. With improvement

in the access to antiretroviral therapy in sub-Saharan Africa, it is necessary to designed studies that investigate the effects of cheaper and more widely available chemotherapeutic argents for the treatment of AIDS-associated Kaposi's sarcoma among patients on highly active antiretroviral therapy.

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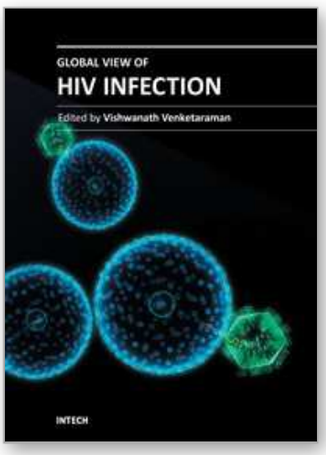
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