THE PREVALENCE AND ASSOCIATED CHARACTERISTICS OF PATIENTS WITH KAPOSI SARCOMA AT PIETERSBURG HOSPITAL, LIMPOPO PROVINCE

by

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Plagiarism declaration

I, Tshimangadzo Mukhithi, hereby declare that this research study is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of in-text citation and list of references. This work has not been submitted for any other degree at any institution.

Signature: Tshimangadzo Mukhithi

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Abstract

Background

Among the most prevalent malignancies associated with AIDS, Kaposi Sarcoma (KS) is one of them. In the developing countries, it is a significant cause of morbidity and mortality, resulting in 2500 deaths per year and it accounts for approximately more than 10% of all cancer deaths in Sub Saharan Africa. Due to the availability of ART, the prevalence of KS has decreased in western nations, but it has increased in Sub-Saharan Africa due to higher rates of co-infection with HIV and the Kaposi Herpes virus (KSHV). Hence, the present study investigated the prevalence of KS in Limpopo Province in the era of ART roll out in South Africa.

Aim and objectives.

To assess the prevalence and associated characteristics of patients with Kaposi Sarcoma at Pietersburg Hospital, Limpopo Province in South Africa.

Methods

The study was a retrospective cross sectional descriptive study in adult individuals (years ± 40yrs) conducted at Pietersburg Medical Oncology clinic over 3 years period (1st January 2015 to 31st December 2018). There was no sample size calculation, and convenient study sample sampling was used. Due to the present study small size, the study's patients were not divided into their respective years.

Results

A total of 117 patients were included in the data analysis. There was no statistical difference in gender groups (p-value = 0.51). The study reported that the overall prevalence of Kaposi Sarcoma at Pietersburg Hospital was 4%. The predominant subtypes were 94% with AIDS associated KS and 6% endemic. Majority of patients (93%) were HIV positive and only 7% were HIV Negative. Males (72%) had increased percentage of KS as compared to their females (45%) counter

parts. All the patients were of African descent with no case of Classic KS seen over the study period.

Conclusion

The study highlighted the positive impact of anti-retroviral therapy (ART) in reducing the prevalence of Kaposi Sarcoma and the late diagnosis of HIV KS with almost 50% of patients not on ART at the time of diagnosis. The study has reported that although KS is still being diagnosed in patients with HIV at Pietersburg Hospital, there was lower prevalence of KS, which does not differ from that of other South African studies. More studies are still warranted using larger sample sizes on patients in order to further investigate the relationship of HIV+ patients and KS.

Keywords

Kaposi Sarcoma, HIV, Prevalence, ART

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Abbreviations and Acronyms

HIV	Human immunodeficiency virus
KSHV	Kaposi sarcoma herpesvirus
KS	Kaposi Sarcoma
AIDS	Acquired immunodeficiency syndrome.
ACTG	AIDS Clinical Trials Group
SSA	Sub Saharan Africa
ART	Antiretroviral therapy
KAART	Kaposi sarcoma AIDS Antiretroviral Therapy
HAART	Highly Active Antiretroviral Therapy
HHV8	Human herpes virus subtype 8
WHO	World Health Organization
NHLS	National Health laboratory Service

Definition of concepts

Prevalence is the occurrence of a particular disease in a specific population at a specific point in time (Polgar & Thomas, 2020).For this study prevalence relates to the number of patients with Kaposi sarcoma as a proportion of group of patients seen at the oncology clinic from 01/01/2015 to 31/12/2018.

Kaposi Sarcoma is a vascular tumour that is aetiologically associated with human herpesvirus 8(HHV8), also known as Kaposi associated herpes virus (KSHV) (Groopman, Aboulafia & Shah 2020).
For this study, Kaposi Sarcoma refers to tumour that is associated with KSHV or HHV8.

AIDS is an acquired immunodeficiency syndrome defined by CD4 count< 200cells/mm^3 or a WHO clinical stage 3 or 4 disease(World Health Organization, 2017).For this study, AIDS is defined by CD 4count< 200cells/mm^3 or a WHO clinical stage 3 or 4 disease.

Radiotherapy is the treatment of disease, usually cancer, by ionizing radiation in order to deliver an optimal dose of either particulate or electromagnetic radiation to a particular area of the body with minimal damage to normal tissues(Radiotherapy | definition of radiotherapy by medical dictionary).
For this study, radiotherapy relates to the treatment of Kaposi Sarcoma through the use of radiation.

Chemotherapy is the treatment of cancer with anti-cancer drugs(Chemotherapy | definition of chemotherapy by medical dictionary).
For this study, chemotherapy relates to the treatment of Kaposi sarcoma through the use of anti-cancer drugs.

Chapter 1

1. Introduction and background to the study

The epidemic of the Human Immunodeficiency Virus (HIV) is a major source of morbidity and mortality worldwide. According to the Joint United Nations Programme on HIV/AIDS (UN AIDS) report, there were an estimated 37.9 million HIV-positive people worldwide in 2018. Of those, 20.6 million were from eastern and southern Africa, with 7.7 million of them living in South Africa (SA) (UNAIDS,2020).

A low-grade vascular tumour known as Kaposi Sarcoma (KS) is connected to Kaposi sarcoma Herpesvirus (KSHV) infection (Shah, 2021). Although they can arise in various organs and anatomical locations, KS lesions are most frequently found at mucocutaneous sites. About a century ago, it was first discovered by Austrian dermatologist Moritz Kaposi (1837–1902) (Radu & Pantanowitz, 2013: 289–294)

Among the most prevalent AIDS-defining cancers, Kaposi Sarcoma is one of the AIDS-defining diseases (Mosam, Shaik & Uldrick *et al.,* 2012: 150–157). In Sub-Saharan Africa (SSA), it is a significant cause of morbidity and mortality, resulting in roughly 25000 deaths annually (Herce, Kalang & Wroe *et al.*, 2015: 19929-n/a). Before the HIV pandemic, it was endemic in SSA. Antiretroviral therapy (ART) has helped reduce the prevalence of KS in western nations, but it has increased in SSA and East Africa due to higher rates of co-infection with HIV and the Kaposi herpes virus ((Mosam, Shaik & Uldrick *et al.*, 2012: 150–157)). In a hospital-based study involving 357 out of 370 KS patients (96.5%), Sengayi et al. found that more than 90% of KS cases were HIV seropositive between 2004 and 2012. (Sengayi, Kielkowski & Egger *et al.,* 2017: 871–876)

Before HAART was made available in SSA, HIV-related KS had a significant mortality rate. Only 30–40% of 470 patients with HIV-associated KS in a prospective research conducted in Zimbabwe in the 1990s that compared palliative chemotherapy, radiotherapy, or supportive treatment exhibited a 12-month overall survival, and similar results were observed in KwaZulu Natal, South Africa (Mosam *et al.,* 2012: 150–157) .The national ART programme for South Africa was launched in 2004 and saw an improvement in coverage from less than

1% to over 50% in 2016 (Majaya, Girdler-Brown & Muchengeti *et al.*, 2021: 20–27).

According to a UNAIDS estimate, South Africa's ART coverage stood at 62.3% in 2018. According to Majaya et al. (2021), in South Africa the implementation of an antiretroviral programme was linked to a more than 50% decrease in the anticipated age-standardized incidence rates of KS (Majaya *et al.*, 2021: 20–27).

1.2 Problem statement

Kaposi sarcoma is still one of the most often diagnosed opportunistic malignancies and a major cause of morbidity and high mortality in South Africa as a result of the HIV epidemic. A respectable CD4 count of at least 200 cells/mm3 and an undetectable viral load are ideal conditions for all patients who have been diagnosed with HIV.

In actuality, a large number of HIV positive patients do not receive ART for a variety of reasons, such as denial of their HIV status, stigma associated with the illness, limited access to care, and occasionally default from their treatment. As a result, many patients develop low CD4 counts and high viraemia, making them more vulnerable to opportunistic infections and cancers.

Due to limited access to ART, the death rate from HIV-KS was high prior to the launch of the national ART program in South Africa. The anticipated age-standardised incidence rates of KS have decreased by 50% since the inception of the ART program, and patients with KS who are on ART have better survival outcomes and improved quality of life (Majaya *et al.*, 2021: 20–27).

Although there are still KS patients being treated in the medical oncology clinic at Pietersburg Hospital in the era of HAART, it is unclear how frequent KS has become since the commencement of the ART roll out program in Limpopo.

The aim and objectives of this study was to assess KS prevalence in the era of HAART roll out in Limpopo Province, related risk factors, the most common clinicopathological subtypes of KS in the era of HAART, and a comparison of the frequency of KS in individuals who tested negative for HIV. Since the start of the

South African National ART program, no study of this kind has been conducted in the area to ascertain this.

1.3 Purpose of the study

1.3.1 Research aim

To assess the prevalence and associated characteristics in patients with KS at Pietersburg Hospital between 1st January 2015 to 31st December 2018 in patients seen at the medical oncology outpatient department.

1.3.2 Research objectives

1.4.1 To measure the prevalence of KS at Pietersburg Hospital adult medical oncology unit.

1.4.2 To determine prevalence of different subtypes of KS.

1.4.3 To determine associated risk factors of patients with KS.

1.4.4 To compare the prevalence of KS in HIV positive and HIV negative patients.

1.4 Research questions

How common is KS at Pietersburg Hospital adult oncology clinic?

Which subtypes of KS are common?

1.5 Significance of proposed research

The prevalence of HIV is significant in South Africa, and a large percentage of individuals have a late presentation of opportunistic infections and cancers. The South African National ART Programme has evolved over time, with uptake rising as recommendations change in response to new evidence. The project will contribute to our understanding of KS prevalence in Limpopo Province in the era of HAART, common KS subtypes, and the effectiveness of ART in preventing HIV and its associated opportunistic infections and cancers. Additionally, it will provide the percentage of KS patients who were not on HAART at the time of diagnosis. This will help in the planning expedited commencement of HAART in patients diagnosed with HIV, and reinforcement of ART adherence. The study hasn't been conducted in the province of Limpopo before, as far as I know.

Chapter 2: Literature review

2.1 Epidemiology

Related to AIDS, one of the most prevalent tumours in patients with HIV is KS, which is an AIDS-defining condition. The skin, mucosa, and viscera are frequently affected by this low-grade vascular tumour (Shah, 2021). The majority of KS cases globally are caused by immunosuppression, either from HIV infection or, less frequently, from immunosuppressive medication used to reduce organ transplant rejection. Since HIV prevalence varies geographically, so does the geographic diversity in KS incidence (Stiller, Botta & Sánchez Perez *et al.,* 2021: 101877). Before the advent of ART, KS was 20 000 times more frequent among people with HIV than in the general population in the United States (Shah, 2021). Less typically found in transfusion recipients, women, children, and haemophiliacs, it is frequently found in homosexual men (Shah, 2021). Sengayi et al. discovered that KS was prevalent in the black population group in South Africa, with up to 98.9% of participants being black South Africans (Sengayi et al., 2017: 871–876)

There are 4 epidemiologic forms of KS that are recognized:

- AIDS related KS
- Organ transplant associated KS
- Endemic or African KS
- Classic KS (Radu & Pantanowitz, 2013: 289–294)

KS can develop at any age with a male predilection. There is a strong correlation between the development of KS, HIV infection and HHV 8 infection. KSHV was first discovered in KS lesions by Chang et al. in 1994(Radu & Pantanowitz 2013).The growth of KS is facilitated by upregulation of several HHV 8 gene products like latency associated nuclear antigen. African KS tend to be more aggressive than classic KS more commonly in the lymphadenopathic form than if found in young individuals (Radu & Pantanowitz, 2013: 289–294).

Endemic or African KS commonly occurs in Sub Saharan Africa in HIV seronegative individuals. It is usually aggressive in children with generalized lymphadenopathy and visceral involvement (Cesarman, Damania & Krown *et al.*, 2019: 9). The presentation in children is that of multiple lymphadenopathies and associated lymphoedema. The course in adults tend to be indolent and rarely has visceral involvement (Cesarman *et al.*, 2019: 9).

Classic KS usually occurs in the lower limbs with few lesions. It tends to be indolent, and it is usually not aggressive. It tends to occur in middle age, elderly people of Mediterranean and Jewish ancestry (Cesarman *et al.*, 2019: 9). It is commonly diagnosed in men than women. According to RARECARENet project, the age adjusted incidence in males was more than four times that in females (Stiller, Botta, Sánchez Perez, *et al.*, 2021: 101877).

Immunosuppression brought on by medications or after transplantation frequently results in iatrogenic KS. It is more frequent in patients who have had renal transplants than in those who have had solid organ or bone marrow transplants. The reactivation of latent HHV 8 infections in recipients or from organ donors may be the cause of post-transplant KS. It typically takes an extended but aggressive course. Following the cessation of immunosuppression, iatrogenic KS may recur (Cesarman *et al.*, 2019: 9).

2.2 Prevalence

Semango *et al.* has reported prevalence KS of 4.6% among HIV positive adult population attending at KCMC hospital in a 4-year study period in Tanzania between 2012 and 2015 and has remained around 4% in HIV infected population in Northern Tanzania (Semango, Charles & Swai *et al.*, 2018). In Malawi KS account for 35% of about 8000 new cancer cases diagnosed annually (Herce *et al.*, 2015: 19929-n/a). In South Africa the incidence of KS remains high with incidence rate of 138 per 100 000 person years reported in a multicohort study done in Cape Town in the ART era (Bohlius, Valeri & Maskew *et al.*, 2014: 2644–2652). Bohlius *et al.* reported prevalence of KS of 1.8% in HIV infected treatment naïve population in a South African cohort study (Bohlius *et al.*, 2014: 2644–2652)

A study done in Khayelitsha, Cape Town found that of 6292 patients in HIV clinics 215(3.4%) had AIDS associated Kaposi sarcoma (Chu, Mahlangeni & Swannet *et al.*, 2010: 23). Similar studies done in South Africa, Northwestern Tanzania and Northern Tanzania reported prevalence of 3.4, 2.4 and 4% respectively on HIV positive adult population (Semango *et al.*, 2018, no. 1).There are other studies done in Mediterranean countries and in East Africa region that have reported higher KS prevalence of 10-20% and 12.3% amongst HIV adult population (Semango, Charles & Swai *et al.*, 2018).

2.3 Risk factors

In patients with a CD4 count < 350 cells/L, HIV-related KS is prevalent. Twenty six out of 33 cases with HIV-related KS in research conducted in Kenya had CD4 counts under 300 at the time of initial presentation (Majaya *et al.*, 2021: 20–27). Fifty eight percent of participants in the Kaposi Sarcoma AIDS Antiretroviral Therapy (KAART) trial had CD4 counts higher than 200 cells per lymphocyte (Mosam *et al.*, 2012: 150–157). Chu *et al.* 'study found that a baseline CD4 count of less than 100 cells/mm3 was related with poor outcomes on a univariate analysis (Chu, Mahlangeni, Swannet, Ford, Boulle & Van Cutsem, 2010: 23). HIV-positive people who are seropositive for the Kaposi Herpes Virus have a higher risk of developing KS. In San Francisco research, 38% of 593 homosexual males had HHV 8 compared to none of 195 heterosexual men, and among HIV-infected individuals with HHV 8 at baseline, the 10-year risk of developing KS was nearly 50%. (Shah, 2021). According to socioepidemiological studies, KSHV/HHV 8 antibodies are present in up to 40% of adults in SSA (Sisolak & Mayaud, 2005: 981–992).

2.4 Clinical Manifestations

Based on the epidemiological forms, the clinical signs of KS may overlap. Skin lesions of all kinds typically appear as many, pigmented, raised or flat lesions that are painless and do not blanch (Semango *et al.*, 2018, no. 1). The initial cutaneous lesions are frequently asymptomatic, pale pink to purple pigmented macules or tiny papules. Different clinicopathological types of KS lesions, such as patch, plaque, nodular, lymphadenopathic, or infiltrative ulcers, can be distinguished (Semango *et al.*, 2018, no. 1).

The typical appearance of lesions is commonly used to make the diagnosis of KS, but a biopsy and histopathology analysis should also be performed. The lesions can occasionally develop exophytic, ulcerated, bleeding nodules with an accompanying severe oedema (Cesarman *et al.*, 2019: 9). In AIDS-related KS, oral lesions are typical and can lead to dysphagia and comorbid infections. Chu *et al.* discovered that 56% of patients had lesions on their lower legs and that 65% of the patients had mouth lesions in their research of AIDS-associated KS (Chu, Mahlangeni, Swannet, Ford, Boulle & Van Cutsem, 2010: 23).

In children and young adults from Africa, endemic KS is typically accompanied by lymphoedema. Visceral lesions typically affect the lungs and digestive system (Cesarman *et al.*, 2019: 9). The most common symptoms of pulmonary lesions are a dry cough, dyspnoea, fever, and haemoptysis. The majority of gastrointestinal lesions are asymptomatic, although they can still bleed or obstruct. At an endoscopy, the diagnosis of a gastrointestinal lesion is typically confirmed (Cesarman *et al.,* 2019: 9). For cancer patients including KS, the performance status assessment using the Eastern Cooperative Oncology Group (ECOG) score is frequently utilized with five grades.

0-fully alive and capable of performing in the same manner as before the disease
1-Limited in physically demanding activity but mobile
2-Ambulatory, able to take care of oneself, but unable to perform any work-related duties.
3. Capable of little self-care and spending more than half of the working day in bed.
4-Totally crippled and unable to perform any self-care
5-Dead (Azam, Latif, Farooq, et al., 2019: 728–736) (Azam, Latif, Farooq, et al., 2019: 728–736)

The TNM staging system has not unified or included the staging of KS. The AIDS clinical Trials Group (ACTG) staging classification, which is based on tumour,

immunological state, and systemic illnes, is utilized in KS that is connected to AIDS (Cesarman et al., 2019: 9).

Table 1

The Modified AIDS Clinical Trials Group Staging of AIDS related KS

TIS staging of KS	**Good risk(T0)**	**Poor risk(T1)**
Tumour	Confined to skin or lymph. Nodes or minimal oral disease	Tumour associated oedema or ulceration, extensive oral KS or gastrointestinal KS
Immune status	CD4 cell count>150 per mm^3	CD4cell count<150per^3
Systemic illness	Karnofsky Performance status>70[b]	Karnofsky Performance status<70[b]

3.5 Management and prognosis

There is currently no cure for KS. Symptom relief, KS progression prevention, aesthetic improvement, and stress reduction are among the objectives of treatment(Radu & Pantanowitz, 2013: 289–294). Surgical excision might be used to address KS lesions that are unsightly. Beam radiation, laser therapy, cryotherapy, and intralesional vinblastine are among local therapies used to treat bulky lesions (Radu & Pantanowitz, 2013).

In individuals with HIV-related KS, HAART is crucial for enhancing survival rates, while chemotherapy enhances responses specific to KS. According to the KAART trial, HAART increases 12-month overall survival in South African patients with HIV-related KS by 77% compared to 30–40% when used with or without chemotherapy. Patients who are new to ART should begin by controlling their HIV with ART, which frequently causes KS regression (Cesarman *et al.*, 2019: 9). With patients taking protease inhibitor-containing regimens, KS resolution has been shown with HAART, and since their widespread usage,

Europe and the USA have seen a 30–50% drop in the incidence of KS (Sissolak & Mayaud, 2005: 981–992). According to a study conducted in South Africa at the Steve Biko Academic Hospital, fatality rates for patients with KS were 63% lower during the late ART period (2009–2012) than during the early ART period (2004–2008) (Sengayi *et al.,* 2017: 871–876). Patients with KS had an overall five-year relative survival of 80% between 2000 and 2007 according to the RARECARENet project, which used data from 59 population-based cancer registries in 22 countries. AIDS-related KS in patients under 65 improved during the HAART era (Stiller *et al.,* 2021: 101877).

Widespread skin involvement, substantial oral KS, rapidly progressing diseases, visceral KS, and significant clinical oedema are indications for systemic treatment (Radu & Pantanowitz, 2013). Herce *et al.* trial 's in rural Malawi shown that standard of care chemotherapy regimens from developed countries can be combined with ART to treat HIV KS with fewer side effects and a lower loss to follow-up.

Advanced AIDS-related KS has been successfully treated with pegylated liposomal doxorubicin and paclitaxel in settings with limited resources. (Krown, Moser & McPhail *et al., 2020:* 1195–1207 *0:).* The anthracyclines and Texan's are currently the foundation of systemic cytotoxic therapy.

In resource-limited settings, the Non-Inferiority Trial, an open-labelled, randomized controlled study comparing various chemotherapeutic regimens in conjunction with effective ART, revealed that intravenous paclitaxel was superior to both the widely used intravenous regimen of bleomycin, Vincristine, and an easy-to-use oral regimen of etoposide in terms of the overall response rate and progression-free survival (Krown *et al.,* 2020: 1195–1207). Different epidemiologic kinds of KS can be treated in the same ways. Age over 50, HHV 8 positivity in plasma upon diagnosis, severe KS with systemic disease, and positive HHV 8 test results are factors that are linked to poor survival in the era of HAART (Radu & Pantanowitz, 2013). Late HIV diagnosis, difficult access to ART, and inadequate treatment of advanced Kaposi's sarcoma are other

contributing variables that are linked to poor outcomes (Chu, Mahlangeni, Swannet, Ford, Boulle & Van Cutsem, 2010: 23).

Conclusion

This chapter reviewed the literature and previous studies done focusing on Prevalence of KS, risk factors, clinical manifestations, and management of KS. The chapter which follows will outline the methods used for data collection and describe the data collection tool.

Chapter 3: Methods

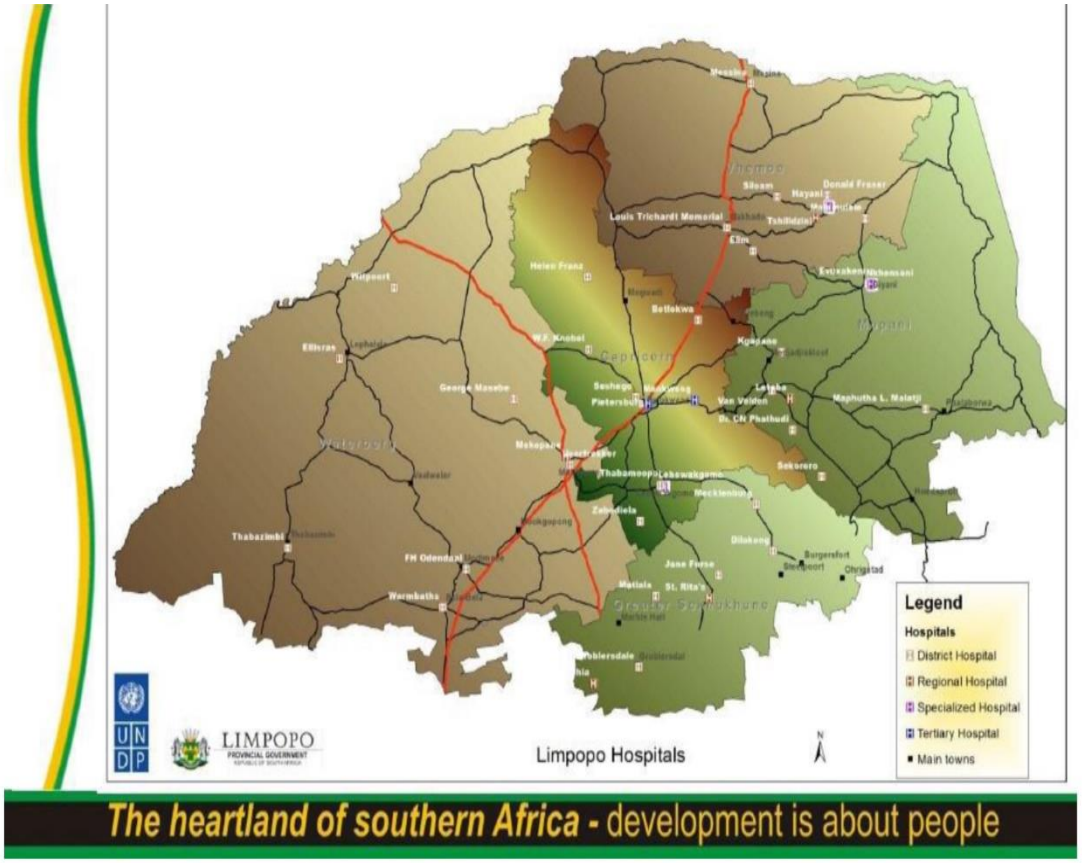
3.1 Study Design

The research was a retrospective cross-sectional descriptive study. Cross sectional study design is an observational study in which the investigator measures the outcome and exposures in the study participants at the same time and are used for population-based surveys and to assess the prevalence of diseases in clinic-based samples (Setia, 2016: 261–264).

The study was conducted at Pietersburg Hospital Oncology unit over a 3-year period. It included all patients seen between January 2016 until December 2018.

3.2 Study area

The study was done at Pietersburg Hospital, medical oncology outpatient department. Pietersburg Hospital is a tertiary referral hospital in Polokwane, Limpopo province in South Africa. It is situated in Polokwane municipality under Capricorn district. South Africa has 9 provinces and Limpopo is the Northernmost province of South Africa named after Limpopo River, which forms the province's western and northern borders, and the capital city is Polokwane, formerly known as Pietersburg. Pietersburg Hospital serves about 5.5 million people most of whom are from rural communities within the province. All patients in public sector that require tertiary care in the province including medical oncology services are referred to Pietersburg Hospital for further management. It is the only centre that offers medical oncology services for public sector patients.



Limpopo Hospitals map (Limpopo Department of Health, 2016)

3.3 Study Population

Study population is a group of people, cases or objects defined as under study (Polgar & Thomas, 2020). In this study, the population included all adult patients seen at the medical oncology clinic between January 2016 and December 2018.

3.4 Study Sampling

Study sample is a subset of the population of participants (Struwig, 2013).
The study was a census one that included all the patients that met the specified criteria over the specified interval. Studies that involve an entire population or a group are called census study (Polgar & Thomas, 2020)

3.4.1 Sample size

Sample size is a group of cases selected from a population (Polgar & Thomas, 2020). All the participants that met the specified criteria over the specified interval

were included in the study. The study was a sample of all adult patients with histological diagnosis of KS. The estimated size of the sample was 100 patients over a 3-year period.

3.4.2 Inclusion criteria

- All patients with histological diagnosis of Kaposi sarcoma seen at the adult medical oncology clinic at Pietersburg Hospital.

3.4.3 Exclusion criteria

- All Patients with no histological confirmation of KS were excluded.
- Children below the age of 12 years were also excluded mainly because the study was conducted at an adult medical oncology unit of which the cut off age used at the unit is 12 years.

3.5 Data Collection

Data was collected from the medical oncology outpatient department. The data was retrieved from the electronic data base which was maintained until 2018 and where the information was not available on data base, patient files were used. Clinic register was used to retrieve the files and to confirm total number of patients seen. Data information tool (see annexure 1) was used to collect information from the data base and patients' files and medical records were reviewed. A specific number was allocated for each patient, hospital file number and names of patients were not used in this study.

Data which was collected included the sociodemographic details which included age, gender, race, occupation and where the patient is from, urban or rural community. The Clinical parameters included HIV status, baseline CD4 count and viral load, smoking history, BMI, and ART duration on treatment. The comorbidities of interest included Tuberculosis, Diabetes and Hypertension. History of organ transplant and the site of skin lesions were documented. Due to the retrospective nature of the study some of the required data were missing which had put some limitations to the study. The histological reports were reviewed for the pathological subtype of KS and the ECOG performance status

at presentation was extrapolated. Other parameters which were extrapolated included baseline haemoglobin, albumin and KS treatment administered.

3.6 Data analysis

Data was captured using Microsoft excel by Microsoft. The captured data was analysed using Statistical Package for the Social Sciences (SSPS) version 25. Descriptive statistics was used to describe the demographic and clinical characteristics of the data collected. Continuous variables were expressed by mean, median, standard deviation, interquartile range, minimum and maximum values. Categorical variables were expressed by frequency counts and percentages. The prevalence of KS was calculated as percentage based on number of patients seen with KS over 3 years period divided by the number of new patients with other cancers seen at the medical oncology over that period. The clinicopathological subtypes of KS prevalence was calculated as a percentage of subtype divided by total number of cases with KS over specified period. The prevalence of KS in HIV negative patients was calculated as a percentage of the number of patients with KS divided by the number of new patients with other cancers seen at the medical oncology over the specified period.

3.7 Reliability and Validity

3.7.1 Reliability

Reliability refers to the extent to which a test or measurement result is reproducible (Polgar & Thomas, 2020). The data was extracted from patient records which are legally binding documents and reliable source of information.

3.7.2 Validity

Validity refers to the extent to which a test measures what it is intended to measure (Polgar & Thomas, 2020). Content Validity is the extent to which a test or assessment matches the real requirements of the situation (Polgar & Thomas, 2020).The study used secondary data, and validity will be that of original observations. To ensure content validity of the study, comprehensive literature

review was done, and the data collection tool was reviewed with the Biostatistician and the supervisors to assess its relevance in answering the research questions.

3.8 Bias

Bias is defined as any source of influence that may distort the data obtained or conclusions drawn (Leedy & Ormrod, 2015).

3.8.1 Selection bias

Selection bias comes from any error in selecting the study participants or factors affecting the study participation. This was avoided through including all patients with KS, but there is a possibility of point of care bias with some patients with KS not referred to oncology or KS being referred than other types of cancers.

3.8.2 Information bias

There was a possibility of information bias in this study due to the retrospective nature of the study. Some of the required data for the study were missing due to poor documentation.

3.8.3 Confounding bias

Confounding bias was avoided by including other comorbid conditions that may influence outcome such as Tuberculosis, Hypertension and Diabetes Mellitus.

3.9 Ethical considerations

3.9.1 Approval

The proposal was presented to the Department of Internal Medicine for quality assurance. It was then sent for approval to the school Research Committee (SREC) followed by Faculty of Higher degree Committee for approval and the Turfloop Research Ethics Committee (TREC) before the study commenced. (TREC/327/22:PG)

3.9.2 Permissions

Permission to access the patient records was requested from Pietersburg Hospital and Limpopo provincial Department of Health before the study commenced. Waiver of Informed consent was requested as the risk for harm was minimal and the study is a secondary review of anonymous medical records.

3.9.3 Privacy and confidentiality

Confidentiality is the agreement to limit access to a subject's information (Ethicist, 2015: 100–102). Confidentiality was maintained throughout the study and the identity of the participants was protected. Hospital numbers were only used to access patient files. To ensure confidentiality each patient was allocated a unique number which was used for data analysis and the patient data was handled by researcher only to ensure confidentiality. No third party was given access to patient records. The data was recorded and stored on password protected google drive account and will be for 10 years after the research final publication.

3.9.4 Potential Harms

There were no potential harms foreseen as this is a retrospective study and the risk is low although harm can be done to the patients whose records are reviewed due to disclosure or inappropriate reporting of the information.

3.9.5 Conclusion

This chapter discussed the methodology that was followed in order to answer the research questions. It also focused on the ethical considerations which included privacy and confidentiality. The chapter that follows will discuss the results obtained from the data collection and interpretation of data.

Chapter 4: Presentation and interpretation of results

Data comprised of categorical and numerical variables. The numerical variables that were normally or abnormally distributed were represented by mean and standard deviation, or by median and interquartile ranges, respectively. Unpaired t-test was used to compare the independent groups. The significance difference of p-value of < 0.05 was considered as statistically significant. The association of variables was conducted using the Chi-square test and the association of variable of p-value of < 0.05 was considered as statistically significant.

Table 4.1: National Health Laboratory Service (NHLS) for normal reference ranges for biochemical variables

No	Variable	Normal reference range
1.	Albumin	35 – 54 g/L
2.	Haemoglobin	13 – 17 g/dL
3.	Urea	2.5 – 10.7 mmol/L
4.	Creatinine – Female	52.2 – 91.9 µmol/L
5.	Creatinine – Male	65.4 – 119.3 µmol/L

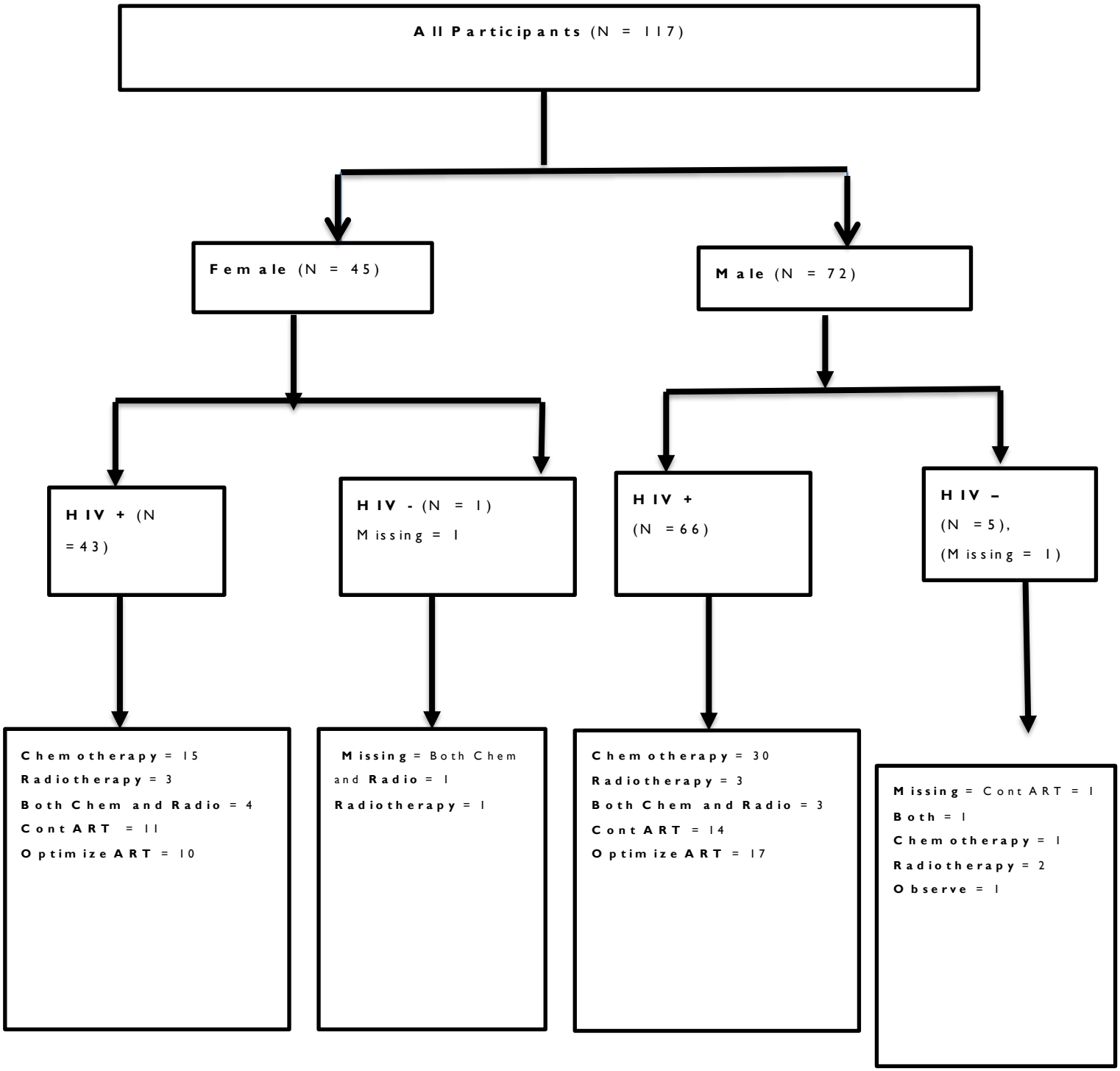


Figure 1: Flow chart of study participants

The study patients were categorised into their respective gender groups, wherein females were smaller in numbers as compared to their male counterparts. Further categorisation in HIV status have shown that HIV + patients were more on chemotherapy as compared to their HIV - groups.

Table 4.1 Age, anthropometric measurements, ART duration, biochemical characteristics of the study population

Variable	All Participants	Female (N = 45)	Male (N = 72)	p-value
Age (Years)	41.6 ± 10.9	41.5 ± 12.9	41.6 ± 9.63	0.51
Height (M)	1.65 ± 0.09	1.62 ± 0.09	1.67 ± 0.09	0.96
Weight (kg)	64.3 ± 9.3	64.3 ± 8.56	64.3± 9.8	0.48
BMI (kg/m2)	24.1± 3.4	25.03 ± 3.44	23.5 ± 3.29	**0.04***
ART Duration in Months Median (Interquartile range)	19.3 (1 – 180)	19.5 (1 – 144)	19.1 (1 – 180)	0.47
CD4 count *Median (Interquartile range)*	293 (3 – 1005)	305 (9 – 1005)	284 (3 – 795)	0.26
Viral load *Median (Interquartile range)*	551 (31 – 948000)	1598 (31 – 948000)	267 (33 – 527000)	0.28
Albumin (g/L)	32.3 ± 7.3	31.6 ± 7.4	32.8 ± 7.3	0.79
Haemoglobin (g/dL)	11.2 ± 2.14	10.69 ± 1.77	11.49 ± 2.29	0.98
Urea (mmol/L)	6.37 ± 8.40	5.11 ± 1.58	7.14 ± 10.54	0.94
Creatinine (µmol/L)	77.7 ± 23.2	74.8 ± 18.3	79.5 ± 25.60	0.87
Urea/Creatinine ratio	0.0 8± 0.101	0.07 ± 0.02	0.09 ± 0.13	0.84

***The significant p-value is illustrated in bold**

The average age of study patients were approximately 40 years, with majority of patients with normal BMI (kg/m^2). However, the female patients had statistically increased BMI as compared to male patient counterparts (**p-value = 0.004**). There was not statistically significance in biochemical markers between female and male patients. Albumin status of the majority of the patient population was below the reference range.

Table 4.2: Biochemical characteristics of the study population as categorised by albumin status.

	Low Albumin (< 35 g/L)			**Normal Albumin (35 – 54 g/L)**		
Variable	Female	Male	P-value	Female	Male	P-value
Haemoglobin (g/dL)	9.9 ± 1.4 (n = 20)	10.8 ± 2.3 (n = 36)	0.94	11.3 ± 1.8 (n = 23)	12.2 ± 2.1 (n = 33)	0.94
Urea (mmol/L)	4.9 ± 1.7 (n = 20)	7.5 ± 9.1 (n = 36)	0.89	5.2 ± 1.5 (n = 23)	6.9 ± 1.2 (n = 33)	0.74
Creatinine (µmol/L)	74.9 ± 21.9 (n = 20)	80.5 ± 29.9 (n = 36)	0.76	74.8 ± 14.9 (n = 23)	75.8 ± 13.2 (n = 33)	0.60
U/Cr	0.07 ± 0.02 (n = 19)	0.08 ± 0.08 (n = 36)	0.84	0.08 ± 0.02 (n = 21)	0.09 ± 0.16 (n = 33)	0.68
CD4 count ***Median (Interquartile range)***	228 (19 – 922) (n = 20)	189 (3 – 577) (n = 36)	0.14	354(9 – 1005) (n = 25)	362 (21 – 795) (n = 36)	0.05
Viral load ***Median (Interquartile range)***	1710 (31 – 350029) (n = 13)	490 (37 – 236000) (n = 24)	0.29	(36 – 948000) (n = 10)	204 (33 – 527000) (n = 22)	0.31

Irrespective of whether the albumin was low or normal, there was no statistically significant difference in biochemical variables and viral load, among gender groups.

Table 4.3: Biochemical characteristics of the study population as categorised by HIV status.

	HIV +			**HIV -**		
Variable	Female	Male	P-value	Female	Male	P-value
Albumin (g/L)	31.3 ± 7.5 (n = 41)	32.5 ± 7.5 (n = 63)	0.79	38.0 (n = 1)	36.2 ± 2.8 (n = 5)	(N/A)
Haemoglobin (g/dL)	10.6 ± 1.72 (n = 43)	11.3 ± 2.23 (n = 66)	0.96	14.3 (n = 1)	13.6 ± 2.6 (n = 5)	(N/A)
Creatinine (µmol/L)	74.3 ± 18.5 (n = 43)	79.5 ± 26.7 (n = 66)	0.86	90.0 (n = 1)	81.8 ± 4.8 (n = 5)	(N/A)
Urea (mmol/L)	5.2 ± 1.6 (n = 42)	7.4 ± 1.4 (n = 66)	0.390	5.0 (n = 1)	4.6 ± 1.1 (n = 5)	(N/A)
U/Cr	0.07 ± 0.2 (n = 40)	0.09 ± 0.1 (n = 66)	0.79	0.06 (n = 1)	0.06 ± 0.01 (n = 5)	(N/A)
CD4 count ***Median (Interquartile range)***	305 (9 – 1005) (n = 41)	270 (3 – 700) (n = 64)	0.13	(n = 0)	685 (577 – 795) (n = 2)	
Viral load ***Median (Interquartile range)***	1598 (31 – 948000) (n = 23)	267 (33 – 527000) (n = 46)	0.27	**No virus present**	**No virus present**	

The albumin levels in HIV+ individuals were below the normal reference as compared to those who were HIV- (**Refer to Table 2.1**). However, there was no statistical difference in biochemical markers in HIV gender groups. Due to smaller sample size in patients who were HIV-, the statistical comparison was impossible.

Table 4.4: Socio-demographic characteristic in a study population

Variable	All Participants	Female	Male	P-value, Chi-square
Gender, N (%)	117	45 (38)	72 (62)	
Rural/Urban Status				
Rural, N (%)	112	42 (38)	70 (63)	0.28
Urban, N (%)	5	3 (60)	2 (40)	
Limpopo Districts				
Capricorn, N (%)	40	15 (38)	25 (62)	0.52
Mopani, N (%)	19	10 (53)	9 (47)	
Waterberg, N (%)	19	8 (42)	11 (58)	
Vhembe, N (%)	19	7 (37)	12 (63)	
Sekhukhune, N (%)	20	5 (25)	15 (75)	
Smoking Status				
Yes, N (%)	43	2 (5)	41(95)	**0.0001**
No, N (%)	74	43 (58)	31 (42)	

There was no statistically significant association in rural/urban patients and Limpopo districts ($p > 0.05$) except in cigarette smoking status (**p-value = 0.0001**).

Table 4.5: Clinical characteristics of the study population

HIV Status				
Positive, N (%)	109	43 (39)	66 (61)	0.26
Negative, N (%)	6	1 (7)	5 (83)	
Missing, N (%)	2			
CD 4 Status				
≤ 200, N (%)	40	13 (33)	27 (77)	0.23
> 200, N (%)	67	28 (42)	39 (58)	
Comorbidity				
No, N (%)	100	39 (39)	61 (61)	**0.02**
Hypertension, N (%)	5	4 (80)	1 (20)	
TB Hypertension, N (%)	1	1 (100)	0 (0)	
TB	11	1 (9)	10 (91)	
ART at Diagnosis				
HIV - (%)	6	1 (2)	5 (98)	**0.04**
No ART, N (%)	54	40 (70)	17 (30)	
Yes ART, N (%)	57	27 (50)	27 (50)	
KS Subtype				
Epidemic, N (%)	110	44 (40)	66 (60)	0.17
Endemic, N (%)	7	1 (14)	6 (86)	
Lymph Oedema				
Yes, N (%)	98	34 (35)	64 (65)	0.12
No, N (%)	17	9 (53)	8 (47)	
Therapy status				
Both Chem/radiotherapy, N (%)	9	5 (56)	4 (44)	0.74
Chemotherapy, N (%)	46	15 (33)	31 (67)	
Radiotherapy, N (%)	9	4 (44)	5 (56)	
Continue ART, N (%)	25	11 (44)	14 (56)	

Observe, N (%)	1	0 (0)	1 (100)	
Optimise ART, N (%)	27	10 (37)	17 (63)	

HIV status, CD4 status, KS subtype status, lympho oedema, and therapy status asssociation was not statistically significant. However, there was significant association in ART at Dx and cormodities among gender groups.

Table 4.6: Prevalence of clinical conditions in a study population

Variable	**Overall Prevalence**	**Female**	**Male**
Kaposi Sarcoma	$\frac{117}{3151}$ X 100% = 4%	$\frac{45}{117}$ X 100% = 38%	$\frac{72}{117}$ X 100% = 62%
Kaposi Sarcoma (Epidemic)	$\frac{110}{117}$ X 100% = 94%	$\frac{44}{110}$ X 100% = 40%	$\frac{66}{110}$ X 100% = 60%
Kaposi Sarcoma (Endemic)	$\frac{7}{117}$ X 100% = 6%	$\frac{1}{7}$ X 100% = 14%	$\frac{6}{7}$ X 100% = 86%
HIV +	$\frac{109}{117}$ X 100% = 93%	$\frac{43}{109}$ X 100% = 39%	$\frac{66}{109}$ X 100% = 61%
HIV –	$\frac{6}{117}$ X 100% = 7%	$\frac{1}{6}$ X 100% = 2%	$\frac{5}{6}$ X 100% = 98%

The overall prevalence of Kaposi Sarcoma was 4%. Patients with Kaposi Sarcoma (Epidemic and endemic) were 94% and 6% respectively. Majority (93%) of the patients were HIV+ with small percentages with HIV- (7%). Male patients had increased % of Kaposi Sarcoma, Kaposi Sarcoma (Epidemic), Kaposi Sarcoma (Endemic), HIV+ as compared to the female patients. The patients with HIV- were small and one patient had indeterminate HIV results twice.

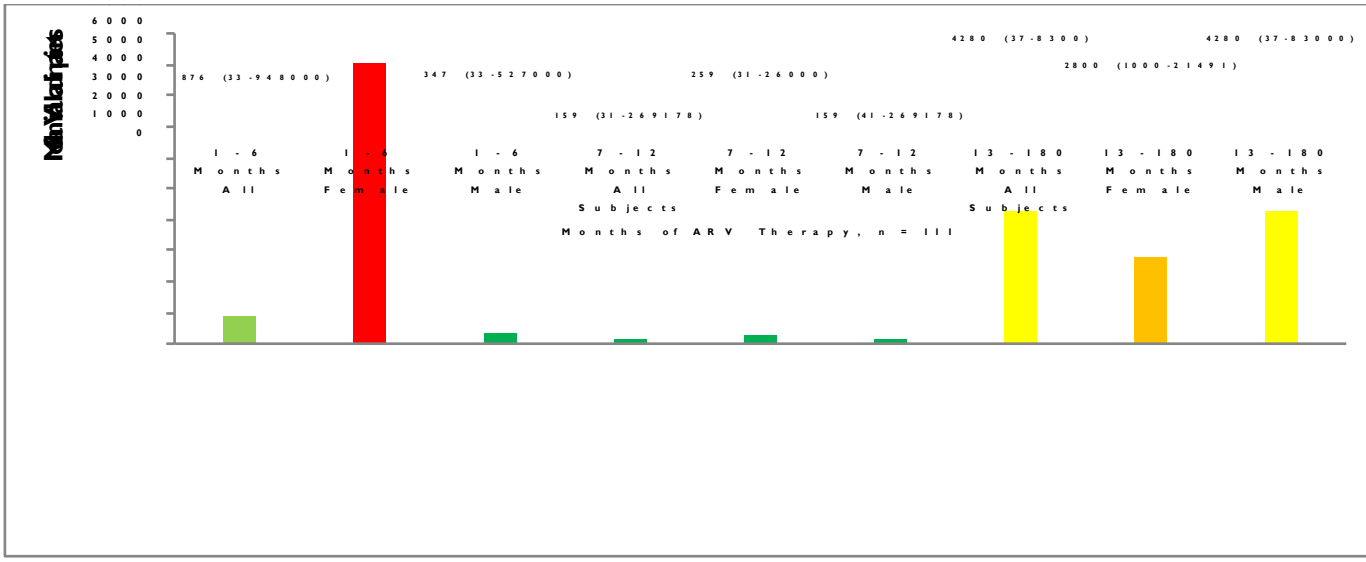


Figure 2: Viral load in patients with respective to months of ARV therapy

The female patients in 1 – 6 months showed increment in median viral load as compared to their male counter parts. The 7 – 12 months had low viral load as compared to 1 – 6 months and 13 – 180 months. In overall, there was lack of viral suppression in across the months in majority of the patients.

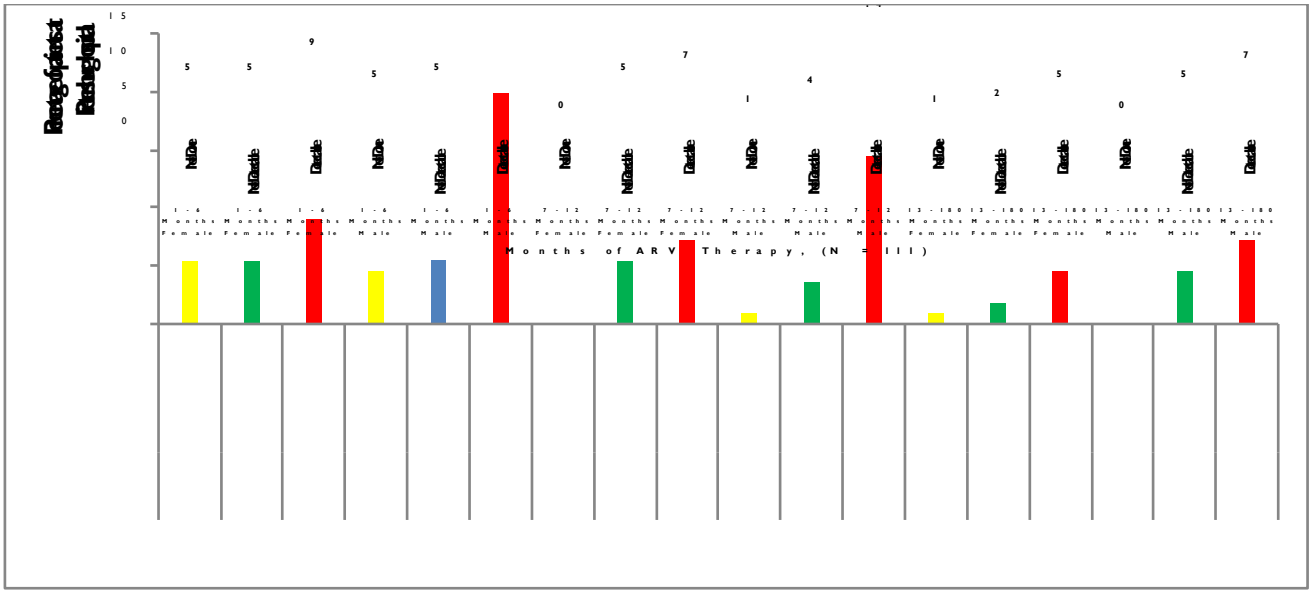


Figure 3: Viral load profile in the patient population

The figure shows that approximately 14 to 20% of the patients had detectable virus in their blood stream, and approximately 5% of the patients had no detectable virus. Some patients had missing, or their blood was not tested for HIV, which compared of approximately 5% of less.

Table 4.7 KS skin lesions distribution

Variable	Number of Lesions	Percentage (%)
Head	**29**	10
Trunk	**31**	11
LL	**106**	36
UL	**30**	10
Oral	**16**	5
Groin	**72**	25
Disseminated	**7**	2
Total	**291**	100

Conclusion

This chapter presented the data obtained which included prevalence table of KS in gender groups, the viral load profile, and the clinical characteristics of the studied population. The chapter that follows will discuss the findings of the study in comparison with other studies, Its limitations, and recommendations for the future studies.

Chapter 5

5.1 Discussion

This chapter will discuss the study results presented in chapter 4 with reference to the prevalence of KS, Clinical presentation, Subtypes of KS, HIV status, CD 4 count, Viral load, Biochemistry and Therapy in comparison with other studies. This will be followed by limitations of the study and Conclusion.

5.2 Summary of results

The overall prevalence of Kaposi Sarcoma at Pietersburg Hospital was 4%. Despite all patients having either form of Kaposi Sarcoma (epidemic or endemic), only a few patients were HIV- (7%). There were no patients seen with Classical KS and Organ transplant associated KS over the study period. There was no statistically significant difference in blood biochemistry in HIV+ patients with respect to gender groups, and when the groups were categorised in nutrition (albumin status), there was no biochemical significant difference as well. The study patients were on anti-retroviral therapy, but unfortunately, there was reasonable presence of viral load in both gender groups. (Fig 3)

5.3 Prevalence of KS

In Pietersburg Hospital, the prevalence of KS was 4% overall, with 62% of male patients and 38% of female patients. It should be noted that this prevalence study was done amongst patients attending oncology clinic which may be different compared to HIV clinic. This is a little lower than the prevalence of 4.6% (51) out of 1100 HIV-positive patients recorded at the KCMC hospital in Northern Tanzania (Semango *et al.*, 2018, no. 1). HIV prevention initiatives and adequate ART coverage have led to a noticeably lower incidence of HIV KS and a better prognosis for patients with the condition in developed countries. In sub-Saharan Africa, ART roll out has lagged, but clinical studies have shown promising results in terms of KS incidence decline and patient prognosis (Motlhale, Sitas & Bradshaw *et al.*, 2022a: 102167). In their study, Semango et al. discovered that

women had higher odds of being diagnosed with KS than males did (OR 0.42, p-value=0.009), but only 38% of the participants in this study were female. According to a retrospective cross-sectional study conducted in South Africa, the male to female ratio at Chris Hani Baragwanath Academic Hospital was 1.2:1. (Mohanlal & Pather, 2015: 375–378).

Chu et al. (2010) found a prevalence of 3.4% in an observational cohort study of HIV-infected individuals conducted in South Africa, which differ slightly from this study (Chu, Mahlangeni, Swannet, Ford, Boulle & Cutsem, 2010: 1–5).
Higher KS prevalence of 10-12% and 12.3% was observed in other studies conducted in Mediterranean countries and the east African region (Semango *et al.*, 2018, no. 1). In this study, 62% of men were diagnosed with KS, compared to 38% of women, which is consistent with previous research on the disease's incidence in underdeveloped nations. Although this does not include patients seen in the private sector, KS was identified in the population of African descent during the study period. In terms of the association, there were no statistical variations amongst Limpopo districts.

5.4 Clinical Presentation

The clinical presentation did not differ from that reported from other studies. The majority of patients had cutaneous lesions with lesions on both the upper (30%) and lower limbs (36%), Head (10%), Oral (5%) some in the trunk (11%), groin (25%) and 2% had disseminated disease. Inguinal lymphadenopathy was quite common and Lymph oedema was common in both gender groups, 65% (64) in males vs 35 % (34) in females. Some patients had visceral involvement with disseminated skin lesions (see table 4.7).

5.5 HIV status and subtypes of Kaposi sarcoma

AIDS associated KS was the mostpredominant subtype at 94% which reflect high burden of HIV in the sub-Saharan Africa. In their retrospective cross sectional study of 1275 cases Motlhale et al found that the majority of their patients were HIV positive ,97% vs 15.7% in 10,309 controls (Motlhale, Sitas & Bradshaw *et al.*, 2022: 102158). AIDS associated Kaposi had increased dramatically since the

onset of AIDS epidemic. According to Mohanlal et al. (2015), of the 66 200 cases of KS worldwide 58800 is said to have occurred in the Sub-Saharan Africa (Mohanlal & Pather, 2015: 375–378). AIDS associated KS can also occur due to KS immune reconstitution syndrome (KS-IRIS). This is due to clinical worsening of existing KS or sometimes unmasking of previously undiagnosed KS after ART initiation. KS IRIS is said to occur from less than 10% to almost 40% depending on definition applied (Cesarman *et al.*, 2019: 9)

African or Endemic KS accounted for 6% (7) of the patients diagnosed with KS over the study period. Other South Africa studies have also shown lower proportions of Pediatrics and endemic KS ,1.4 and 1.3% respectively out of 901 biopsy proven cases (Mohanlal & Pather, 2015: 375–378).

There were no patients diagnosed with Organ Transplant associated KS probably due to lower number of transplanted patients that are managed within our center. All the patients were of African descent and there were no patients that meet criteria for Classical KS that was seen over the study period.

5.6.1 CD 4 Count, Viral load, and Comorbidities

The CD 4 count appears to be a significant risk factor for the onset of KS in patients with AIDS-related KS. There were 40 patients out of the 117 evaluated in this study that had CD 4 counts below 200, and 77% of them were men. Less than half of cases with CD 4 counts below 200 and 29% of those with viral loads below 500 copies per ml were found in a study of 466 individuals with AIDS-associated KS between 2007 and 2011. (Shah, 2021). The median CD 4 count was 128 cells/microL in a retrospective cross-sectional analysis by Mohanlal and Pather (2015) of 901 diagnosed patients of KS (Mohanlal & Pather, 2015: 375–378). In contrast to patients with CD 4 counts above 200 cell/uL, Semango et al. discovered that many HIV positive patients with CD 4 counts of less than or equal to 200 cells per microlitre had a higher likelihood of being diagnosed with KS (OR 2.07, p0.137) (Semango *et al.,* 2018, no. 1). According to other investigations, a baseline CD4 count of less than 100 cells/microL was associated to death on a univariate analysis, however multivariate analysis did not support this (Chu, Mahlangeni, Swannet, Ford, Boulle & Cutsem, 2010: 1–5). This is further

supported by the KAART trial, 54% of participants had a CD 4 count below 150 cells/uL, and 58% had a CD 4 count below 200 cells/uL.

Despite the fact that the majority of the study subjects were on ART, almost 50% were not at the time of KS diagnosis and those who were on ART were not virologically suppressed, which is concerning. Patients who used ART for one to six months had inadequate virological suppression and a substantial increase in the median viral load in female patients. The causes of inadequate virological suppression are unclear; however, they may be related to late HIV diagnosis and subpar ART adherence given that a sizable portion of patients were not on ART at the time of KS diagnosis. There aren't any studies available right now that could help with some of these questions that looked at adherence to ART.

The most prevalent comorbidity of interest was tuberculosis, which affected 9% of patients and 91% of them were men. This was presumably brought on by the delayed HIV diagnosis and ART start-up. In the KAART trial, 36% of participants had TB, making it the most prevalent comorbidity (Mosam *et al.*, 2012: 150–157). To lower TB-related morbidity and death in individuals with HIV KS, active TB screening is advised. It is unclear why other comorbidities like hypertension were less prevalent in a community that was primarily black.

5.6.2 Other risk factors associated with KS

Seroepidemiological studies have reported high rates of KSHV/HHV 8 in Sub Saharan Africa and up to 40% of the of the general adult population have antibodies of KSHV/HHV 8 detected. In South Africa, seroprevalence of KSHV have been found to be 32% among blood donors and patients with other cancers with prevalence increasing to 83% among KS patients (Sissolak & Mayaud, 2005: 981–992).

Apart from lower CD 4 count, the study did not find other risk factors associated with KS. The majority of male patients ,95% who were diagnosed with KS were smokers compared with 42% non-smokers. In further analysis there was no positive correlation between smoking status and development of KS. In their study, Semango et al. (2018) found that HIV patients who were smokers were not at risk to suffer from KS as compared to non-smokers (Semango *et al.*, 2018, no.

1). Other studies found no evidence of interplay of smoking and alcohol consumption by sex although they suggest that this might provide explanation for the KS sex differences as both exposures are predominant in men (Motlhale *et al.*, 2022: 102158). The impact of these behaviours on HIV and KSHV viral loads warrants further investigation.

5.6.3 Blood Biochemistry

In this study there were no statistical differences in biochemical variables among gender groups irrespective of the albumin status at presentation. The albumin levels were noted to be lower than normal in HIV positive patients. This is probably due to chronicity of the disease and poor nutritional status as the majority of this patients are from rural poor communities and relies on social grants for survival. The biochemical abnormalities reported in the literature seems to be mainly due to adverse event of ART drugs and chemotherapy itself with elevated Creatinine, Hyponatremia and Hepatotoxicity being common.

5.6.4 Therapy for KS

ART has been demonstrated in various trials to enhance clinical outcomes since some lesions recover and do not require chemotherapy or radiotherapy. The aim of AIDS-KS treatment should be to control the HIV. In this study 25 of the 117 patients ,56% of them men responded well to ART and did not require chemotherapy or radiotherapy. It has been demonstrated that HAART regimens, either alone or in conjunction with other anti-neoplastic drugs, provide both immediate and long-term advantages in the treatment and prevention of KS (Sissolak & Mayaud, 2005: 981–992). This was also supported by a randomised controlled, wherein 39% of patients with KS, reacted favourably to ART alone demonstrating the effectiveness of ART in treating HIV-KS in Sub-Saharan Africa (Mosam *et al.*, 2012: 150–157).

It is concerning that 23% of the patients participants could not begin either medication because their ART was not well optimized. This can be the result of a delayed HIV-KS diagnosis, poor ART adherence, or a delayed start to life-

saving ART. The majority of individuals had an ECOG performance status of 1, hence there were no gender differences in the presentation stage.

Clinical outcome studies have demonstrated that it is feasible and safe to treat HIV-KS in sub-Saharan Africa with standard of care chemotherapy regimens from industrialized countries when combined with ART (Herce *et al.*, 2015: 19929-n/a). In this study, 8% of the patients had both chemotherapy and radiotherapy in addition to ART, while 39% of the patients received the chemotherapy regimen of Adriamycin, Bleomycin, and Vincristine (ABV regimen). Patients who did not respond to the first line were switched to the second line, which included Paclitaxel and ART. Chemotherapy has been proven in the KAART research to enhance KS-specific response while ART manages HIV. In some parts of Sub-Saharan Africa, there is poor availability to less toxic chemotherapeutic medications, and in some areas, ART is still difficult to obtain.

Only 9 of the 117 patients in this study received radiotherapy in addition to ART (P value=0.74) with no differences in gender distribution. The majority of treatment for people with oral KS is radiotherapy, which has been proven to be beneficial in cases of localised disease where up to 20–70% of patients experience complete remission (Sissolak & Mayaud, 2005: 981– 992).

5.7 Limitations of the study

The sample population were only from Pietersburg hospital. It does not include patients seen in private sector and some patients may have not visited healthcare due to lack of funds or may have opted for alternative treatment (Traditional healing or faith religious healing); hence the present study cannot be a representative of the entire population of Limpopo province. The retrospective nature of the study design cannot allow the principal investigator to improve or make any changes to the data collected. No data on ARV therapy and compliance in the present patient population, hence it was a challenge to deduce whether the patients were complying with the treatment or not.

5.8 Conclusion

This study emphasizes the significance and function of HAART in HIV KS patients, late diagnosis of HIV KS, and the fact that the majority of patients were not taking ART at the time of diagnosis. Another crucial issue that must be addressed is patient adherence to ART, as many patients did not achieve virological suppression. Despite the fact that chemotherapy increases patient lifespan, some of the more modern medications, such as Paclitaxel, are still out of reach for several underdeveloped African nations with a high prevalence of KS. Although there are still KS instances in the region of Limpopo, the prevalence is the same as in other South African studies that demonstrated the beneficial effects of ART on KS prevalence. Adherence to ART remains a challenge which needs to be addressed by authorities and health education as it has an impact on KS, other opportunistic infections, and HIV transmission.

5.9 Recommendations

Further studies are warranted which will investigate the outcomes of this patients treated with ART alone, ART and chemotherapy and ART and Radiotherapy. Almost 50% of the patients were not virologically suppressed at the time of diagnosis of KS, hence future studies need to also look at patient's adherence to ART and how much of those on ART are achieving virological suppression.

6.References

1. Azam, F., Latif, M., Farooq, A., Tirmazy, S., Alshahrani, S., Bashir, S. And Bukhari, N., 2019. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. *Case Reports in Oncology*, **12**(3), pp. 728-736.
2. UNAIDS DATA, 2020.
3. Bohlius, J., Valeri, F., Maskew, M., Prozesky, H., Garone, D., Sengayi, M., Fox, M.P., Davies, M. And Egger, M., 2014. Kaposi's Sarcoma in HIV-infected patients in South Africa: Multicohort study in the antiretroviral therapy era. *International Journal of Cancer,* **135**(11), pp. 2644-2652.
4. Cesarman, E., Damania, B., Krown, S.E., Martin, J., Bower, M. And Whitby, D., 2019. Kaposi sarcoma. Nature reviews. *Disease primers,* **5**(1), pp. 9.
5. Chemotherapy | definition of chemotherapy by medical dictionary. Available: https://medical-dictionary.thefreedictionary.com/chemotherapy.
6. Chu, K.M., Mahlangeni, G., Swannet, S., Ford, N.P., Boulle, A. And Cutsem, G.V., 2010. AIDS-associated Kaposi's sarcoma is linked to advanced disease and high mortality in a primary care HIV programme in South Africa. J*ournal of the International AIDS Society* 2010 13:1, **13**(1), pp. 1-5.
7. Chu, K.M., Mahlangeni, G., Swannet, S., Ford, N.P., Boulle, A. And Van Cutsem, G., 2010. AIDS-associated Kaposi's sarcoma is linked to advanced disease and high mortality in a primary care HIV programme in South Africa. Journal of the International AIDS Society, **13**(1), pp. 23.
8. Ethicist, P., 2015. Simplifying the Complexity of Confidentiality in Research. *Journal of Empirical Research on Human Research Ethics*, **10**(1), pp. 100-102.
9. Groopman, A., Shah, 2021-last update, AIDS-related Kaposi sarcoma: Staging and treatment – Up To Date. Available: https://www.uptodate.com/contents/aids-related-kaposi-sarcoma-staging-and-treatment?source=history_widget.
10. Herce, M.E., Kalanga, N., Wroe, E.B., Keck, J.W., Chingoli, F., Tengatenga, L., Gopal, S., Phiri, A., Mailosi, B., Bazile, J., Beste, J.A., Elmore, S.N., Crocker, J.T. And Rigodon, J., 2015. 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. *Journal of the International AIDS Society*, **18**(1), pp. 19929-n/a.
11. Krown, S.E., Moser, C.B., Macphail, P., Matining, R.M., Godfrey, C., Caruso, S.R., Hosseinipour, M.C., Samaneka, W., Nyirenda, M., Busakhala, N.W., Okuku, F.M., Kosgei, J., Hoagland, B., Mwelase, N., Oliver, V.O., Burger, H., Mngqibisa, R., Nokta, M., Campbell, T.B., Borok, M.Z. And A5263/Amc066 Protocol Team, 2020. Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: a three-arm, open-label, randomised, non-inferiority trial. *Lancet* (London, England), **395**(10231), pp. 1195-1207.
12. Krown, S.E., Moser, C.B., Macphail, P., Matining, R.M., Godfrey, C., Caruso, S.R., Hosseinipour, M.C., Samaneka, W., Nyirenda, M., Busakhala, N.W., Okuku, F.M., Kosgei, J., Hoagland, B., Mwelase, N.,

Oliver, V.O., Burger, H., Mngqibisa, R., Nokta, M., Campbell, T.B., Borok, M.Z., Moses, A., Kanyama, C., Mukwekwerere, P., Gudza, I., Chauwa, F., Ulaya, G., Kutto, I., Cheruiyot, P., Okello, C., Nakaganda, A., Koskei, G., Keter, W., Netto, J., Baião, T., Govender, I., O'connell-Maritz, J., Cain, K., Okanda, J., Cornelissen, L., Van Schalkwyk, M., Sikhosana, R., Ngcobo, M., Lee, J.Y., Harrison, T., Wachsman, W., Shin, K., Evans, S., Rothenberg, J., Hosey, L., Mccarthy, S., Martinez-Maza, O., Rinaldo, C., Dittmer, D., Rinaldo, C., Fletcher, C., Rudek, M., Asmelash, A., Hughes, V., Schouten, J., Shugarts, D., Kujinga, T., Zadzilka, A., Kerui, F., Robertson, D., Rooney, J., Sewal, K. And Gottshall, B., 2020. Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: a three-arm, open-label, randomised, non-inferiority trial. *The Lancet*, **395**(10231), pp. 1195-1207.

13. Leedy, P.D. And Ormrod, J.E., 2015. *Practical research: planning and design.* Pearson Education.
14. Majaya, E., Girdler-Brown, B.V., Muchengeti, M. And Singh, E., 2021. The impact of the South African antiretroviral treatment programme on the age-standardised incidence rate of Kaposi sarcoma, 1999–2016: An interrupted time series analysis. *International journal of infectious diseases,* **102**, pp. 20-27.
15. Mohanlal, R.D. And Pather, S., 2015. Kaposi's sarcoma, a South African perspective: Demographic and pathological features. *South African Medical Journal* ,**105**(5), pp. 375-378.
16. Mosam, A., Aboobaker, J. And Shaik, F., 2010. Kaposi's sarcoma in sub-Saharan Africa: a current perspective. *Current opinion in infectious diseases,* **23**(2), pp. 119-123.
17. Mosam, A., Shaik, F., Uldrick, T.S., Esterhuizen, T., Friedland, G.H., Scadden, D.T., Aboobaker, J. And Coovadia, H.M., 2012. *A randomized controlled trial of HAART versus HAART and chemotherapy in therapy-naïve patients with HIV-associated Kaposi sarcoma in South Africa.*
18. Motlhale, M., Sitas, F., Bradshaw, D., Chen, W.C., Singini, M.G., De Villiers, C.B., Lewis, C.M., Muchengeti, M., Waterboer, T., Mathew, C.G., Newton, R. And Singh, E., 2022a. Epidemiology of Kaposi's sarcoma in sub-Saharan Africa. *Cancer epidemiology*, **78**, pp. 102167.
19. Motlhale, M., Sitas, F., Bradshaw, D., Chen, W.C., Singini, M.G., De Villiers, C.B., Lewis, C.M., Muchengeti, M., Waterboer, T., Mathew, C.G., Newton, R. And Singh, E., 2022b. Lifestyle factors associated with sex differences in Kaposi sarcoma incidence among adult black South Africans: A case-control study. *Cancer epidemiology*, **78**, pp. 102158.
20. Polgar, S. And Thomas, S.A., 2020. *Introduction to research in the health sciences.* Seventh edition. Edinburgh; London; New York ; Oxford ; Philadelphia ; St. Louis ; Sydney: Elsevier.
21. Presentation of The Limpopo Department of Health, 2016. Health Market Inquiry.
22. Radu, O. and Pantanowitz, L., 2013. Kaposi Sarcoma. *Archives of Pathology & Laboratory Medicine* (1976), **137**(2), pp. 289-294.
23. Radiotherapy | definition of radiotherapy by medical dictionary. Available: https://medical-dictionary.thefreedictionary.com/radiotherapy.

24. Semango, G.P., Charles, R.M., Swai, C.I., Mremi, A., Amsi, P., Sonda, T., Shao, E.R., Mavura, D.R., Joosten, L.A.B., Sauli, E. And Nyindo, M., 2018. Prevalence and associated risk factors for Kaposi's sarcoma among HIV-positive patients in a referral hospital in Northern Tanzania: A retrospective hospital-based study. *BMC Cancer*, **18**(1).

25. Sengayi, M.M., Kielkowski, D., Egger, M., Dreosti, L. And Bohlius, J., 2017. Survival of patients with Kaposi's sarcoma in the South African antiretroviral treatment era: A retrospective cohort study. *South African Medical Journal,* **107**(10), pp. 871-876.

26. Setia, M.S., 2016. Methodology Series Module 3: Cross-sectional Studies. *Indian Journal of Dermatology*, **61**(3), pp. 261-264.

27. Sissolak, G. And Mayaud, P., 2005. AIDS-related Kaposi's sarcoma: epidemiological, diagnostic, treatment and control aspects in sub-Saharan Africa. *Tropical Medicine & International Health*, **10**(10), pp. 981-992.

28. Stiller, C.A., Botta, L., Sánchez Perez, M.J., Chirlaque López, M.D., Marcos-Gragera, R., Scuderi, T., Huws, D.W. And Trama, A., 2021. Kaposi sarcoma incidence, survival and trends: Data from the information network on rare cancers in Europe (RARECAREnet). *Cancer Epidemiology*, **70**, pp. 101877.

29. Struwig FW and Stead G.B 2013. Research: planning, designing and reporting (2nd edition)

30. WORLD HEALTH ORGANIZATION, 2017. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy.

Annexure 1: Data collection sheet

Section A: Demographic details

Patient unique number:

Age:

Gender:

Urban/Rural:

Race:

District :

Section B: Clinical Parameters

Weight:

Height:

Smoker:

HIV serostatus:

History of organ transplant:

Baseline CD4 count:

HIV Viral load:

Documented comorbid conditions:

1.Tuberculosis:

2.Diabetes Mellitus:

3.Hypertension:

ART status at diagnosis:

ART duration:

KS pathological subtype:

Histological diagnosis:

ACTG KS stage:

Radiotherapy:

Chemotherapy:

Haemoglobin:

Urea and Creatinine:

Albumin:

Site of KS lesions:

Upper limbs		Lungs	
Lower limbs		Gastrointestinal tract	
Oral		Disseminated skin lesions	
Head		Presence of lymph oedema	
Trunk		Groin	

Annexure 2: TREC Approval letter

University of Limpopo
Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 3935, Fax: (015) 268 2306, Email: anastasia.ngobe@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE

ETHICS CLEARANCE CERTIFICATE

MEETING: **26 July 2022**

PROJECT NUMBER: **TREC/327/2022: PG**

PROJECT:

Title:	The Prevalence and Associated Characteristics of Patients with Kaposi Sarcoma at Pietersburg Hospital, Limpopo Province
Researcher:	T Mukhithi
Supervisor:	Dr RA Tamayo
Co-Supervisor/s:	Prof RA Ratsela
School:	School of Medicine
Degree:	Master of Medicine in Internal Medicine

PROF D MAPOSA
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE

The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:

i) **This Ethics Clearance Certificate will be valid for one (1) year, as from the abovementioned date. Application for annual renewal (or annual review) need to be received by TREC one month before lapse of this period.**

ii) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee, together with the Application for Amendment form.**

iii) **PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.**

Finding solutions for Africa

Annexure 3: NHRD Approval letter

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref	:	LP_2022-07-015
Enquires	:	Ms PF Mahlokwane
Tel	:	015-293 6028
Email	:	Phoebe.Mahlokwane@dhsd.limpopo.gov.za

Tshimangadzo Mukhithi

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below;
THE PREVALENCE AND ASSOCIATED CHARACTERISTICS OF PATIENTS WITH KAPOSI SARCOMA AT PIETERSBURG HOSPITAL, LIMPOPO PROVINCE.

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
    a. Present this letter of permission to the Office Clinical Executive Director a week before the study is conducted.
    b. This approval is **ONLY** for **Pietersburg Hospital**.
    c. In the course of your study, there should be no action that disrupts the routine services, or incur any cost on the Department.
    d. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
    e. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
    f. The approval is only valid for a 1-year period.
    g. If the proposal has been amended, a new approval should be sought from the Department of Health
    h. Kindly note that, the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated

Mmahlwane

01/09/2022

pp **Head of Department** **Date**

Recommended

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