A retrospective review of treatment outcomes of HIV positive patients with Kaposi's sarcoma receiving antiretroviral therapy at Charlotte Maxeke Johannesburg Academic Hospital (2011-2013)

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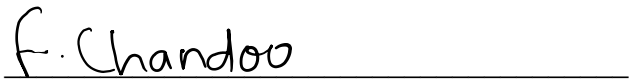
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Medicine.

Johannesburg, 2019.

DECLARATION:

I, Dr Fatema Aonali Chandoo, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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26 day of July 2019 in Johannesburg.

ABSTRACT

Background: South Africa in 2015 had approximately 7 million people living with Human Immunodeficiency Virus (HIV)[1]. This constitutes one of the highest numbers of people living with HIV in any single country. Acquired Immunodeficiency Syndrome (AIDS)-related Kaposi's sarcoma (KS) has also been identified as one of the most common malignancies in the HIV infected population in South Africa[2]. The incidence of KS in South Africa initially increased substantially with the HIV epidemic[3] however with the increasing availability of antiretroviral therapy (ART) the incidence of AIDS-related KS has dropped dramatically in the last few years from 1220 to 669 in females and 1491 to 978 in males from 2008 to 2014 [4, 5].

Objectives: To assess the demography and response to treatment of KS patients on ART at a quaternary hospital.

Design: Retrospective record review of patients' files.

Methods: Patients with a histological diagnosis of KS were recruited from the Medical Oncology clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Their demographic, laboratory and treatment information were recorded on a data sheet (see appendix A).

Results: There were 109 patients in the study cohort (1st January 2011 to 31st December 2013). The majority of patients (71%) were male. Mean age of the group was 39 (range 21 – 63) years. The mean CD4 count at KS diagnosis was 212 (range 17 – 696) cells/ µL. Almost half (49%) of the cohort were ART- naïve at the time KS was diagnosed, however almost all the KS symptomatic patients (99%) were on ARTs upon Medical Oncology clinic enrolment/at the time of their inclusion in the study. Concomitant systemic infections were documented in 49% of patients at the time of initial diagnosis. The most common co-infection was tuberculosis (TB). The majority (80%) of patients received chemotherapy most of whom (66.7%) received doxorubicin, bleomycin, vincristine (ABV). The mortality at two years was 45%. The majority of deaths occurred within

the first six months of the diagnosis of KS with 50% of the dead patients having concomitant TB on TB treatment together with HIV-KS.

Conclusion: Mortality related to HIV-KS remains high in our setting despite widely available ARTs. The possible factors associated with high mortality in this cohort were concomitant coinfection with tuberculosis (TB), possibly ART initiation timing and immune reconstitution inflammatory syndrome (IRIS), bulk of KS disease burden with visceral involvement and probably the choice and toxicity of chemotherapy agents especially doxorubicin.

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I would like to express my heartiest and sincere gratitude towards my supervisors Professor Paul Ruff and Dr Kapila Hari for their invaluable guidance, support and patience throughout the study period. Many thanks to Professor François Venter for his kind assistance during the early phases of the study.

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A huge thank you to my mother, my extended family for their unconditional love and support throughout my career and to my friends who have been my inspiration all along.

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LIST OF ABBREVIATIONS

ABV	Adriamycin/Vincristine/Bleomycin
ACTG	AIDS Clinical Trials Group classification
AIDS	Acquired Immune Deficiency Syndrome
APL	Acute Promyelocytic Leukaemia
ART:	Antiretroviral therapy
BMI	Body mass index
BV	Bleomycin/ Vincristine.
CD	Cluster of Differentiation
CDC	Centres for Disease Control (Atlanta, GA, USA)
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
GRID	Gay-related immune deficiency
cGy	Centigray
Gy:	Gray (a unit of radiation dose)
HCG	Human Chorionic Gonadotropin
HHV8	Herpes Hominem Virus 8
HIV	Human Immunodeficiency Virus
IRIS	Immune reconstitution inflammatory syndrome
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma associated Herpes Virus
LTF	Lost to Follow Up

MCD	Multicentric Castleman's Disease
MeV	Mega (Million) electron volt
mTOR	Mammalian target of rapamycin
NHL	Non-Hodgkin's Lymphoma
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
PI	Protease Inhibitors
PLD	Pegylated Liposomal Doxorubicin
RT	Radiotherapy
SIV	Simian Immunodeficiency Virus
SPSS	Statistical Product Service Solutions
sSA	sub-Saharan Africa
TB	Tuberculosis
TNM	Tumour Node Metastasis Staging
UNAIDS	United Nations Programme on HIV and AIDS
VL	Viral Load
WHO	World Health Organization

CHAPTER 1

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Human Immunodeficiency Virus (HIV) background

It is believed that HIV emerged from Africa from the then Belgian Congo (now Democratic Republic of Congo) in the 1920s [6]. HIV is reported to be a strain similar to that of Simian Immunodeficiency Virus (SIV) which was isolated from the common chimpanzees, subspecies Pan troglodytes' troglodytes (plus possibly from low-land gorillas) and transferred to the human population most likely by the human consumption of bush meat[7]. Before the 1980s HIV related acquired immunodeficiency syndrome (AIDS) was not yet established as a disease entity however thereafter this disease grew rapidly in its number globally with sex workers implicated as pivotal in its spread across the African continent[7].

In the 1980s due to its presentation as an immunodeficiency disease predominantly in homosexual men in America, this disease was initially termed gay-related immune deficiency (GRID). Around mid-1982 the scientists also found that the disease was present among haemophiliacs and intravenous drug users. In September 1982 the United States of America (USA) Centres for Disease Control (CDC) in Atlanta, Georgia named it as AIDS[6].

In South Africa the first AIDS cases were discovered in homosexual white men in 1983 and by the 1990s it was well established that the heterosexual mode of transmission was the major cause of the epidemic in South Africa just like the rest of Africa[7].

1.1.2 HIV epidemic: global view

The world has been facing the current HIV epidemic for more than three decades. For almost fifteen years there have been various efforts globally to try and curb this epidemic. In 2016, the

United Nations general assembly put up a target to achieve by 2020 to try and end the AIDS epidemic by 2030[1]. According to the United Nations Programme on HIV and AIDS (UNAIDS) Prevention Gap report of 2016 there has been a steady decline globally in the number of new HIV infected cases among adults per annum from the year 2000 to around 2010 (figures 1.1A, 1.1B). However, from 2010 onwards this decline for many countries has been stagnant at an estimated 1.9 million new adult cases per year[1]. According to the UNAIDS, reasons for such stagnation are gaps in the HIV prevention and reduced ART adherence with a lack of viral suppression below the planned 2020 target level[1].

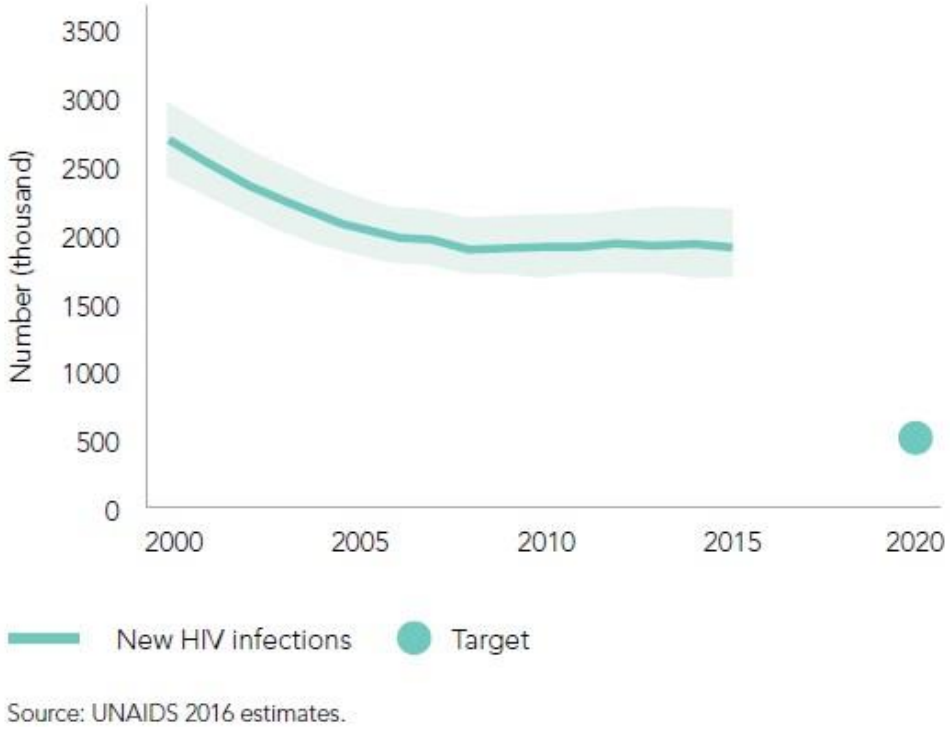


Figure 1.1A New HIV infections among adults, global, 2000-2015 [1]

(UN Joint Programme on HIV/AIDS (UNAIDS), *Prevention Gap Report*, January 2016)[1]

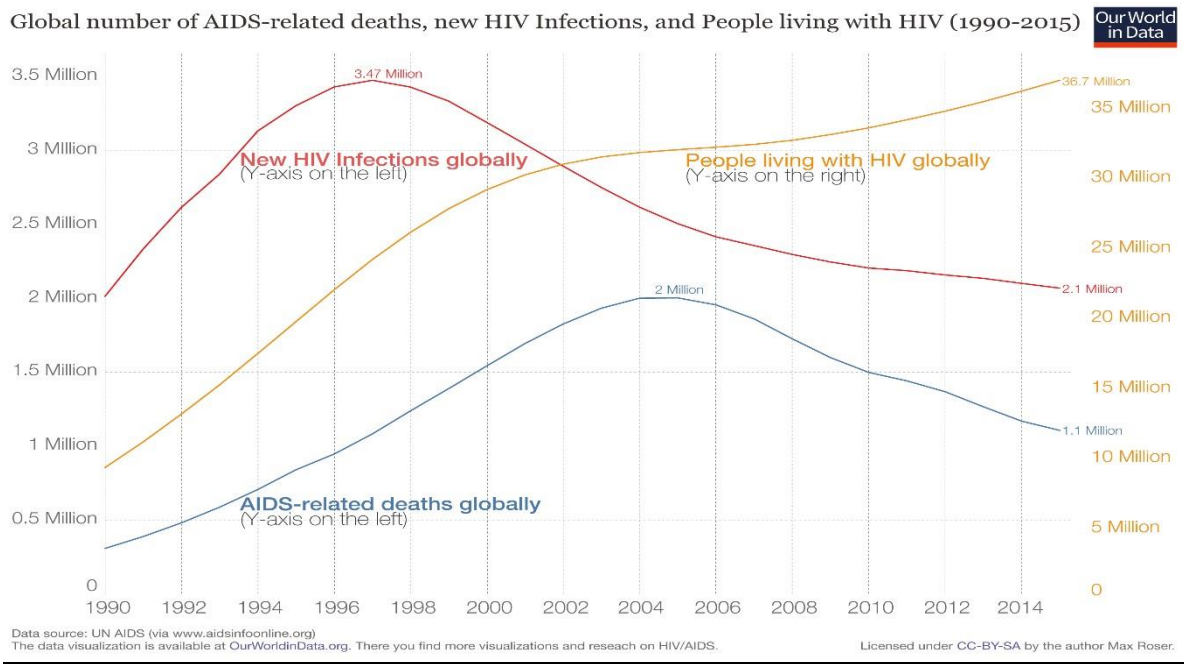


Figure 1.1B Global trend on HIV [8]

Data source: UN AIDS (via www.aidsinfoonline.org)
The data visualization is available at OurWorldinData.org. There you find more visualizations and reseach on HIV/AIDS.
Licensed under CC-BY-SA by the author Max Roser.

1.1.3 HIV in sub-Saharan Africa (sSA) with a focus on South Africa

SSA accounts for just 12% of the global population, but it represents about 70% of the global HIV load with regional variation[9]. To further zoom into the statistics "Eastern and Southern Africa has only 6.2% of the world's population but is home to half of the world's people living with HIV"[1]. In 2015 alone almost 40% of the new HIV infections from eastern and southern Africa were reported from South Africa alone and the remainder from the remaining regions (figure 1.2)[1].

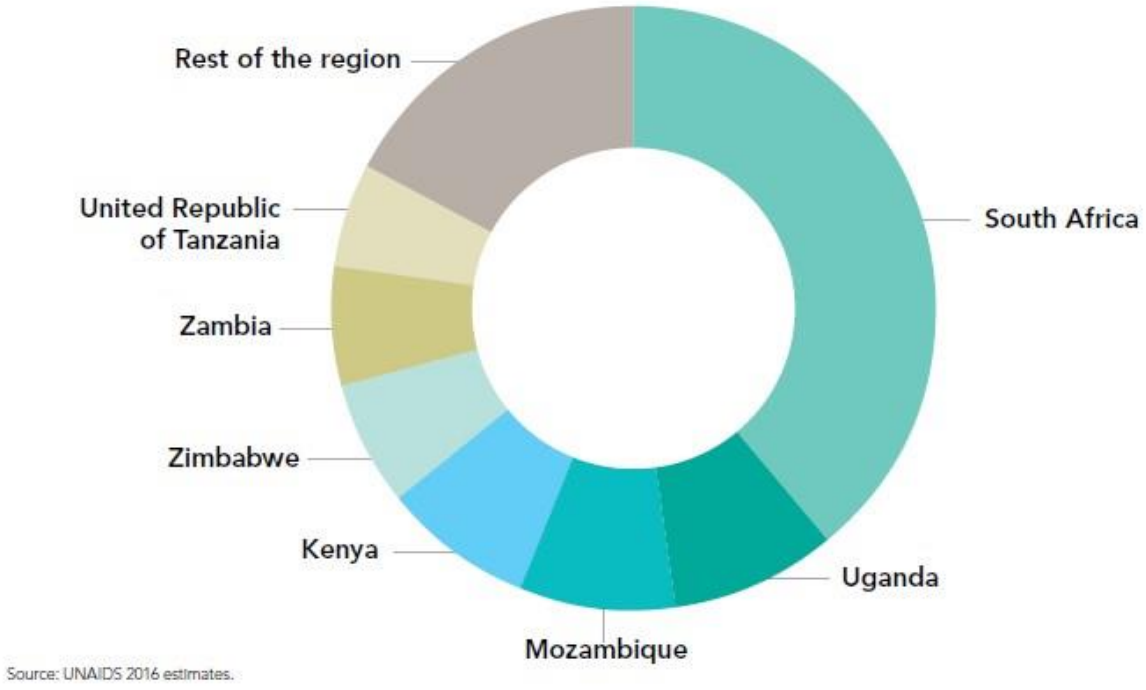


Figure 1.2 Distribution of new HIV infection by country, eastern and southern Africa, 2015[1]

(UN Joint Programme on HIV/AIDS (UNAIDS), *Prevention Gap Report*, January 2016)[1]

1.2 AIDS response

Among the efforts put forward to try and retard the AIDS epidemic there has been a significant upscale of the antiretroviral therapy (ART) programme globally by various national and international programmes. In 2015 about 54% of the people living with HIV in the Eastern and Southern region were on ART[1]. South Africa has made tremendous efforts to increase ART roll out to its people and it has the biggest ART programme globally with over 3 million people on therapy[10]. According to recent statistics "One third of the increase in the number receiving ART worldwide was in South Africa" (figure 1.3)[9].

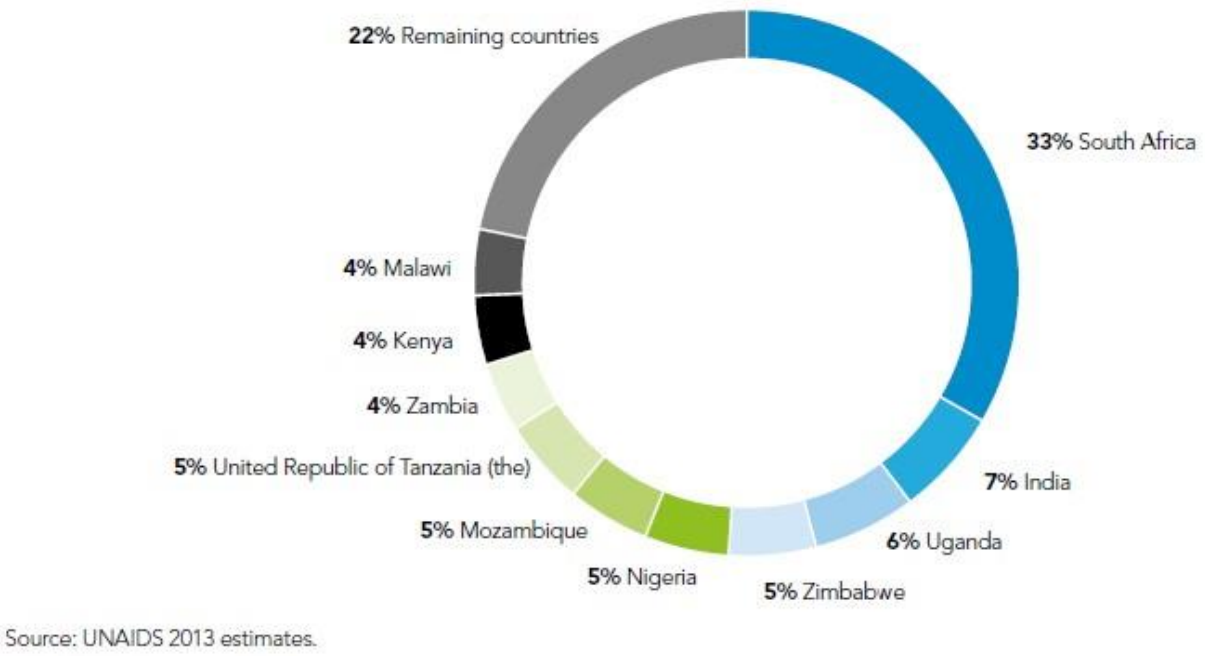


Figure 1.3 Number of people receiving ART by 2013 [9]

(UN Joint Programme on HIV/AIDS (UNAIDS), *The Gap Report*, 2014)[9]

Due to their low immunity, AIDS patients are at an increased risk of developing opportunistic infections as well as specific malignancies including non-Hodgkin's lymphoma (NHL), cervical cancer and Kaposi's sarcoma (KS) [11].

1.3 Kaposi's sarcoma

1.3.1 Background

KS is one of the most common AIDS defining malignancies in sSA[11, 12]. It is a multifocal malignancy that arises from the endothelial cells of the lymphatic and blood vessels[12, 13]. Infection with Kaposi's sarcoma Herpes Virus (KSHV) is a pre-requisite for the development of this malignancy (more information on KSHV is explained in the section 1.3.2 below). Superimposed infection with HIV and the immunosuppression associated with it as well as additional local and systemic inflammatory stimuli leads to reactivation of the latent KSHV genes (Orf73) and thus production of larger numbers of KSHV virus protein leading to KS angiogenesis and oncogenesis [11, 14]. Chronic inflammation in patients with AIDS places such patients at higher risk of developing KS [14].

1.3.2 KSHV

1.3.2.1 Virus background and prevalence

KSHV, also known as Human Herpes Virus 8 (HHV8), is a double stranded DNA virus of the gamma herpes viridae family, with oncogenic properties[14]. It was first isolated in 1994 from KS tumours by Yuan Chang et al [14, 15]. KSHV has been described as a causative agent of KS, Primary Effusion Lymphoma and Multicentric Castleman's Disease (MCD)[14]. Unlike other herpes virus "KSHV infection is not ubiquitous" thus a geographical variation in the seroprevalence of this virus is observed [15,16]. KSHV is predominantly limited to sSA, some areas of Europe, Asia and America [15,16]. According to literature KSHV seroprevalence is described as follows [16]:

a) Non-endemic areas (seroprevalence of less or equal to 10%): most European countries, Asia especially Xinjiang province in China and America.
b) Intermediate endemic areas (10%-25% seroprevalence): mostly involving the Mediterranean countries.
c) High endemic areas (>50%) seroprevalence): mainly consisting of African countries.

KSHV seroprevalence is documented to be high in sSA especially within the black population[11, 17]. Maskew M in 2014 reported that the "prevalence of KSHV in sSA is, in fact, among the highest in the world"[11]. Earlier studies for instance by Sitas et al in 1999 looked at the prevalence of anti-KSHV antibodies among the black South African

population and found that “among the 51 patients with Kaposi’s sarcoma, the standardized sero-prevalence of antibodies against HHV-8 was 83 percent, significantly higher than the prevalence among those without Kaposi's sarcoma”[17]. A recent (2017) publication consisting of data across Europe, America, Asia–Pacific and South Africa, looked at the risk of developing KS among HIV positive patients. They reported a higher risk of KS in South African population likely due to high KSHV seroprevalence[18].

1.3.2.2 KSHV modes of transmission

KSHV can be transmitted through sexual and/or non-sexual route.
In the non-endemic areas, the sexual route is reported to be the main mode of transmission especially in the gay population [(16)]. In the endemic areas especially in the African continent data on heterosexual mode of transmission is inconsistent [(15,16)]. Studies done in sex workers in Nigeria and Kenya show there is evidence for heterosexual transmission however, a study from South Africa showed no such association. The south African study was large and involved sex workers [(15,16)].

The non-sexual route of transmission involves blood and blood products transfusion, vertical transmission through mother to child especially in the African endemic areas. Exchange of saliva is another considerably important route of transmission in the endemic areas among children as well as adults. Viral DNA has been detectable at various levels in the saliva of KSHV infected people [(15,16)]. There is “strong evidence that horizontal transmission predominantly via saliva is the major route of transmission especially in the endemic areas” [(15)]. KSHV can be located in various other body fluids apart from saliva including semen, vaginal secretions, prostate gland and peripheral white blood cells (mononuclear cells). KSHV can be contracted at any time of the life i.e. childhood and/or adulthood [(15)].

Once inside the host cell KSHV persists as a latent infection and can remain dormant in the body for many years following primary infection in an immunocompetent population [11]. Active disease occurs when the host opportunity is favourable. This virus has the ability to hijack the host antiviral immune mechanism upon first entry into the cell and further down regulate immune mediated pathways/responses upon subsequent cell replication so as to favour its long-term survival inside the host cells[14, 19, 20]. This process involves complex pathways involving

the type 1 interferon (alpha and beta) of the innate immune system and the mammalian target of rapamycin pathways (PI3-K/AKT/mTOR) to mention a few[14, 19, 20]. KSHV infection is a necessary causal factor for KS tumour formation however not all KSHV infected people develop KS therefore co-factors like immunosuppression and other systemic inflammatory conditions are important in the development of KS[13]. KSHV causes vascular endothelial cells to grow in an aberrant fashion. Through complex mechanisms the viral antigens promote cell replication and prevents cell apoptosis which prolongs the viral survival [(16)]. It interacts with the anti-tumorigenic check points of the body and increases the cells abnormal angiogenic properties, all of which paves the way for tumorigenesis [(16)] (Figure 1.4)[14]

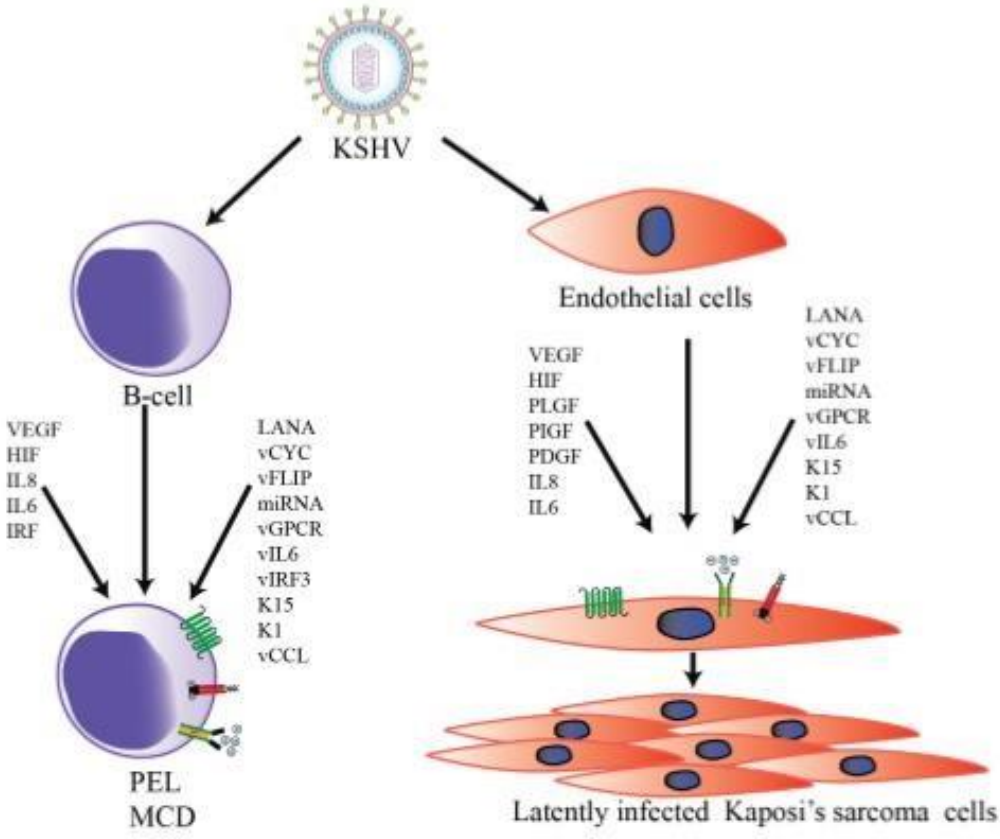


Figure 1. Schematic representation of Kaposi's sarcoma-associated herpesvirus (KSHV)-induced transformation of B-cells and endothelial cells. KSHV infection activates the expression of multiple viral as well as cellular autocrine and paracrine factors to modulate numerous signaling pathways in order to to promote KSHV-mediated angiogenesis.

Figure 1.4 KSHV mediated angiogenesis[19] (with permission)

(Purushothaman P, Uppal T, Sarkar R, Verma SC. KSHV-mediated angiogenesis in tumor progression. Viruses. 2016 Jul 20; 8(7):198)[19]

1.3.3 Epidemiology of KS

Various types of KS have been described in the literature depending on the geographic location, disease stage i.e. plaque/patch/nodular, and clinical presentation i.e. Mucocutaneous/visceral/Lymph node[13, 14, 21]. Epidemiologically five main forms of KS have been mentioned (Table 1.1).

Table 1.1 Epidemiology of KS [13, 14, 21]

Types of KS	Clinical course	Population	Localization
Classic KS	Indolent/chronic, benign,	Associated with Eastern European, Mediterranean or North African HIV-negative elderly population.	Predominantly skin of the lower limbs. This variant does not involve the lymph nodes as much as in other types nor does it involve the viscera.
African/endemic KS	Benign but can be aggressive and chronic	Occurs mainly in East and Central Africa. It occurs in HIV negative adults as well as children.	Can be more extensive Involving the limbs and may involve the viscera as well as mucocutaneous regions. It can be invasive and involve the underlying bones.
Epidemic or AIDS related KS	More aggressive, multifocal,	HIV positive men and women who are ART naive. Additional variants of this group: a) HIV-KS on ART (high CD4 low viral load) b) HIV-KS who are failing ART c) HIV-KS secondary to IRIS	Can occur in any area e.g. the mucocutaneous region, lymph nodes or viscera especially involving the gastrointestinal tract and lungs.
Iatrogenic/transplant associated KS		Occurs when donor organ with KSHV virus is transplanted into immunosuppressed KSHV negative recipient.	
MSM	Indolent	Among homosexual male populations who are HIV negative but KSHV positive.	

ART: antiretroviral therapy, IRIS: Immune reconstitution inflammatory syndrome, KS: Kaposi's sarcoma, KSHV: Kaposi's sarcoma associated Herpes Virus, MSM: men who have sex with men

(Robey RC, Bower M. Facing up to the ongoing challenge of Kaposi's sarcoma. Current opinion in infectious diseases. 2015;28(1):31-40.) [13]

(Schulz TF, Cesarman E. Kaposi Sarcoma-associated Herpesvirus: mechanisms of oncogenesis. Current opinion in virology. 2015;14:116-28.) [14]

(Schneider JW, Dittmer DP. Diagnosis and treatment of Kaposi sarcoma. American journal of clinical dermatology. 2017;18(4):529-39.) [21]

1.3.4 KS incidence

Before the HIV epidemic, KS was rare in the high income countries[22]. In sSA it occurred in the form of endemic KS[11]. "In South Africa KS was not endemic before the HIV epidemic and cases were rare before 1995"[13]. This was documented in a review article, "Facing up to the ongoing challenge of Kaposi's sarcoma", Robey and Bower (2015). KS incidence has increased markedly in Africa in conjunction with the rise in incidence of HIV. The largest burden has been reported in the region of sSA.

Incidence of KS in South Africa has markedly decreased in the past few years. In a case control report, KS incidence in South Africa was as high as 20 cases/1000 per year between 1995 & 1999 [11]. However, comparing to the year 2008 National Cancer Registry data, KS incidence in South Africa was documented as 1491 and 1220 in males and females respectively[5]. The incidence has further reduced in the year 2014 to 978 for males and 669 for females[4]. This decline could mostly likely be due to the increased ART availability nationally. Bohlius et al, 2014 in their multi cohort study in Cape Town and Johannesburg, South Africa report the incidence of KS in those on ART to be much lower (138/100,000-person years) compared to those not on ART (1682/ 100,000-person years)[23].

Similarly, such a decline is also observed internationally. Van Leeuwen et al, 2009 in their retrospective cohort study done in Australia looked at the incidence of cancer in the pre, early and late ART era[24]. The study involved 17,000 patients and they found that with ART availability the rate of KS has been on the decline. These patients were followed up for eight years. More recently, Groopman in the year 2016 in his article reports that "incidence rate for new cases of KS" has fallen from "32 per 1000 person-years in 1993-1994" (which marks the early ART era) to "3 per 1000 person-years after 1999" (reflecting post ART era)[25].

1.3.5 KS Risk factors

1.3.5.1 Immunosuppression/the role of HIV

AIDS patients have a 5000 times increased risk of developing KS compared to the general population within the same country[14]. This was noted by Schulz and Caserman (2015) that due to the impaired immunity in AIDS patients and reduced KSHV surveillance these patients are at an increased risk of developing KS[14]. Guiguet et al (2009) documented a higher risk of acquiring KS in patients with a HIV viral load (VL) greater than 100,000 copies/ml[26]. Bohlius et al (2014) documented that lower CD4 counts, especially lower than 350 cells/ul were associated with an increased risk for developing KS in people living with HIV. Their study did not find an association between KS and HIV VL[23].

1.3.5.2 Gender and race

Male gender, regardless of HIV status, has been associated with an increased risk for developing KS[23]. The reason behind the gender disparity is not clear. Initially it was thought to be due to the possible hormonal influence of beta human chorionic gonadotropin (βHCG), however successive studies have not yet established this as βHCG was only implicated in the *in-vitro* studies[27]. In South Africa however, the gender disparity is not conspicuous as men and women have an almost equal risk of developing KS[18].

In their article, "Facing up to the ongoing challenge of KS" Robey RC & Bower M also mention that a higher rate of KS has been noted in the Hispanic and African men in the United States compared to the white population[13].

1.3.6 KS Clinical presentation (Table 1.2, Figure 1.5)

HIV-KS may present in various ways clinically however in terms of histology all forms of KS are alike.

KS may present clinically as:

Mucocutaneous lesions: these generally initially occur on the skin but at times lesions in the other regions of the body may precede these[27]. They may vary from macules and plaques to nodules. Oedema may be present. Lesions can be found on mucosal surfaces of the mouth, gastrointestinal system, on the skin of the extremities and external genitalia.

Visceral lesions: these commonly involve the respiratory and gastrointestinal tracts. The symptoms depend on the body system involved.

Table 1.2 Clinical presentation of KS [27]

Location	Presentation
Non-Visceral A) Skin lesions	<u>Pre-treatment</u> 1. Size: lesions may be small (millimetres) to large (several centimetres). 2. Colour a) Pigmented: the colour of the lesion ranges from pink (new, early lesions) to red/purple/black macules, papules, plaques or nodules. The lesions usually get darker with time. b) Non-pigmented: the lesions may present as subcutaneous nodules without skin colouration. <u>Post-treatment</u> The size and colour of the lesions gradually fade. Raised lesions become flattened. At times attenuated colour of the lesions may persist without active KS.
B) Oral lesions	The hard palate is a common site but other sites may be involved such as the gums, uvula, soft palate, tonsils and pharynx. Lesions can be asymptomatic or symptomatic if large and ulcerated. They may affect the speech and feeding as well as compromise the airway.
C) Lymph nodes	This can occur in isolation or in conjunction with other organ involvement. These nodes will be quite enlarged and may be asymmetrical. A biopsy is required for definitive diagnosis.
D) Lymphoedema	Non-pitting oedema of the involved body part especially of the lower limbs is common. This can be persistent and disabling which may lead to further complications for instance serosanguinous discharge, limb sepsis and contractures[27].
Visceral A) Lungs	It involves the bronchopulmonary tree as well as the pleura. Patients are usually symptomatic (dyspnoea, wheezes, haemoptysis). It usually occurs in those with advanced AIDS. The chest x-ray may show nodules, alveolar infiltrates or pleural effusions. CT scans describes the lesions better and demonstrates peribronchovascular patterns. Bronchoscopy may show endobronchial lesions.
B) Gastrointestinal lesions	Any site of the gastrointestinal tract may be involved and can be asymptomatic or symptomatic. It may present as a bleeding episode or obstruction and it may be involved in the absence of skin involvement. Endoscopy is required for the diagnosis.
C) Other	Many other organs can have KS lesions like the liver, spleen, heart, bone marrow etc.

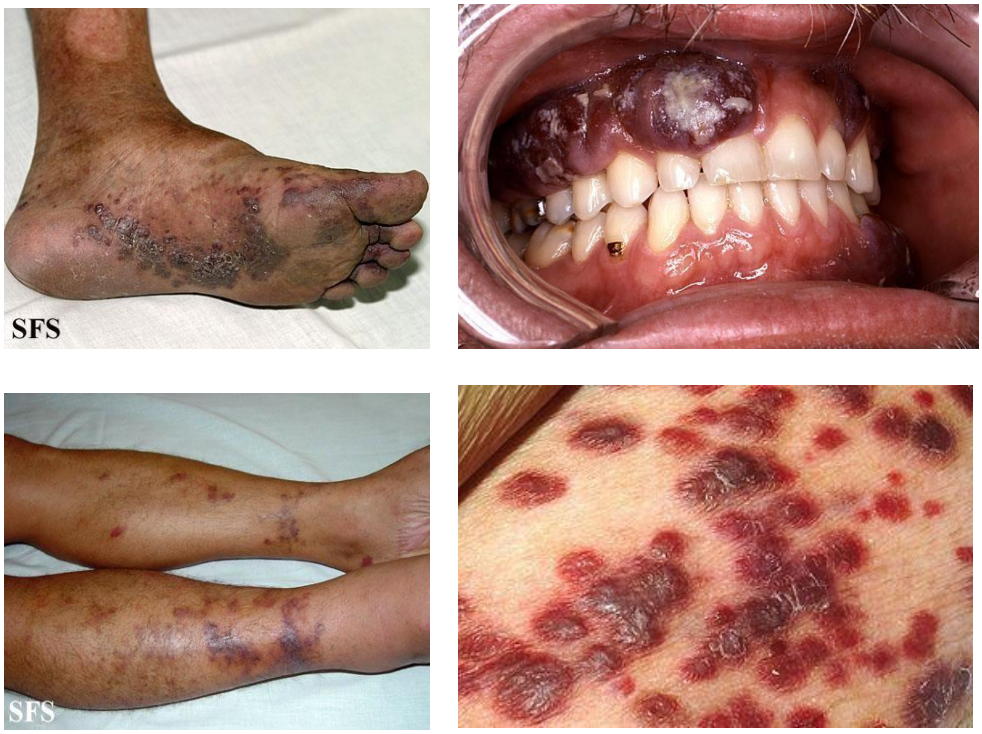


Fig 1.5 Pictures of Kaposi's sarcoma sourced from Wikimedia Commons and Dermatology Atlas Brazil courtesy of Samuel Freire da Silva, M.D.[28]

(Available from: http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=211) [28]

All images are free to use for non-commercial purposes, it's required to provide a link to the website. Created by Samuel Freire da Silva, M.D. in homage to The Master and Professor Delso Bringel Calheiros. First created in 1999.

1.3.7 Diagnosis

KS is confirmed by tissue histology which shows "proliferations of spindle cells and of small blood vessels, formation of vascular slits filled with erythrocytes, haemorrhage and deposition of hemosiderin" [29] (figure 1.6). It is necessary to establish the diagnosis with tissue biopsy as conditions like bacillary angiomatosis and cutaneous fungal infections may look similar [12].

Figure 1.6 KS histology [(21 p530)] (with permission)

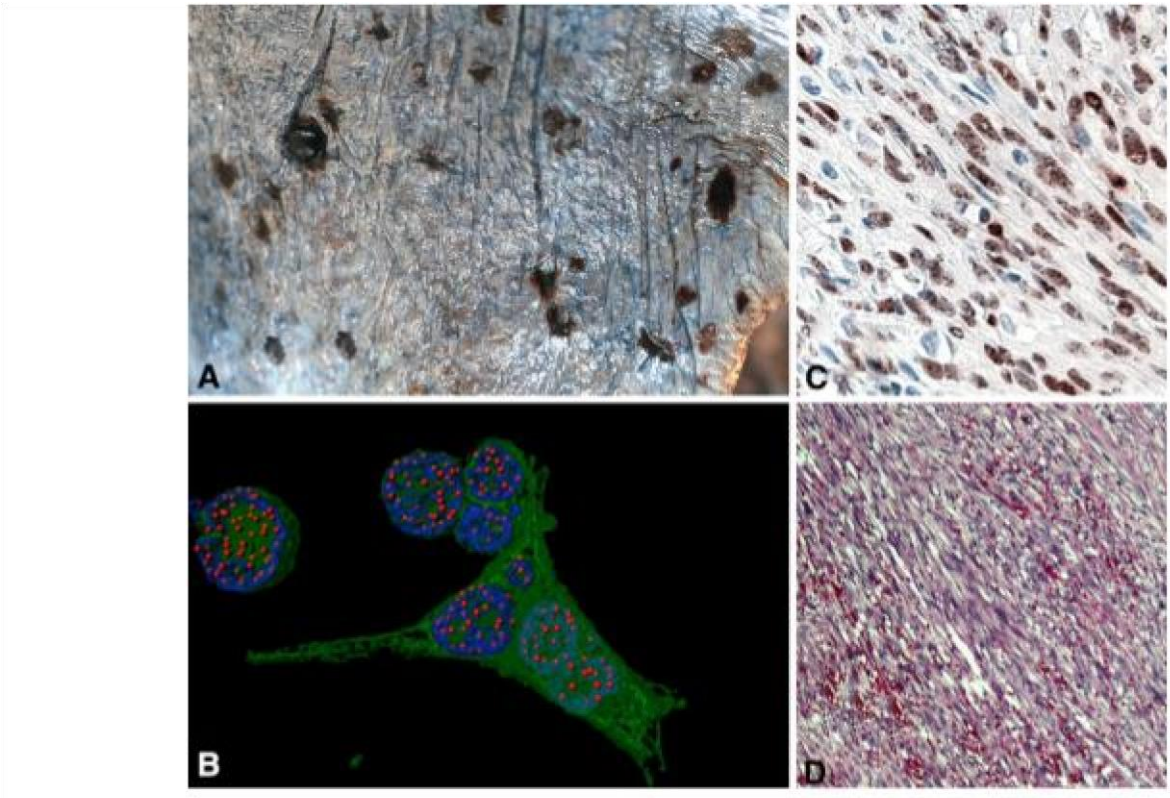


Fig. 1 KS pathology and histology. **a** Shows an image of gross morphology of disseminated KS on the surface of the lung. Note the single, raised, nodular lesion in the *upper left*, as compared to the flat lesions. **b** Shows a computer-enhanced image of immunofluorescence in a KSHV recombinant virus that also expressed green fluorescent protein (gfp) in a PEL cell line. LANA staining is in *red*, nuclear DNA staining in *blue*, and gfp (to indicate infected cells) in *green*. This analysis clearly shows the presence of discrete "LANA dots," each indicating a place where the viral genome is tethered to the host chromosome. **c** Shows an image of LANA staining of a KS lesion by immunohistochemistry (*brown*) with hematoxylin counterstain (*blue*). Note all LANA staining is nuclear and the appearance of darker spots or dots within the nuclear staining. **d** Shows an H&E stain of a KS lesion. Note the spindle-shaped nature of the cells, which are of endothelial cell lineage. Slit-like spaces in between the cells contain extravasated red blood cells. *KS* Kaposi sarcoma, *KSHV* KS-associated herpesvirus, *H&E* hematoxylin and eosin, *LANA* latency-associated nuclear antigen

(Schneider JW, Dittmer DP. Diagnosis and treatment of Kaposi sarcoma. American journal of clinical dermatology. 2017 Aug 1;18(4):529-39)[21]

1.3.8 Staging/prognosis

Consensus is lacking regarding a standardized staging system for KS. Due to the nature of this disease, the Tumour Node and Metastasis (TNM) classification cannot be used like in other tumours[13]. For the purpose of this study, the AIDS Clinical Trials Group classification will be used (Table 1.3)[25]. This classification was developed in 1997 by the AIDS Clinical Trials Group (ACTG) Oncology Committee and it's based on the severity of immunosuppression using CD4 levels (high or low) **(I)**, the disease extent i.e. localised or disseminated **(T)** and the presence or absence of systemic illness **(S).**

This classification also uses the Karnofsky Performance Status (Appendix A) to gauge the level of disability of the patient. It may also be used to assess the treatment response in cancer patients. It uses percentages to score the patient, the lower the percentage the worse the prognosis.

Table 1.3 ACTG Classification table [25]

	Good Risk (0) (if all of the following factors present)	**Poor Risk (1)** (if any of the following factors are present)
Tumour **(T)**	**(T0)** Confined to skin and/or lymph nodes and/or minimal oral disease [Note: Minimal oral disease is non-nodular KS confined to the palate.]	**(T1)** Tumour-associated oedema or ulceration, Extensive oral KS, gastrointestinal KS, KS in other non-nodal viscera
Immune system **(I)**	**(I0)** CD4 cells ≥ = 200/microL	**(I1)** CD4 cells <200 per cubic millimetre
Systemic illness **(S)**	**(S0)** No history of OIs or thrush No "B" symptoms Performance status ≥70 (Karnofsky)	**(S1)** History of OIs and/or thrush, "B" symptoms present, Other HIV-related illness (e.g., neurological disease or lymphoma). Performance status <70

OIs: opportunistic infections, "B" symptoms: unexplained fever, >10% involuntary weight loss, night sweats or diarrhoea lasting >2 weeks.

(Groopman JE. AIDS-related Kaposi sarcoma: staging and treatment. Uptodate. 2016; Topic 8034 Version 28.0 http://www.uptodate.com/contents/aids-related-kaposi-sarcoma-staging-and treatment?source=search_result&search=kaposi+sarcoma+staging+and+treatment&selectedTitle=1%7E150)[25]

1.3.9 Treatment

There are various treatment options available for KS however ART is considered an integral therapy and the first line in the management of all KS patients. ART should be initiated as soon as possible[25]. Additional therapy depends on factors such as the KS extent and severity; as well as the rate of KS spread; levels of CD4 and HIV viral load[25]. Resources available in a particular setting will influence the provision of chemotherapy and the specific choice of agent.

1.3.9.1 Role of ART

It has been shown that patients on ART can achieve total resolution of their KS lesions[30]. Forty six percent of the HIV-KS patients in a prospective study done by Dupont et al in 2000 had complete resolution of their lesions within two years of ART initiation[30]. Twenty eight percent of the study population had a partial response even without specific KS treatment. ART reduces the number as well as the size of KS lesions. The histological evidence for this decrease was documented by DiLorenzo et al in 2007 [31]. The KS remission in HIV patients on ART has been associated with recovery of the immune system and the rise in their CD4 cell count plus reduction in the HIV VL [30, 32]. However the rate of rise of CD4 is lower in these patients compared to HIV positive KS negative patients reflecting a "sluggish immunologic response" in KS patients[11].

1.3.9.1.1 Role of Protease Inhibitors (PIs) in AIDS-related KS

Sgadari et al in 2002 showed that PIs block proliferation of KS-like lesions in mice as well as having antiangiogenic effects on tumour cells, supporting the idea that PIs may be superior to other non-protease inhibitor agents in the treatment of HIV-KS patients[33]. Martinez et al in 2006 were however unable to confirm this finding[32]. They conducted a study on 73 patients who were ART naïve at baseline and were initiated on ART containing either PIs or nonprotease inhibitors and were followed up for two years on the same ART regimen. They found similar outcomes in both the arms. Similarly, a retrospective cohort study by Nguyen et al in 2008 documented

no difference in KS response whether patients were on PIs based treatment or non-nucleoside reverse transcriptase inhibitors (NNRTI) based treatment[34].

Krown et al, 2008 studied 442 KS patients with a mean age of 42 years[27]. They found that 31% of their patients had persistent KS in both groups i.e. PIs regimen and NNRTI regimen. To date, there is no definitive evidence to suggest a particular ART regimen being more effective than the other. However, it is important that patients be started on ART.

1.3.9.2 Local KS therapy

This can be used for cosmetic purpose and where the lesions are not extensive enough to require chemotherapy. Options such as cryotherapy with liquid nitrogen, intra-lesional chemotherapy, surgical excision and topical agents like Alitretinoin gel, a retinoic acid derivative, have been used[25]. However, these modalities are rarely used in the current era and the references provided in support of their use are almost twenty years old. For instance, earlier studies done by Epstein (1993)[35] and McCormick (1996)[36] looking at intralesional injections of vinblastine in KS patients. Both these studies concluded this to be an effective mode of therapy [35, 36]. Epstein looked at 42 patients with oral KS. He noted more than 50% regression in the size of the lesion in 74% of the patients with mean duration of 3.5 months follow up time[35]. Similarly, McCormick in his study consisting of 18 patients with oral KS reported all his patients to have responded to intralesional vinblastine injection at 2 years follow up time. However, depending on the size of the lesion these patients required between one to three injections in the same lesion with no complications encountered[36].

1.3.9.3 Radiotherapy (RT)

Electron-beam RT, a form of local therapy, "is a valuable means of pain relief, bleeding control and oedema palliation" and "it is also an effective treatment modality for local control of skin and mucosal lesions in KS"[37]. Donato et al in 2013 "assessed the efficacy of RT in the treatment and local control of KS"[37]. Eighteen patients at the Radiotherapy Unit in Rome and a total of thirty eight lesions were studied. RT was individualized depending on the lesion location, its size and the depth. A total dose of 24-30 gray (Gy) was used. Depending on the location, for

instance mucocutaneous or spinal column, and depth of the lesions 200-300 centigray per fraction (cGy/fraction) and 6-18 million electron volt (MeV) electron beam energy was used. These patients were studied for ten years from 2002 to 2012. Complete response was established in thirty one out of thirty eight lesions. Most of the patients had achieved palliation except those with lesions in the vertebra and mean overall survival was 4.7 years. RT may cause local discomfort which in most cases settles within a fortnight[25].

1.3.9.4 Role of Chemotherapy

In the search for improved outcomes several chemotherapeutic agents have been utilized in the management of HIV-KS patients. There isn't a recent standardized World Health Organization (WHO) guideline stipulating type of chemotherapeutic agent as a first line therapy in HIV-KS patients. The choice of agent depends on local availability and patient profile[12]. In the high-income countries pegylated liposomal doxorubicin (PLD) is the first line of treatment while paclitaxel is used as second line or as rescue treatment for those who have failed first line[13]. Some of the low- and middle-income countries use doxorubicin (Adriamycin), bleomycin and vincristine (ABV) as their first line. Robey RC & Bower M in their review article in 2015 report that "PLD has achieved greater response rates and less toxicity" than combination treatments like ABV[13].

1.3.9.4.1 Chemotherapy plus ART versus ART alone (Table 1.4)

In 2004 Martin-Carbonero et al compared ART alone and ART plus PLD in the treatment of 28 patients with HIV-KS[38]. They reported a better response rate in the ART plus chemotherapy group on follow up at forty eight weeks. The patients in both the arms were randomly selected with similar characteristics. Two thirds of the patients in the ART only arm had to receive PLD as a rescue predominantly due to the progression of disease which mostly occurred in the first three months of ART initiation. Besides, they excluded immune mediated cause as a reason as there was no rise in the CD4 counts[38].

Likewise, a prospective study done in Nigeria by Ahmed et al in 2011 showed similar findings[39]. This study involved 98 HIV-KS patients out of which 86 patients were on ART. They reported that with the initiation of ART plus chemotherapy, more than 80% of the patients had good tumour response compared to 42% treated with ART alone. These findings suggested that adding chemotherapy and/or radiotherapy as an adjuvant treatment for KS has a positive impact on outcome.

In 2014, Gbabe et al in Durban, South Africa, reviewed six randomized control trials and three observational studies comparing ART alone with ART plus chemotherapy[12]. They concluded that the combination of ART plus chemotherapy was superior to ART alone in terms of decreased disease progression but not survival. Their review included the study by Mosam et al, 2012, conducted in Durban South Africa[40]. This study compared ABV and where ABV was not available oral etoposide was utilized. Patients were followed up for a year. The conclusion from that study was that, combining ART and chemotherapy improved overall response rate to KS treatment over one year, however "ART alone provided similar improvement in survival" compared to ART and chemotherapy[40]. Of note is that patients in this study did not have advanced disease involving the viscera.

In some low-income countries a single chemotherapeutic agent e.g. vincristine has been used while others have used two agents consisting of bleomycin and vincristine (BV)[41]. A retrospective cohort study by Herce et al in 2015 from Malawi compared overall survival between those that received ART plus BV to those receiving ART plus paclitaxel as a single agent. They demonstrated that overall survival after one year was "not significantly different" in the two groups[41]. The authors concluded that it is "safe, effective and feasible to provide paclitaxel or combination therapy with BV integrated with ART to treat HIV-KS".

Table 1.4 Comparing chemotherapy alone versus ART plus chemotherapy

Treatment	Study location	Year of study	Number of patients	Study duration	Results
ART alone versus ART plus PLD (Martin-Carbonero et al)[38]	Spain, Europe	2004	28	48 weeks	Better treatment response rate in the ART plus chemotherapy group (76% versus 20%).
ART alone versus ART plus ABV (Ahmed et al)[39]	Nigeria, West Africa	2011	86	4 years	80% of the patients in the ART plus chemotherapy arm had good tumour response compared to the 42% treated with ART alone.
ART alone versus ART plus ABV or etoposide (Mosam A et al)[40]	Durban, South Africa	2012	112	1 year	ART improves survival in HIV-KS patients. Chemotherapy improved overall response rate to KS treatment.

ABV: Adriamycin, bleomycin, vincristine, ART: antiretroviral therapy, PLD: Pegylated liposomal doxorubicin

(Martín-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS. 2004;18(12):1737-40.)[38]

(Ahmed A, Muktar HM. Epidemiology and treatment of Kaposi's sarcoma in HIV-1 infected individuals in a poor resource setting. InGlobal View of HIV Infection 2011. InTech.)[39]

(Mosam A, Shaik F, Uldrick TS, Esterhuizen T, Friedland GH, Scadden DT, et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy naive patients with HIV-associated Kaposi sarcoma in South Africa. JAIDS (1999). 2012;60(2):150-7.)[40]

1.3.9.4.2 Side effects of Chemotherapy

Many chemotherapeutic drugs have been associated with myelotoxicity as well as other adverse effects including nausea, vomiting, nephrotoxicity and neurotoxicity [42, 43]. MartinCarbonero et al performed a study in 2008 to assess for adverse events, KS relapse, and death associated with the use of PLD[42]. It was a retrospective review of 98 patients who had received PLD and were followed up for about two years. Their study showed a mortality rate of about 14% per year. A total of 29 patients died during the follow up period. Some of the deaths were presumed to be due to KS progression (3 patients) while 9 patients developed new tumours mostly lymphoma and the relapse rate among those alive was 13%. The rate of relapse in this study group was higher in the first year after stopping chemotherapy. Cianfrocca et al in the year 2010, USA, compared toxicity and efficacy of PLD and paclitaxel in 73 patients[43]. These patients had advanced KS and 50% or more in both the groups were of African American or Hispanic descent and most were on ARTs. Two year overall survival rate and infection rate was similar in both the arms but overall severe adverse event rate (grades 3 to 5) was slightly higher in paclitaxel (84%) compared to PLD (66%) group in terms of myelotoxicity, alopecia and sensory neuropathy. Both therapies resulted in improvement in the HIV-KS patients' symptoms for instance swelling and pain.

1.3.10 KS in the ART era

1.3.10.1 KS with higher CD4 counts

KS can occur in patients with high CD4 counts and low HIV VL measurements, even in those receiving ARTs [27, 34]. Multiple trials documented patients with KS in the setting of higher CD4 (more than 300cells/ul) and low HIV VL. In 2008 Stebbing et al reported that 7% of the HIV-KS patients in their study had undetectable HIV VL and 5% of them also had a CD4 count greater than 300 cells/ul[44]. In 2010 Crum-Cianflone et al surveyed the "rates of KS and trends in CD4 cell counts at the time of diagnosis during the HIV epidemic"[45]. They looked at patients from 1985 to 2008 and reported that the overall incidence of KS decreased in the ART era, especially between 2002 and 2008. They surmised that "lower CD4 cell counts remain an important risk factor, but that a greater proportion of KS cases are now occurring at higher CD4 cell counts" and clinical practitioners should be aware of this[45].

1.3.10.2 Immune reconstitution inflammatory syndrome

Flare up of KS lesions has been documented in severely immunocompromised patients who are initiated on ART and this could be considered part of an immune reconstitution inflammatory syndrome (IRIS)[30, 32]. IRIS can be due to paradoxical worsening of underlying illness in HIV patients following initiation of ART or due to unmasking of a subclinical disease in such patients[30]. More recent prospective studies incorporating data from sSA as well as the United Kingdom documented the occurrence of KS-IRIS. Levels of CD4 at the time of diagnosis is of particular importance in the development of IRIS. Several studies have shown that low CD4 levels and high HIV VL at the time of ART initiation are associated with an increased risk of developing KS-IRIS.[13, 23, 46]

1.4 Outcomes

Worldwide data has shown that in people living with HIV, KS still remains high on the list as a common cause of morbidity and mortality in such a population[21].

1.4.1 AIDS related deaths

AIDS related deaths have reduced globally according to the data from 2014 UNAIDS Gap report[9]. In the past decade sSA has experienced an almost 39% reduction in such deaths. In South Africa AIDS-related mortality has decreased by 51% [9]. This reduction has been associated with the upscale and availability of ART to people living with HIV.

1.4.2 KS related deaths

In the pre-ART era the HIV-related KS associated mortality in sSA was high with the one year overall survival was only about 30% [40]. It should be noted though, death in these patients is usually more due to complications of AIDS rather than the KS itself. The availability of ART

has led to a decrease in the incidence of HIV-KS and mortality has reduced especially in the high-income countries. In sSA the disease burden varies across the region however it is still generally higher compared to the high-income parts of the world[13]. A study done in Johannesburg, South Africa by Maskew (2014), documented mortality among HIV-KS patients to be at least three times higher compared to those without KS, with the highest risk of death happening within the first year of ART initiation[11]. The cause of death was not clearly mentioned in this study. Of note is that the KS negative HIV patients in her study was of similar characteristics in terms of CD4 counts at presentation, co-infection with TB and age.

1.4.3 A glance at outcomes in the high and low-middle income countries (Table 1.5)

The mortality rate of KS is different amongst the high income and low to middle income countries. In the United Kingdom (UK) and the USA the overall survival rate has been higher than overall survival rates in sSA in general[43, 47]. In a prospective study by Bower et al from the UK 254 patients with HIV-KS were followed up for a maximum of twelve years[47]. Patients were recruited from 1996 to 2008. They documented an overall five year survival rate of 89% in their study. Cianfrocca et al in USA (2010) in their randomized trial involving 73 patients with severe KS documented an overall two years survival rate of over 75% [43].

In a more recent study in the sSA region conducted in Malawi there has been some improvement in the overall survival rate. However, this finding is not uniform across the sSA[41].
Herce et al in 2015 in their study in rural Malawi reported "excellent overall annual survival" of over 80% in HIV-KS co-infected patients on ART and KS specific chemotherapy with low rate of adverse effects[41]. In a retrospective cohort study, they looked at 114 patients on ART and chemotherapy. Most of the patients had advanced KS from the start of the study. One year after the initiation of chemotherapy (paclitaxel or PLD) 77% of the study population survived, 17% died and 5% were lost to follow up.

In South Africa HIV-KS associated mortality still remains high [11, 48]. Chu et al in their study done in South Africa in 2010 reported that half of their study population with advanced KS died at one year, however one quarter of these patients were ART-naïve and only 29% of the study population received chemotherapy[48]. Bohlius et al in their large multicohort study done in South Africa in 2014 looked at the incidence of KS and survival of HIV patients who were on ART

and ART naïve[23]. The reported survival of their study population at one year was 72.2%. Their study further noted that the survival rates were similar in those who started ART prior to the KS diagnosis compared to those recently initiated. However, of note, their study did not incorporate data on clinical presentation of KS, histology results and details of chemotherapy.

1.4.4 Effect of race on outcome

Differences in KS survival have been documented amongst different races. Dutta et al in their study done in the USA in 2010 looked at trends associated with racial differences influencing KS survival between the white and the black population[49]. They demonstrated that white patients survived longer in the ART era than the black patients. They reviewed patients from 1980 to 2004 and their results showed that until 1995 survival rates between white patients and black patients were similar an average of about one year for black patients and one and half years for white patients. From 1996 onwards, the rate of survival for whites was greater than that for blacks. Whether such a discrepancy is due to a background genetic predisposition or socioeconomic factors requires further explanation.

Limited studies are available in South Africa on the outcomes of patients with KS. In our study we wished to explore the demography and treatment outcomes of HIV positive patients with KS referred to a Specialist Medical Oncology centre at a Johannesburg Academic Hospital, in the modern ART era.

Table 1.5 Comparing outcomes in the high income and low-middle income countries.

Study title	Study location	Year published	Sample size	Median Follow up duration	Outcomes
"The effect of ARTs in 254 consecutive patients with AIDS-related Kaposi's sarcoma"[47]	UK	2009	254	over 4 years	5 years OS 89% on ART use predominantly in early stage KS (T0)
"Randomized Trial of paclitaxel versus PLD for Advanced AIDS related KS : Evidence for Symptom Palliation from Chemotherapy"[43]	USA	2010	73	3 years (36 months)	2 years OS 79% in the PXT arm and 78% in the PLD arm
"Excellent clinical outcomes and retention in care for adults with AIDS related KS treated with systemic chemotherapy and integrated ARTs in rural Malawi"[41]	Malawi	2015	114	1 year	They looked at ARTs plus BV versus ARTs plus paclitaxel and document an OS of 80% at 1year
"AIDS-associated Kaposi's sarcoma is linked to advanced disease and high mortality in a primary care HIV programme in South Africa"[48]	South Africa	2010	215	278 days.	At 1 year, the overall cumulative survival was 60%) for those on ARTs and 39% for those ART naïve.
"Kaposi's sarcoma in HIVinfected patients in South Africa: multi-cohort study in the ART era"[23]	South Africa	2014	162 (162 incident KS patients)	660 days	At 1 year, estimated survival was 72.2% and the survival rates were similar in those who started ARTs prior to KS diagnosis compared to those recently initiated.

BV: Bleomycin/vincristine, IQR: Interquartile range, OS: Overall survival, PLD: Pegylated liposomal doxorubicin, PXT: Paclitaxel

(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. IJC. 2014;135(11):2644-52.)[23]

(Herce ME, Kalanga N, Wroe EB, Keck JW, Chingoli F, Tengatenga L, et al. Excellent clinical outcomes and retention in care for adults with HIV-associated Kaposi sarcoma treated with systemic chemotherapy and integrated antiretroviral therapy in rural Malawi. JIAS. 2015;18(1).)[41]

(Cianfrocca M, Lee S, Von Roenn J, Tulpule A, Dezube BJ, Aboulafia DM et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma. Cancer. 2010;116(16):3969-77.)[43]

(Bower M, Weir J, Francis N, Newsom-Davis T, Powles S, Crook T et al. The effect of HAART in 254 consecutive patients with AIDS-related Kaposi's sarcoma. AIDS. 2009;23(13):1701-6.)[47]

(Chu KM, Mahlangeni G, Swannet S, Ford NP, Boulle A, Van Cutsem G. AIDS-associated Kaposi's sarcoma is linked to advanced disease and high mortality in a primary care HIV programme in South Africa. JIAS. 2010;13(1):23.)[48]

CHAPTER 2

2.0 OBJECTIVES

1. Describe the demography of HIV positive patients diagnosed with KS at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Division of Medical Oncology, Department of Medicine.

2. To assess the response to therapy of HIV positive patients diagnosed with KS on ART at CMJAH two years from diagnosis.

CHAPTER 3

3.0 METHODOLOGY

3.1 Study design and site

This was a retrospective review of patient files conducted at CMJAH, Johannesburg, South Africa. CMJAH is a tertiary/quaternary referral hospital and one of the academic teaching hospitals affiliated with the University of the Witwatersrand Faculty of Health Sciences.

3.2 Study population

This study involved a random selection of 109 patients referred to and treated at CMJAH, Division of Medical Oncology with a diagnosis of KS in a 3year period from 1st January 2011 to 31st December 2013.

3.3 Inclusion criteria

1. HIV positive patients aged 18 years and above.
2. A positive histological diagnosis of KS.

3.4 Exclusion criteria

1. HIV status unknown
2. Patients lost to follow up. Patients were termed as LTFU if they had not revisited Oncology clinic after registration and no data could be captured from their files such that no information was available from their files manually or the Oncology department computer system at two years' follow up time.

3.5 Data collection

The study patient cohort was recruited from the available new patient registration books located at the Division of Medical Oncology during the data collection period. All patients from 2011 to 2013 were manually noted and a total of 315 patients were selected from all the register books present at the department. Using the departmental computer database all those patients with a known outcome at the end of two years from the first Oncology clinic registration date were selected. This totalled to 205 patients. The remaining 110 patients were lost to follow up (LTF) thus excluded from the study.

A subgroup of 110 patients was then randomly selected from the 205 patients using an Excel spreadsheet with a simple random sampling method. 110 patient files were manually reviewed, and relevant clinician notes were recorded using a data collection tool (Appendix B). One patient was further excluded from the study during review of the files due to a reviewed tissue diagnosis of NHL. This patient was initially registered as KS. Thus, the study cohort consisted of 109 patients.

Data collected included patient demographics, ART status plus regimen(s). ART were defined as a combination of at least triple antiretroviral medication from any class i.e. NNRTIs, nucleoside reverse transcriptase inhibitors (NRTIs) and/or PIs. These medications could consist of one drug per pill or as a fixed dose combination (FDC) ART. The FDC commonly used is a single tablet containing triple ARTs namely efavirenz 600mg, tenofovir disoproxil fumarate 300mg and emtricitabine 200mg. This FDC became available in South Africa at the state level in the year 2013 although will be replaced by TDL consisting of tenofovir, dolutegravir and lamivudine.

Patient baseline CD4 levels and HIV Viral Loads were noted where available. Information on chemotherapy, radiation therapy and subsequent follow ups was recorded. Specific chemotherapy regimens and the number of cycles was documented. Timing of ART and KS treatment relative to each other was captured. Doctors' notes in the files were used to describe the lesions on presentation and follow up visits. The first date of the individual patient visits at

the Division of Medical Oncology marked the start date of the study period. Patients were then followed up for two years.

Response/outcome of treatment was measured as follows [12]:

a) Alive.

Patients in this category were sub-categorized depending on

their response as:

Complete Response, which is defined as complete resolution of the disease for a minimum of four weeks without evidence of new disease.

Improved, reflecting incomplete response to treatment but attenuation of original lesions/symptoms.

Progressive Disease, defined as change in character of all previously flat lesions to raised; development of new or worsening tumour-associated oedema or development of new or progressive visceral disease.

Unknown, the data was insufficient to categorize patients into any of the above.

b) Dead (all-cause mortality including AIDS related and non-AIDS related).

c) Lost to Follow up (LTFU). Patients were termed as LTFU if they had not revisited Oncology clinic after registration and no data could be captured from their files such that no information was available from their files manually or the department computer at two years' follow up time.

3.6 Data analysis

Microsoft excel programme and SPSS software (originally, Statistical Package for the Social Sciences and now called Statistical Product and Service Solutions) was used for data analysis. Descriptive analysis in terms of frequencies/proportions was utilized to answer objectives. The study population was the denominator and demographic parameters as the numerator. Guidance from statisticians as per university facilitation was utilized.

3.7 Ethics and approvals

Clearance certificate no. M160419 (Appendix C). Date considered 06/05/2016.

Approval from the Human Research Ethics Committee of the University of Witwatersrand, Head of Department of the Division of Medical Oncology and the CEO of the CMJAH was obtained. Written permission from the Head of the Department of Medicine at CMJAH was also obtained. This being a retrospective study, specific written consent from the individual patients was not required. All the data was collected by myself and patient records were not removed from the hospital premises. Patient identities remained confidential and anonymous and each patient file was allocated a specific number only known to the investigator to represent their data.

CHAPTER 4

4.0 RESULTS

4.1 Demographics

This study comprised of 109 patients (n=109). The majority i.e. 77 patients (70.6%), were males. Mean age of the study population was 39 (range 21- 63) years and the median age was also 39 years. The mean body mass index (BMI) was 25.4 (range 16.9 - 40.7). All the patients were on ART except one (n=108) at enrolment. At KS diagnosis, 27 patients (24.7%) had an unknown CD4 count while the average CD4 count for the other 82 patients (75.2%) was 212 (range 17- 696) cells/ul. Only 12 patients had known HIV VL and the average VL of those available was 248,496.3 (range 40 - 1,395,621) copies/ml (Table 4.1).

Table 4.1 Patient demographics and characteristics

Variable	Category	Frequency	Percent (%)
Gender	Male	77	70.6
	Female	32	29.4
On ART (At actual study enrolment)	Yes	108	99.1
	No	1	0.9
On ART at initial KS diagnosis	Yes	37	33.9
	No	53	48.6
	Unknown	19	17.4

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Duration of ART at case diagnosis (months)	29	0*	72	14.3	19.5
CD4 cells/ul (at KS diagnosis)	82	17	696	212.9	148.5
HIV VL copies/ml (at KS diagnosis)	12	40	1,395,621	-	-

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	109	21	63	39.1	9.4
BMI	100	16.9	40.7	25.4	5.8

ART: Antiretroviral therapy, BMI: Body mass index, HIV VL: HIV viral load, KS: Kaposi's sarcoma, std. deviation: Standard deviation. n: Sample size. *On ART for few days but less than a month

4.2 ART profile

Forty seven patients (43.5%) did not have their ART regimen documented in the files and were therefore categorized as unknown. However, many of the patients in the unknown category would likely be taking tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) or FDC pill as it was the recommended first line regimen and the most widely available regimen during the years 2011 to 2013 (Table 4.2). FDC consisted of three ART in one tablet. The combination drug contained TDF/EFV and emtricitabine (FTC) instead of lamivudine (3TC). Five patients (4.6%) had their ART regimen changed mainly due to Virological failure (VF). Another reason for ART change was due to better drug availability i.e. from Stavudine (d4T) to Tenofovir Disoproxil Fumarate (TDF) because of Stavudine related side effects (Table 4.2).

Table 4.2 ART regimen of the study population

Variable	Category	Frequency	Percent (%)
ART Regimen (n= 109)	TDF, 3TC, EFV	38	35.2
	FDC (TDF/FTC/EFV)	7	6.5
	NVP, 3TC, TDF	5	4.6
	NVP, 3TC, d4T	3	2.7
	d4T, 3TC, EFV	7	6.5
	TDF, 3TC, d4T	1	0.9
	AZT, 3TC, EFV	1	0.9
	Unknown	47	43.5
ART regimen Change (n=109)	Yes	5	4.6
	No	102	94.4
	Unknown	2	1.8
Reason for change (n= 5)	Side Effects	0	0.0
	Virological failure	3	60.0
	Other	2	40.0

AZT: Zidovudine, EFV: Efavirenz, FDC: fixed drug combination, 3TC: Lamivudine, NVP: Nevirapine, d4T: Stavudine, TDF: Tenofovir Disoproxil Fumarate.

4.3 Co-morbidities

Fifty three patients (48.6%) from the study population had concomitant systemic illnesses on top of the HIV-KS throughout the study period. Some of these diseases were opportunistic infections thus part of AIDS spectrum while other had non-AIDS defining conditions (Table 4.3). Patients with pneumonia were not categorized as those with Pneumocystis jirovecii related pneumonia, (formerly known as Pneumocystis carinii pneumonia), or other pneumonias. Of the illnesses encountered tuberculosis (TB) was the most frequent with 18 patients (33.96%) reported on anti TB medication simultaneously. Some were confirmed sputum positive TB while others had extra pulmonary TB. Standard TB medications consists of ethambutol, isoniazid, pyrazinamide and rifampicin for those on intensive phase and rifampicin and isoniazid for continuation phase. A few of the patients had multiple systemic conditions. The "other" category included conditions like Interstitial Lung Disease, Cardiomyopathy, acute promyelocytic leukemia (APL) etc. (Table 4.3).

Table 4.3 Concomitant systemic conditions/illness profile of the study population

Variable	Category	Frequency	Percent (%)
Concomitant systemic illness (n=109)	Yes	53	48.6
	No	52	47.7
	Unknown	4	3.7
Type of systemic illness (n= 53)	Tuberculosis	18	33.9
	Oral thrush	10	18.8
	Urinary tract infection	6	11.3
	Pneumonia	5	9.4
	Kidney disease	5	9.4
	Hepatitis	3	5.6
	Metabolic condition	3	5.6
	Deep vein thrombosis	2	3.7
	Cancer (APL)*	1	1.8
	Other	12	22.6
Number of systemic illnesses (n= 53)	Single systemic illness	41	77.4
	Multiple systemic illnesses	12	22.6

*APL Acute Promyelocytic Leukemia

4.4 Cancer treatment modalities

Besides ART, patients also received RT as well as Chemotherapy depending on the indications. However, those receiving chemotherapy comprised the majority as the sample size was derived from the Division of Medical Oncology which is separate from the Division of Radiation Oncology. Eighty seven patients (79.8%) of the 109 received chemotherapy. Most of the patients i.e. 58 (66.7%), received the ABV regimen only. Twenty patients (23%) had to receive paclitaxel as second line after unsatisfactory results with ABV regimen. Four patients (4.6%) required further intervention with a third chemotherapeutic agent (described as other agent in this study). The main other chemotherapeutic agent used was Etoposide. A few patients were considered for agents like Gemcitabine as they had failed other regimens (Table 4.4).

Fifteen patients (13.8%) from the 109 received radiation therapy at some stage of their disease according to clinicians' notes. A small number were referred from RT department for chemotherapy while some were referred from chemotherapy department to RT for residual localized disease (Table 4.4).

Table 4.4 Cancer treatment modality used during patient illness

Variable	Category	Frequency	Percent (%)
RT during the treatment course (n= 109)	Yes	15	13.8
	No	94	86.2
Chemotherapy (n= 109)	Yes	87	79.8
	No	22	20.2
Types of chemotherapy (n= 89)	ABV only	58	66.7
	ABV, paclitaxel	20	23.0
	ABV, paclitaxel, Other	4	4.6
	Paclitaxel only	5	5.7

ABV: Adriamycin, bleomycin, vincristine, RT: Radiotherapy

4.5 Adverse effects profile

Thirty nine patients (35.8%) from the study population were reported to have side effects/adverse effects whilst concomitantly on ART and chemotherapy. Majority (58.9%) of these patients had grade 3/4 neutropenia mostly after their third or fourth cycles of chemotherapy (Table 4.5). Some of the patients had haematological adverse effects including neutropenia and anaemia requiring filgrastim, a granulocyte colony stimulating factor (22 patients), and blood transfusions (21 patients).

Table 4.5 Adverse effect profile

Variable	Category	Frequency	Percent (%)
Side Effects (n= 109)	Yes	39	35.8
	No	68	62.4
	Unknown	2	1.8
Types of Side effects on concomitant treatment (n= 39) *	Anaemia	26	66.7
	Neutropenia	23	58.9
	Peripheral neuropathy	11	28.2
	Gastroenteritis	5	12.8
	Lipodystrophy/atrophy	1	2.6
	Other	1	2.6
Number of Side Effects (n= 39)	One side effect	31	79.5
	Multiple side effects**	8	20.5

*some patients had multiple side effects

**mostly anemia and neutropenia

4.6 Treatment outcomes

At the end of two years from the time of first clinic enrolment, 49 patients (45%) of the total 109 had died and 60 patients (55%) were alive, some with elements of residual/progressive disease (Table 4.6).

Of the 60 patients (55%) that were alive at two years, 27 patients (24.8%) had complete response whilst the remaining 33 patients (30.3%) had some disease activity further categorized in Table 4.6. The category named other comprised of 2 patients whose files did not clearly mention patient disease status.

From the 49 patients that had died, 34 patients (69.4%) died within the first six months from the date of first Oncology clinic enrolment (Table 4.6). Causes of death was not always mentioned in the files by the clinicians. However, of note is that most of these deaths did not occur within the Medical Oncology clinic. These patients were reported dead in the hospital computer system implying that these patients died in other departments within the hospital. Refer to table 4.8 for a further subcategorization of concomitant co-morbidities in the dead population.

Table 4.6 Cancer treatment outcomes

Variable	Category	Frequency	Percent (%)
Overall treatment outcome at 2 years (n=109)	Dead	49	45.0
	Alive	60	55.0
Clinical outcomes on treatment at 6 months and at 2 years' time from first Oncology clinic visit.			
Treatment outcome at 6 months (n= 49) *	Dead	34	69.4
	Improved	7	14.3
	Progressive disease	4	8.2
	Other	4	8.2
Treatment outcome at 2 years (n= 109) **	Dead	49	45.0
	Complete response	27	24.8
	Stable	11	10.1
	Progressive disease	16	14.7
	Relapse	4	3.7
	Other	2	1.8

*Treatment outcomes of patients from the dead category was subcategorized at the 6th month of study duration.
**Subcategorization of treatment outcomes at 2 years of the entire study population.

4.7 Survival rate

Survival percentages of entire study population at various time of the study was calculated and is summarized in Table 4.7

Table 4.7 Survival rate of the study population

Time	Alive	Dead	Percentage (%)
6 months	75	34	68.8
1 year	67	42	61.5
2 years	60	49	55.0

4.8 Concomitant illness among the dead population

Data was further analysed to assess for the frequency and types of concomitant systemic conditions among patients that had died. It was found that 28 patients (57.1%) did have an additional illness. Half of these patients had TB and were on TB treatment. Included in the category other were end stage Interstitial Lung Disease, cardiomyopathy, Leukaemia etc. (Table 4.8). Some of the patients had multiple infections

Table 4.8 Table showing frequency and types of concomitant systemic conditions/illness among dead patients

Variable	Category	Frequency	Percent (%)
Concomitant systemic conditions/illness (n = 49)	Yes	28	57.1
	No	17	34.7
	Unknown	4	8.2
Type of systemic conditions (n = 28)	Tuberculosis	14	50.0
	Oral candidiasis	5	17.9
	Pneumonia	4	14.3
	Renal dysfunction	3	10.7
	Hepatitis B	2	7.1
	Deep vein thrombosis	1	3.6
	Urinary tract infection	1	3.6
	Cancer (APL)*	1	3.6
	Other	8	28.6

*APL Acute Promyelocytic Leukemia

4.9 Visceral KS

Eleven patients (10.1%) from the study population had visceral KS predominantly involving the lungs and the gastrointestinal tract (Table 4.9).

Table 4.9 Number of patients with visceral KS with or without skin involvement

Variable	Category	Frequency	Percent (%)
Visceral involvement at diagnosis (n= 109)	Yes	11	10.1
	No	71	65.1
	Unknown	27	24.8

4.10 ACTG stage of the dead patients

Patients were attempted to be classified into poor risk or good risk for prognostication purposes using the ACTG classification however this was not possible for the entire study population due to the scarcity of clinical information in the patients' files. Therefor the patients in the dead category were the only ones' risk stratified using available data. What was established from our study though was that our entire study population consisted of patients with advanced KS tumor with extensive KS lesions and tumor associated edema (T1). Based on this finding and the ACTG classification table all our patients can be categorized as poor risk patients.

Among the patients with available CD4 cell counts almost 50% of the patients in the dead category had lower than 200 cells/ul and more than half (57%) had history of concurrent opportunistic infections (table 4.8 and table 4.10).

Table 4.10 ACTG staging of the dead patients

Stage n=49	frequency	Percentage (%)
T1	49	100
I1	22	44.9
S1	28	57.1

T1: tumor associated edema/ulceration, extensive oral KS, visceral KS. I1: CD4 cells <200,
S1: opportunistic infection, diarrhea >2weeks, >10% involuntary weight loss, unexplained fevers

CHAPTER 5

5.0 DISCUSSION

5.1 Study findings

The majority (70.6%) of the patients in the study were young males. Male sex has previously been identified as a risk factor for the development of KS [13, 23, 48]. Bohlius et al examined the risk of KS in 20 000 HIV-infected South Africans. They found that men were almost twice as likely as women to develop KS[23]. Robey et al in 2015, noted that male gender was a risk factor for developing KS, in Africans and Hispanics when compared to the white population, regardless of HIV status[13]. Chu et al studied 215 patients with AIDS-related KS. Their study was based in Khayelitsha, Cape Town. In their study 59% of the patients were male. The gender difference has not been fully elucidated; although it has been postulated that it is related to different rates of KSHV infections in males and females[23]. As this was a retrospective study we did not have information on the ethnicity of our patients. It is likely however that the majority were black African[50].

The mean CD4 count at KS diagnosis in our patients was 212 cells/µl. In the study by Bohlius et al it was noted that patients with a CD4 count >350 cells/ µl had a lower risk of developing KS[23]. This risk is further reduced to more than 50% when the CD4 count is more than 500 cells/ul[51]. Five patients in our study developed KS with CD4 counts of more than 500 cells/ul. The association between a low CD4 count and the development of KS has been well documented[26, 51]. While 38.5% of our patients typically developed KS with CD4 counts of less than 200 cells/ul, 36.7% of our patients developed KS with CD4 counts of more than 200 cells/ul. According to recent studies from an African population, high CD4 count has not offered absolute immunity against developing KS in South Africans and other Africans in general[18]. A recent multi-cohort, multiregional study has shown that the HIV positive population in South Africa had an increased risk of developing KS compared to the HIV population in Europe[18]. Bower et al from the European cohorts documented similar findings. Twelve patients from his study had CD4 counts of more than 300 cells/ul at KS diagnosis[47]. In addition, 8% of the 214 of his patients had a less than detectable HIV VL at KS diagnosis. Only 12 patients from our study had their HIV VL recorded at their initial visit and this number was too low for us to

record any inference. However, in these few patients we noted that 2 of our patients had less than detectable HIV VL and 4 others had HIV VL of less than 40 copies/ml.

In our cohort almost half of the patients (48.6%) at KS diagnosis were ART-naïve. These patients were subsequently initiated on ART and at the two year follow-up visit almost all (99%) of the patients were on treatment. Immunosuppression and HIV infection in particular is a vital risk factor in the occurrence of KS. Early ART initiation has been shown to reduce the incidence of KS[51].

Guiguet et al reported that ART is protective against KS after six months of treatment[26]. We observed that a subset of our patients (see Table 3.1 for details) developed KS even though they were well established on ART with an average duration of fourteen months on treatment. This is consistent with the findings of Crum-Cianflone et al in 2010 and more recently by Robey RC & Bower M in 2015 [13, 45]. Robey and Bower noted that the risk of developing KS is present, even in patients with fully restored immunity. These patients may have a milder course[13]. Similarly, a prospective multi cohort study from Southern Africa, which also included patients from the ART program in South Africa. They documented that the risk of KS incidence remains high up to three months following ART initiation and declines at about twenty four months on ART[51].

In this study half of the patients had a concomitant systemic illness predominantly consisting of TB followed by oral candidiasis and pneumonia. Multiple opportunistic infections are well described in the immunocompromised patients. Co-infection with KSHV and mycobacterium tuberculosis is common especially in the sSA[40, 52]. Co-infection with HIV and TB has been shown to carry an increased mortality and is likely to have contributed to the higher mortality in this sub-group[53].

Most of our patients had cutaneous KS. The lower limb was noted as the most common site and the lymphedema associated with it was persistent. A few patients (10%) had documented visceral plus cutaneous KS in our study. Visceral lesions predominantly involved the lungs and the gastrointestinal tract. Only 1 patient had visceral gastrointestinal KS without any skin

lesions who presented mainly with symptomatic anaemia. Gastrointestinal KS was confirmed on endoscopy.

At the end of the two year follow up time from their first Oncology clinic presentation, almost half of the study population had died (45%). The majority of these deaths occurred within the first six months (69.4%) of the patients' first clinic presentation. The high mortality rate in our study is consistent with previous studies describing HIV-KS mortality in our region[48, 11]. Chu et al reviewed 215 patients with KS. During the first year of their study approximately half of their patients had died or were lost to follow-up; presumed dead[48]. They identified late access to ART as a contributor to their high mortality. In our study almost half the patients were ART-naïve at the time of diagnosis with KS. This finding was confirmed by Maskew M who described 247 patients with KS in a cohort of 13 847 people initiating ARTs[11]. She concluded that at ART initiation, the presence of clinical disease with KS raises the risk of mortality significantly and the response to treatment becomes poorer[11]. In our cohort almost half the patients' initiated ART at/ after the diagnosis of KS and this likely contributed to our high mortality. Herce et al studied 114 HIV-infected patients with KS in Malawi[41]. All their patients received at least one cycle of chemotherapy. The majority (96%) of their patients were on ART at the time of enrolment. Their one year survival was 83%.

In the sub-group of patients that died, almost half of our patients on ART at KS diagnosis were on the therapy for less than six months. It is possible that these patients had KS-IRIS. The incidence of KS-IRIS has increased in the ART era and has been shown to have a high mortality (almost 50%) in sSA[13, 54]. Letang et al did a study looking at the incidence, predictors and outcomes of KS-IRIS in those initiated on ART. They found that KS-IRIS is a significant and a serious cause of mortality especially in sSA compared to the developed world (UK) [54]. KS-IRIS is twice as common in Africans compared to Europeans and KS related mortality three times higher in Africans[54].

We noted from our study population that patients who had died had advanced disease consistent with the ACTG classification of T1 I1 S1 (Appendix 3.3). These patients had extensive KS lesions as well as tumour associated oedema and constitutional symptoms (B symptoms). T1 I1 S1 KS has been classified as a poor risk and carries a higher risk factor for mortality[25, 54]. Among the 11 patients documented with visceral disease, 6 of these patients died of whom 5

had lung associated KS and 1 with gastrointestinal KS. Additionally, 2 other patients died with pulmonary symptoms in whom visceral KS was not confirmed.

Co-existence of KS and MCD is well-known in literature[14, 47]. We noted one patient in our study with a CD4 count of 291 cells/ul and an unknown HIV VL being referred for a repeat/re-evaluation of biopsy results. This patient demonstrated extensive lymphadenopathy on top of multiple KS mucocutaneous lesions. Unfortunately, the patient died within the first six months of the clinic enrolment therefore no further follow up notes was available in the files and MCD diagnosis was not confirmed.

One patient among those with progressive KS who received six cycles of ABV followed by eight cycles of paclitaxel, was diagnosed with APL at one year of follow up. This patient was initiated on all-trans retinoic acid (ATRA) however at the two years follow up the patient was documented as dead with severe sepsis.

High HIV VL in KS patients have been linked to mortality[13, 54]. However we observed that 2 KS patients, from the 7 patients in the dead category with available HIV VL, had their HIV VL as low as less than 40 copies/ml as well as CD4 counts of more than 500 cells/ul.

Both ART and chemotherapy play important roles in the clinical course of HIV-KS thus impacting on the outcome of disease[34]. Most of our patients were initiated on the ABV chemotherapy regimen as their first line, followed by paclitaxel as the second line treatment for KS. The initial choice of chemotherapeutic regimen may have had a role to play in the high mortality in our setting. Survival rate in the high-income countries is better compared to that in the low middle income countries[34, 43]. Among the reasons for such success is probably the availability of newer chemotherapeutic agents. Cianfrocca et al in 2010, from USA, in their randomized trial involving 73 patients with severe and symptomatic HIV-KS compared the use of paclitaxel and pegylated liposomal doxorubicin[43]. They documented an overall two years survival rate of over 75% in their study population for both drugs. They also reported significant improvement in the lymphedema, and pain associated with the disease. These clinical conditions were not well controlled in our patients.

At two years of study period 55% of the study population was alive. In subcategorizing the living patients, complete response of the KS lesions was seen in 24.8% of these patients over the course of time. Some responded within few cycles of their first chemotherapy regimen while others required change of regimen(s) to attain complete response.

Majority of the patients with progressive disease (14.7%) required to receive paclitaxel as a second line chemotherapeutic agent. One of the patients in this category showed persistent progression of KS despite being on the fourth regimen change of chemotherapy, including the use of gemcitabine, as well as poor response to radiotherapy. Interestingly the HIV VL of this patient was less than detectable. Only 2 patients out of the 16 in the progressive disease category tended to default therapy, both ART and chemotherapy, upon showing signs of improvement. Available HIV VL among the patients with progressive disease was inconsistent some being virally suppressed and others with lower viral loads of around 500 copies/ml to those with high HIV VL. Recurrence of KS was noted in few patients (3.7%) with all of them developing lesions in the same site.

5.2 Limitations

This was a retrospective review of the files using clinicians' notes available in it, therefore incomplete data was a challenge. A specific problem area encountered was that the dimensions of KS lesions before and during the treatment phase was not obtained. An evaluation for partial response (by definition) to treatment was difficult.

ACTG classification, (Table 1.3), for prognostication purposes was not possible for all patients due to the nature of the available clinical notes in the files.

This study consisted of a small sample size and thus likely reduces the power of the study.

5.3 Conclusion

HIV-KS related mortality is still high in our setting despite wide coverage of ART. Opportunistic infections like TB in our setting furthermore adds on to the burden of morbidity and mortality in the HIV-KS patients. Fifty percent of our patients that died were simultaneously on TB treatment. ART initiation timing and therefore development of KS-IRIS may also be contributory to the high mortality in our study as a proportion of our dead patients diagnosed with KS despite being on ART were on it for less than six months.

This disease is also associated with high morbidity in those who are alive and who have not achieved complete response. They suffer with residual disease, persistent lymphedema as well as pain. There exists a need for palliation options for such patients.

More research is needed to explain the incidence of KS in virally suppressed patients and in the setting of high CD4 counts.

During the study population recruitment phase over one hundred patients who did not re-visit the Medical Oncology department after registration and whose outcomes at two years was unknown, (manually from the files and using the department computer), were excluded from the study for being lost to follow up after clinic enrolment. Another study is needed to further define this population. In our study a large number of dead patients were lost to follow up from the Medical Oncology clinic. It was with the help of the computer records that their death status was confirmed.

Our setting is a tertiary/quaternary referral hospital, with referrals also from the neighbouring countries from sSA, involving qualified and highly trained experts in various fields of medicine therefore we suggest alternative first line management rather than ABV if financially feasible. Since this was a retrospective record review of files from 2011 to 2013, we suggest another study to investigate the treatment outcomes of HIV-KS patients in the more recent years (where

paclitaxel has now become widely available as first line treatment in the department and is being used in place of ABV in many patients) as well as excluding patients with TB co-infection.

6.0 APPENDICES

Appendix A Karnofsky Performance Status scale (KPS) [55]

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

Appendix B Data collection sheet

1) Patient number: ……..

2) Age (Years) at entry to Med Onc. Clinic …… Unknown…….

3) Gender: Male..... Female..... Unknown……

4) Height…… (cm), Unknown…… 5) Weight…… (Kg), Unknown……

5) Race: Black…… White..... Coloured..... Indian……. Other..... Unknown…….

6) Date of first clinic visit (YY, MM, DD)……..

7) HIV positive yes……. No..... Unknown…….

8) At the time of KS diagnosis, was patient on ARTs?

Yes…… Duration (YY, MM) ……. No…… Unknown…….

9) ART started? No…… Yes…… Date…….. Unknown……

10) If yes, type of ART regimen at the time of referral

REGIMEN on initiation	3TC	TDF	EFV	NVP	ABC	d4T	AZT	LOP/RIT (ALLUVIA)	FDC	Other	Unknown

11) CD4 level at KS diagnosis/1st Oncology clinic visit (cells/ul)…….. Unknown…….

12) HIV Viral load at KS diagnosis/1st Oncology clinic visit (copies/ml)……. Unknown……...

13) Side effects on concomitant treatment with ARTs and KS? (At least once along the course of treatment) Yes…… No…….
Unknown……..

14) If yes, type of adverse effects

Side effects	Rash	Kidney injury	Hepatitis	Peripheral neuropathy	Gastroenteritis	Lipodystrophy /atrophy	Other

15) Was ART regimen changed along the course of KS treatment? Yes..... No..... Unknown….

16) If yes, reason for ART change?

Side effects	Virological failure	Other

17) Date of KS diagnosis (YY, MM, and DD)..... Unknown……...

18) How was KS diagnosed?

Clinically without histology	
Clinically plus histologically	

19) Lesion of KS (based on ACTG Classification)

Clinic date	Skin lesion site	Oral lesion	Oedema	Visceral involvement
At KS diagnosis				
1st Onc. clinic visit/1st chemo cycle				
3rd Onc. Clinic visit/3rd chemo cycle				
Last chemo cycle				

20) Concomitant systemic illness during KS/ART's? Yes..... No..... Unknown…….

21) If yes, mention type of illness

TB	Cryptococcus meningitis	Pneumonia	Other

22) KS specific treatment? Yes……..... No..... Unknown……

23) Information on KS treatment

Type of treatment	Regimen	Doses/no of cycles
Radiation		
Chemotherapy		

24) Was steroids used during the time of KS Diagnosis? Yes..... No.....Unknown…….

25) Treatment status at 2years on KS treatment and ART.

Alive……..

Dead……

26) If alive,

Patient status	Improved	Complete Response	Progressive Disease
At 6 months			
At 1 year			
At 2 year			

27) Last follow up date at oncology clinic…

Appendix C Human Research Ethics Committee (HREC) Medical clearance certificate

R14/49 Dr Fatema Aonali Chandoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160419

NAME: (Principal Investigator)	Dr Fatema Aonali Chandoo
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Retrospective Review of Treatment Outcomes of HIV Positive Patients with Kaposi Sarcoma receiving Highly Active Anti-Retroviral Therapy at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	06/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Francois Venter
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/05/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of May each year.

F. Chandoo — Principal Investigator Signature

23/10/18 — Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D Author consent

Dear professors Johann Schneider and Dirk Dittmer, Hope
this email finds you well.

I would like to request for your permission to use Kaposi Sarcoma histology images from your review article titled “Diagnosis and Treatment of Kaposi Sarcoma”. This is for the purpose of my Mmed research report with the University of Witwatersrand.

Thank you.

Kind regards,
Fatema Chandoo (MD,
FCP (SA)).

Reply Reply to all Forward

Dittmer, Dirk P dirk_dittmer@med.unc.edu via adminliveunc.onmicrosoft.com Apr 6

to me, jws2

Please feel free, just acknowledge the source.

With best wishes,
Dirk

From: Subhash C Verma scverma@med.unr.edu

Date: 20 August 2018 at 22:02:00 EAT

To: F chandoo <drfchandoo@gmail.com>

Cc: "sukainac2@gmail.com" <sukainac2@gmail.com>

Subject: Re: Permission to use image from your article

Dear Fatema,

Thanks for contacting me to use the figures for your research report, It is totally fine with me to use our figure.

Best regards,

Subhash

Subhash C. Verma, Ph.D.

Associate Professor,

Department of Microbiology & Immunology

University of Nevada, Reno School of Medicine

1664 North Virginia Street, MS 320

Center for Molecular Medicine, 211F

Reno, NV-89557

Phone: 775-682-6743

Lab:775-784-1383 Fax: 775-327-2332

e-mail: scverma@medicine.nevada.edu

https://med.unr.edu/directory/subhash-

verma

From: F chandoo <drfchandoo@gmail.com>

Date: Friday, August 17, 2018 at 11:07 AM

To: Subhash C Verma <scverma@med.unr.edu>

Cc: "sukainac2@gmail.com" <sukainac2@gmail.com>

Subject: Permission to use image from your article

Dear Professor Verma,

Greetings to you.

I got this email address from my sister who spoke to you telephonically today. Thank you for taking her call.

I have been trying to reach you since April through the email address scverma@medicine.nevada.edu which was provided in your review paper titled “KSHV-mediated angiogenesis in tumor progression”.

I read your article and with your permission I would like to use “figure 1: schematic representation of KSHV induced cell transformation” for my Mmed research report.

I am affiliated with the University of the Witwatersrand, Johannesburg, South Africa.

Hoping for your earliest positive response.

Thank you.

Kind regards,

Fatema Chandoo

(MD, FCP-SA)

Begin forwarded message:

From: F chandoo <drfchandoo@gmail.com>

Date: 31 July 2018 at 14:47:07 EAT

To: scverma@medicine.nevada.edu

Cc: pravinp@medicine.nevada.edu, tuppal@medicine.nevada.edu, rsarkar@medicine.nevada.edu

Subject: Permission to use image from your article

Dear professor Verma,

Hope this email finds you well.

I would like to request for your permission to use an image (figure 1: schematic representation of KSHV induced cell transformation) from your review paper titled "KSHV-mediated angiogenesis in tumor progression".

This is for the purpose of my Mmed research report with the University of Witwatersrand in Johannesburg, South Africa.

Hoping for your earliest response.

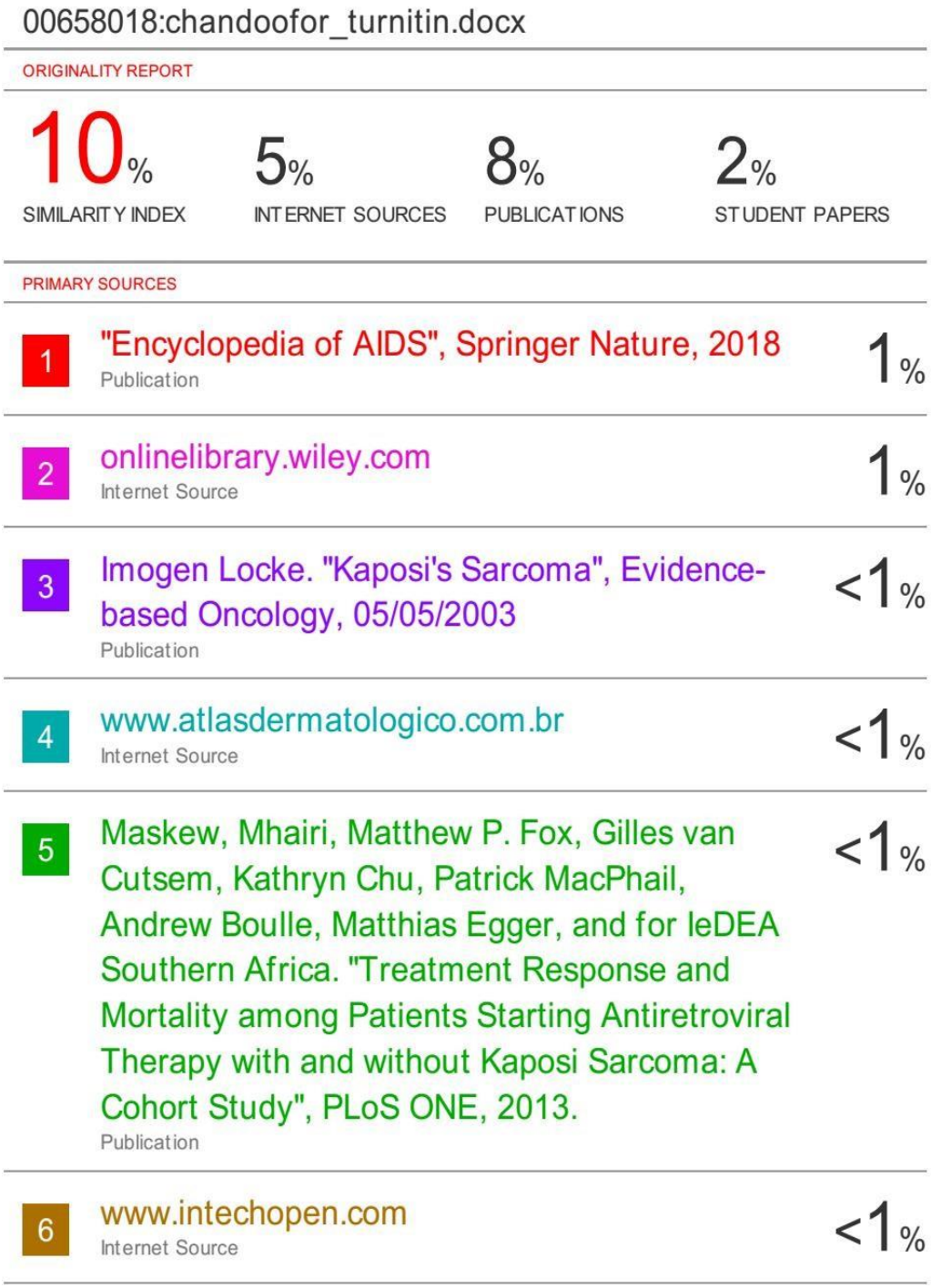
Thank you.

Kind regards,

Fatema Chandoo

(MD, FCP (SA)).

Appendix E Turnitin Report



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