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Trends in Kaposi Sarcoma at the Charlotte Maxeke Johannesburg Academic Hospital after the antiretroviral drugs rollout in 2004 (from December 2004 to December 2019)

Hute, Fortune

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TRENDS IN KAPOSI SARCOMA

AT THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

AFTER THE ANTIRETROVIRAL DRUGS ROLLOUT IN 2004

(FROM DECEMBER 2004 TO DECEMBER 2019)

FORTUNE HUTE

1933515

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine in Dermatology.

Johannesburg May 2021

DECLARATION

I, Fortune Hute, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

13th day of May 2021

DEDICATION

This masters research is dedicated to my family who have supported me throughout my studies.

ACKNOWLEGDEMENTS

I thank my supervisor, Prof D Modi for his unmeasurable supervision during this research journey**.**

I am also thankful to the NHLS staff who provided me with the data and that includes Fadila, Thomas and Maanda**.**

I also appreciate the great work done by Hlengiwe who assisted with my data analysis of this research report.

ABSTRACT

Background

Kaposi sarcoma (KS) is an angioproliferative cancer of endothelial cells secondary to HHV8.It is classified as one of the most common presenting signs of AIDS during the HIV epidemic. Since HAART introduction in 1996, a worldwide reduction of AIDS associated KS was observed especially in developed countries.
Factors influencing this improvement include compliance, effective treatment regimens and health conscious social circumstances.

Objectives

To illustrate the prevalence and demographic pattern of patients with KS seen at the CMJAH dermatology outpatient clinic during the period of December 2004 to December 2019 (post ARV rollout on 1 April 2004).

Methods

A retrospective record review of patients with a confirmed histological diagnosis of KS who attended the CMJAH from December 2004 to December 2019.
CD4 count, viral load were compared throughout the study period.
2 significant time frames were also compared during the study (2009 and 2010)
And (2014 and 2015), which were the periods when ARV initiation protocols were adjusted in South African by WHO. The Kruskal Wallis analytic test was used.

Results

878 patients were enrolled into the study, with the majority being males (57% with n=499) and females(47% with n=379) .The mean age was 37,85 with a Standard Deviation of 10, 29.

The most affected age group range was between 30 to 49 years.

The comparison of CD4 counts between KS patients from 2004 to 2019 did not show any statistical significance as the *p* value was 0, 424.

The highest mean value of CD4 count was 373 and lowest was 90.

P<0, 05 for viral load equated to a statistically significant difference in the viral load of KS patients after HAART introduction (2004 to 2019).

The highest mean value of viral load was 430 253 and lowest was 399.

2 significant time frames were also compared during the study (2009 and 2010) and (2014 and 2015), which were the periods when the ARV initiation protocols were adjusted by the WHO.

Between 2009 and 2010, there was a 9% decrease in CD4 count numbers of KS patients in comparison to period between 2014 and 2015, which had a decrease of only 6% with introduction of new ARV regimen protocols. Within the same time frame, there were no statistically significant changes in the prevalence of KS as both p values were >0,05 with the period 2009 and 2010 *p* value of 0,486 and 2014 to 2015 *p* value of 0,808.

Conclusion

Our study revealed a general surge in the frequency of KS cases,
despite the initiation of HAART, with the highest number of cases being 112 in 2018. However the use of the Mann Whitney U test concluded that sex variation had no significant influence across gender when comparing the frequency of KS cases in both males and females to CD4 count and viral load. This was evidenced by a p value of 0,867(for CD4 count) and 0,203(for viral load) which were both greater than 0, 05.

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LIST OF ABBREVIATIONS

KS	Kaposi Sarcoma
KSHV	Kaposi Sarcoma Herpes Virus
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ARVs	Antiretroviral Drugs
AIDS	Acquired Immunodeficiency Syndrome
HIV	Human Immunodeficiency Virus
HHV8	Human Herpes Virus 8
IRIS	Immune Reconstitution Inflammatory Syndrome
H&E	Hematoxylin and Eosin
NHLS	National Health Laboratory Service
HAART	Highly Active Antiretroviral Therapy
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
IARC	International Agency Research on Cancer
ELISA	Enzyme Linked Immunosorbent Assay
FSH	Follicle Stimulating Hormone
LH	Luteinizing Hormone
WHO	World Health Organisation

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 **Introduction and extended Literature review**

The peak incidence of KS worldwide was in the 1980's, which was proportional to the patterns of HIV and AIDS seen then and has generally been declining with the introduction of. HAART from 1996[1, 2, 3]. HAART itself was defined in 1997 by the US National Institute of Health Guidelines [4] as provision of greater than two NNRTI's and a protease inhibitor. Compliance was defined as taking HAART for a period of greater than one month [5].

In economically stable countries, a widespread reduction in KS incidence was observed with an estimated percentage decline of around 33% to 95% from the time HAART was introduced in KS patients [6]. Studies documented in developed countries showed a decline in the incidence of KS following the introduction of HAART [7] .A study done in Switzerland after HAART rollout in 1997, displayed a decline in KS incidence by 92% [8].This trend was also observed in other developed countries like USA and Australia. In these countries, the decline was further explained by a general decrease in the prevalence of the causative agent KSHV[9].

This decline in prevalence of KSHV itself was influenced by social and medical risk factors which included preventative measures, ethnicity, minority of race, use of traditional medication, history of blood transfusion and a positive family history of cancer[10].

Studies from Europe, also showed a progressive decline in KS with the introduction of HAART[11]. This finding was despite a general decline in KS numbers even before the initiation of HAART in 1994 estimated at less than 10 % incidence in 1994[12, 13].A study from Algeria, despite its poor economic development, documented over 23 years also showed a decline in KS incidence from 5% to 2% following the introduction of HAART in 1998[14], with HAART being introduced in 1998[15].

Early initiation of HAART, irrespective of age and diagnostic stage of HIV/AIDS influenced the reduction in the incidence of KS cases in Uganda and Zimbabwe [16], despite being both underdeveloped countries. In South Africa, where up to 48% of the HIV positive population is also confirmed HHV8 infection [17], the initiation of HAART reduced the risk of developing KS by over 70% to 80%.Despite this significant percentage reduction seen in the adult South African population, the incidence of KS in the pediatric population continues to rise even with HAART availability. [18]

The above findings were not clearly illustrated in studies done at other underdeveloped countries, which did not show any strong decrease in the incidence of KS cases during the HAART era. This was due to the lack of data from their poorly resourced institutions, [19]. Both HIV and HHV8 are still predominant viruses in Sub Saharan Africa despite HAART rollout, mostly because of poor socioeconomic factors especially poor access to HAART.[20]This possibly explains why KS is still a major public health cancer in this region. In contrast to the developed countries, Sub Saharan Africa did not experience a decline in KS after initiation of HAART. This variation was explained by long term KSHV infection and economic challenges which reduced access to HAART [21].

In contrast to the above findings, a study done in Tanzania showed an increase in KS incidence actually, despite HAART initiation over a 10 year period. The increase was also explained by limited access to HAART and substandard prevention methods [22]. The wide difference in incidences magnified the influence of development in Western countries (which had KS incidences decrease from 15% to 0, 3% [23] and of 30% to 50% reduction in both USA and Europe [24] compared to Africa. In the USA even though there was a decline in KS incidence of 87% during HAART introduction in 1996 [25], incidence during early HAART era in a cohort study done between 1984 to 2007 showed elevated incidence of KS. This could have been explained by the reduced availability of HAART in early 1996, or missed diagnosis of preexisting KS before HAART initiation [26].

Studies done in Mozambique revealed different results in incidence of KS across its different provinces. This was due to variable differences in HIV prevalence across the provinces which clearly indicated the influence of different socioeconomic classes to the response to HIV education [27]. A few other studies showed an increase in the KS incidence rates despite HAART initiation. This variation was explained by inclusion of patients who developed KS soon after initiation of HAART or missed cases of KS diagnosis on initiation of HAART [28], with other patients receiving less effective HAART protocols generally [29].

The introduction of HAART more than a decade ago in healthcare changed the pathological course of AIDS associated KS in developed countries.[30,31].On a worldwide scale, research showed a yearly decline in KS incidence by 3,6% after HAART rollout [32,33] .The decrease in KS incidence during the HAART era may be explained by either a decrease CD4 count[34,35,36,37,38,39] or use of protease inhibitors ,which have a direct antiangiogenic and antitumor affects [40,41]. Worldwide racial differences also explained variations in KS incidence. Asians and Whites had the greatest incidence compared to black people[42,43] with another study showing white males having a higher incidence worldwide[44].In Africa, there is a predominance of KSHV which explains the high incidence of KS in the black community[45,46].

A study done in Alberta Canada between 1984 and 2005 was inconclusive as it did not clearly illustrate the effect of HAART on the incidence of KS. This led to the need for

further research to explain those findings [47, 48, 49].This was despite the decrease in incidence of KS only after HAART was introduced in 1996 [50, 51].

In 2012, an IARC report showed that HIV infection had a direct influence on the pathogenesis of KS [52], this was observed in the pre HAART era [53] and was supported by a research done in Rwanda. In comparison of the pre HAART era and HAART era, a study done in France showed improvement in survival of KS patients after diagnosis of KS and rollout of HAART [54, 55].

1.2 AIM AND OBJECTIVES

The study aim was to assess the KS trends in patients who attended the CMJAH dermatology clinic post the nationwide HAART rollout on the 1st of April 2004.

This was over a 15 year period (from December 2004 to December 2019).

In addition we documented the demographic characteristics of KS patients over this 15 year period.

We also studied the impact of variations in CD4 count and viral load (which are parameters of HAART initiation) on the prevalence of KS.

1.3: MATERIAL AND METHODS

1.3.1 Study design

A retrospective analysis of confirmed KS patients who presented to the CMJAH from December 2004 to December 2019.

Diagnosis is determined by performing a skin punch biopsy.

1.3.2 Study population

All patients who attended the CMJAH dermatology clinic from December 2004 to December 2019.

1.3.3 Inclusion criteria

All histopathology reports of adults with confirmed diagnosis of KS attended at CMJAH from December 2004 to December 2019.

1.3.4 Exclusion criteria

Inconclusive biopsy reports (patients with non-specific histopathology).

Unknown or negative HIV status.

1.3.5 Data abstraction

Data was collected from NHLS lab track using SNOWMED extract application.

The following considerations were followed:

Demographics which included:

. Age at diagnosis (>16years): patients were categorized according to different age ranges, with the pediatric range being (0-17) years, range of young adults(18-29) years, adult range (30-49) years and those greater than 50 years of age.

.Gender

Other variables which included:

.HIV status (all cases reactive of HIV)

.CD4 count in cells/uL

.Date of histological diagnosis report

.Viral load in cps/Ml

.Ethnicity was not considered

.Names were not recorded

1.3.6 Site of study

The research site was at the Charlotte Maxeke Johannesburg Academic Hospital, located in Parktown Johannesburg.

1.3.7 Measurements

A data collection sheet is attached with all the variables that were recorded from the NHLS database.

1.3.8 Sample size and statistical analysis

A data capture sheet was used to keep study records which were then transcribed onto an excel spreadsheet. When descriptive statistics were parametric, means and standard deviation was used, whereas non-parametric data was reported using medians and interquartile range. Percentages were used to report categorical data. Comparison between various groups was analyzed using the Kruskal Wallis test and Mann Whitney U test. With these tests, a *p* value of < 0, 05 was considered to be significant.

1.4 Limitations

Missing records from the NHLS database, which included absent CD4 count, viral load and dates of diagnosis.

Inconclusive diagnosis (without HHV8 stains done or adequate biopsy specimens submitted).

1.5 Ethical approval

The Human Research Ethics Committee of the University of Witwatersrand approved the study with the clearance certificate number being M190509.

1.6 Funding

The study was self-funded

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CHAPTER 2: SUBMISSIBLE ARTICLE

Title: Trends in Kaposi Sarcoma at the Charlotte Maxeke Johannesburg Academic Hospital after the Antiretroviral drugs rollout in 2004(from December 2004 to December 2019)

Authors: Prof Deepak Modi

Fortune Hute

Affiliations:

1. University of Witwatersrand

2. Division of Dermatology, department of internal medicine, faculty of health sciences, University of Witwatersrand Johannesburg Republic of South Africa.

Format: As per South African Medical Journal (SAMJ) format.

Corresponding Author: Fortune Hute

Email: fhuteng@yahoo.com

Cell: +27734542142

Postal address: 38 Farnham Drive Mulbarton 2190

Johannesburg RSA

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ABSTRACT

Background

KS is an endothelial cell carcinoma with a multicentric origin first described in 1872. It is caused by HHV8, a form of herpes virus and can be clinically characterized by local aggression. It is considered to be the most common AIDS related malignancy since the classification of HIV as an epidemic .After HAART was rolled out on a worldwide scale in 1996,reduction of KS cases has been observed especially in developed countries. Factors determining this decline include compliance to HAART, effective treatment regimens and education of society about the importance of HIV testing and treatment adherence.

Objectives

To describe the prevalence and demographic characteristics of patients with KS seen at the CMJAH dermatology outpatient clinic during the period of December 2004 to December 2019(post ARV rollout in 2004).

Methods

A retrospective analysis of patients' records with a confirmed histological diagnosis of KS who attended the CMJAH from December 2004 to December 2019.
CD4 count, viral load were also compared for the same study period.
2 significant time frames were also compared during the study (2009 and 2010) and (2014 and 2015), which were the periods when ARV initiation protocols were adjusted by the WHO in South Africa.

The Kruskal Wallis analysis Test was used.

Results

878 patients were enrolled in this study, with the majority being males (57% with n =499) and females (47% with n = 379).The mean age of confirmed KS cases was 37, 85 with a Standard Deviation (SD) of 10, 29.The peak age group range affected was between 30 and 49 years .*P*=0,424 for the trend of CD4 count. This showed that the change in the CD4 count of KS patients was not significant after initiation of HAART (2004 to 2019).The highest mean value of CD4 count was 373 and lowest value was 90. *P* value < 0, 05 for viral load showed that there was a significant variation in the viral load of KS patients after the rollout of HAART in 2004.

The highest mean value of viral load was 430 253 and lowest was 399.

2 significant time frames were also analyzed during the study (2009 and 2010) and (2014 and 2015), which were the periods when the ARV initiation protocols were reviewed by the WHO in South Africa. Between the period of 2009 to 2010 and 2014 to 2015, there were no significant changes in the frequency of KS as both p values were >0, 0 5 (0,486 and 0,808) respectively.

Conclusion

The study concluded that there was a continued increase in the frequency of KS cases despite the initiation of HAART in 2004 , with the highest number of cases being 112 in 2018. However the use of Mann Whitney U test concluded that difference in sex had no

significant influence on the frequency of KS cases both in male and female patients. A *p* value of 0,867 for CD4 count between males and females and *p* value of 0,203 for viral load between males and females showed that the study result was insignificant between both gender after introduction of HAART as both values were greater than 0,05.

2.1 INTRODUCTION

The introduction of HAART as an AIDS regimen over a decade ago transformed the pathological course of AIDS associated KS in developed countries [1, 2]. Worldwide research concluded that there was an annual decline of 3,6% of KS incidence after the rollout HAART[3,4].The decrease in KS incidence during the HAART era may be explained by either a decrease CD4 count[5,6,7,8,9,10] or use of protease inhibitors ,which have a direct antiangiogenic and antitumor affects[11,12]. Worldwide racial differences also explained variations in KS incidence. Asians and Whites had the greatest incidence compared to black people [13, 14] with another study showing white males having a higher incidence worldwide [15]. Africa has the highest prevalence of KSHV in the world, which explains the high incidence of KS in the black population generally [16, 17].

The peak incidence of KS worldwide was in the 1980's, which was proportional to the patterns of HIV and AIDS seen then and has generally been declining with the introduction of. HAART from 1996[18, 19, 20]. HAART itself was defined in 1997 by the US National Institute of Health Guidelines [21] as provision of greater than two NNRTI's plus a protease inhibitor. Compliance to therapy was defined as taking HAART for a period of greater than one month [22].

In economically stable countries, a widespread reduction in KS incidence was observed with an estimated percentage decline of around 33% to 95% since the rollout of

HAART as an AIDS treatment [23].This decline is supported by other studies documented from developed countries, which showed that HAART introduction influenced the decrease in the incidence of KS cases following its initiation as an AIDS therapy [24].A study done in Switzerland displayed a decline in KS incidence by 92% following the introduction of HAART in 1997[25]. This trend was also observed in the USA and Australia. In these countries, the decline was further explained by a general decrease in the prevalence of the causative agent KSHV [26].

This decline in prevalence of KSHV itself was influenced by social and medical risk factors which included preventative measures, ethnicity, minority of race, use of traditional medication, history of blood transfusion and a strong family history of cancer [27].

The decline in KS incidence in poorly developed countries was explained by the initiation of HAART early, irrespective of age and diagnosis of HIV/AIDS [28], which is a practice followed as guidelines in other countries. South Africa which has up to 48% of HIV positive people being infected with the HHV8 virus [29], introduction of HAART reduced the threat of developing KS by over 70% to 80%.Despite this positive reduction seen in adult cases, the South African pediatric population continues to have an escalating number of KS cases despite the availability of HAART [30].

In 2012, an International Agency Research on Cancer (IARC) report concluded that HIV infection had a role in the pathogenesis of KS [31]and this was observed before

initiation of HAART [32] .This was supported by a research done in Rwanda. After the introduction of HAART ,a study done in France showed improvement in survival of patients after the diagnosis of KS, which was a similar result to several other studies which further compared the pre HAART and HAART era evolution of KS [33, 34].

2.2 AIM AND OBJECTIVES

The aim of this research was to assess the trends of KS in patients who attended the CMJAH dermatology clinic post the nationwide HAART rollout on the 1st of April 2004.

This was over a 15 year period (from December 2004 to December 2019).

In addition we documented the demographic characteristics of KS patients over this 15 year period.

We also analyzed the impact of variations in the CD4 count and viral load (which are parameters of HAART initiation) on the prevalence of KS.

2.3: MATERIAL AND METHODS

Study population

A retrospective record analysis of all the patients with a confirmed KS diagnosis who attended the CMJAH from December 2004 to December 2019 with a confirmed KS diagnosis. Diagnosis is determined by performing a skin punch biopsy. The study included all patients above 16 years of age who were known HIV positive with a confirmed ELISA test presenting at area 457 dermatology department. All these patients

had skin punch biopsy confirmed diagnosis of KS which is characterized by (HHV8 stain positive and confirmatory histological changes of biopsied skin which included increased spindle cell proliferation with vascular slits and extravasated red blood cells).Excluded from the study population were patients who had inconclusive biopsy reports, uknown or negative HIV status, patients not on HAART on first presentation at CMJAH dermatology clinic and those less than 16 years of age.

Data collection

Data was collected from NHLS lab track using SNOWMED extract application and presented on an excel spreadsheet which tabulated the following:

Demographics which included:

. Age at diagnosis (>16years): patients were categorized according to different age ranges which included with pediatric range (0-17)years, young adults range(18-29) years, adult range (30-49) years and those with age greater than 50years.

.Gender of patients

Other variables which included:

.HIV status (all cases analyzed were reactive of HIV on ELISA at first presentation)

.CD4 count in cells/uL

.Date of histological diagnosis report with all confirming KS (positive HHV8 immunostain, slit like vascular spaces and red blood cell extravasation on histology).

.Viral load in cps/Ml.

.Ethnicity was not considered.

.Names of the patients were not recorded (identity was in form of unique numbers).

Assays

The analysis of blood serum samples and skin punch biopsies were performed by the Johannesburg NHLS.HIV test was done by ELISA test, which is an immunosorbent based test detecting HIV antibodies and antigens. The normal absolute CD4 count range is between 500 and 2010 cells/UL. CD4 lymphopenia is considered when the value is less than 500 cells/UL. The viral load lower limit of detection is 150 RNA copies/mL. The linear range for that assay is 150 to 10 000 000 RNA copies/mL. In our study, our patients had a CD4 count less than 500 which meant that they were immunosuppressed on presentation but had variable viral loads. Skin punch biopsies for suspected KS lesions were subjected to an HHV8 immunostain, which when positive distinguished it from other vascular tumours. Other features included slit like vascular spaces formed by spindled endothelial cells, hemorrhage, hemosiderin and plasma cells. The histology reports did not differentiate between the different clinical types of KS. Protocols were adjusted by the World Health Organisation for the initiation of HAART with regards to CD4 count. This initially happened between 2009 and 2010, where all patients with CD4 count less than 350cells/UL were required to start HAART and again between 2014 and 2015 when the eligibility criteria was set at 500cells/UL.

Statistical analysis

Descriptive statistics on general characteristics/ demographics of the patients such as age, gender were collated. Data was captured using a data capture sheet and was transcribed onto an excel spreadsheet with patient identity in form of unique numbers. When descriptive statistics were parametric, means and standard deviation was used, whereas non-parametric data was reported using medians and interquartile range. Percentages were used to report categorical data. Comparison between various groups was analyzed using the Kruskal Wallis test and Mann Whitney U test. A *p* value of < 0, 05 was deemed to be significant.

2.4 RESULTS

Demographic characteristics

A total of 878 patients were enrolled into the study. The patients were grouped into four categories according to their age and 70% of the patients were comprised of adults age in group(30-49)years(Figure 1). The mean age group of KS patients was 37, 85(+-10, 29) years with age ranging from 16 years to 74 years. The majority were males (57% with n: 499) with females being (47% with n: 379) (Figure 2).

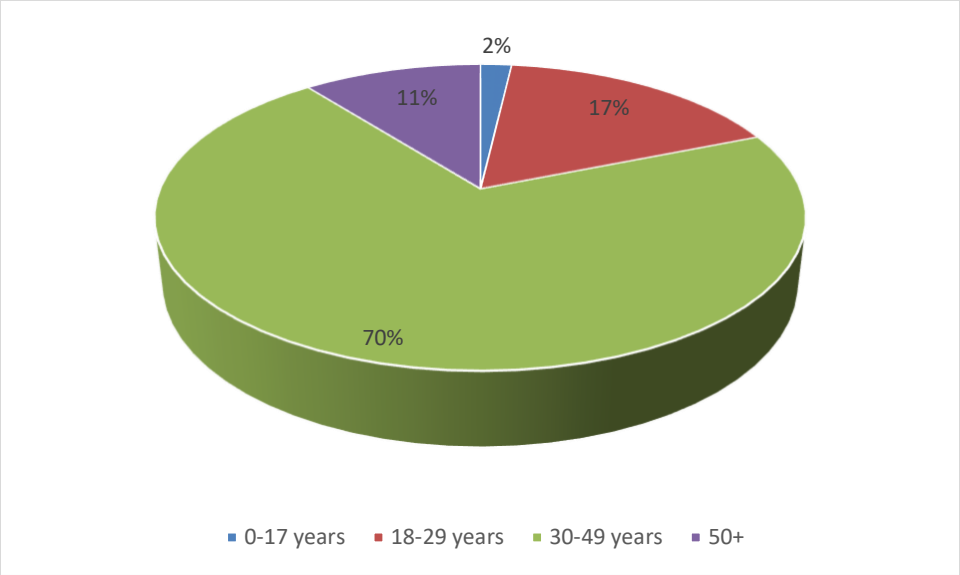


Figure 1. Age groups (pediatric, young adults, adults and over 50years

Age groups were categorized into pediatric range (0-17) years, young adults range (18-29), Adult range (30-49) years and older patients of (50 or more) years.

The youngest patient was aged 16 whilst the oldest was 74 years of age.

70% of the study population was in the age group (30-49) years.

Standard Deviation for Age = 10, 29

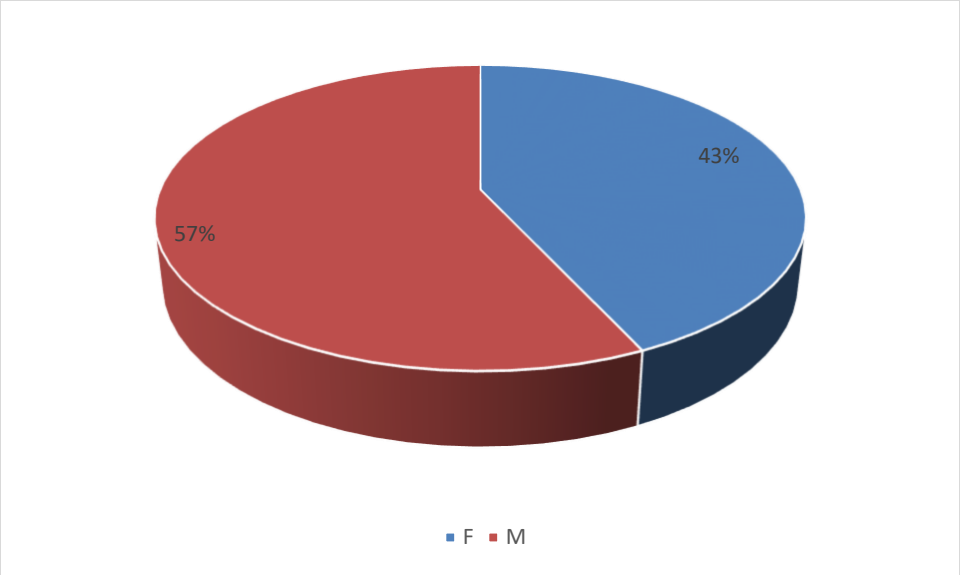


Figure 2: Gender distribution of KS patients (Females n: 379) (47%); (Males n: 499) (57%)

FREQUENCY OF KS BETWEEN 2004 AND 2019

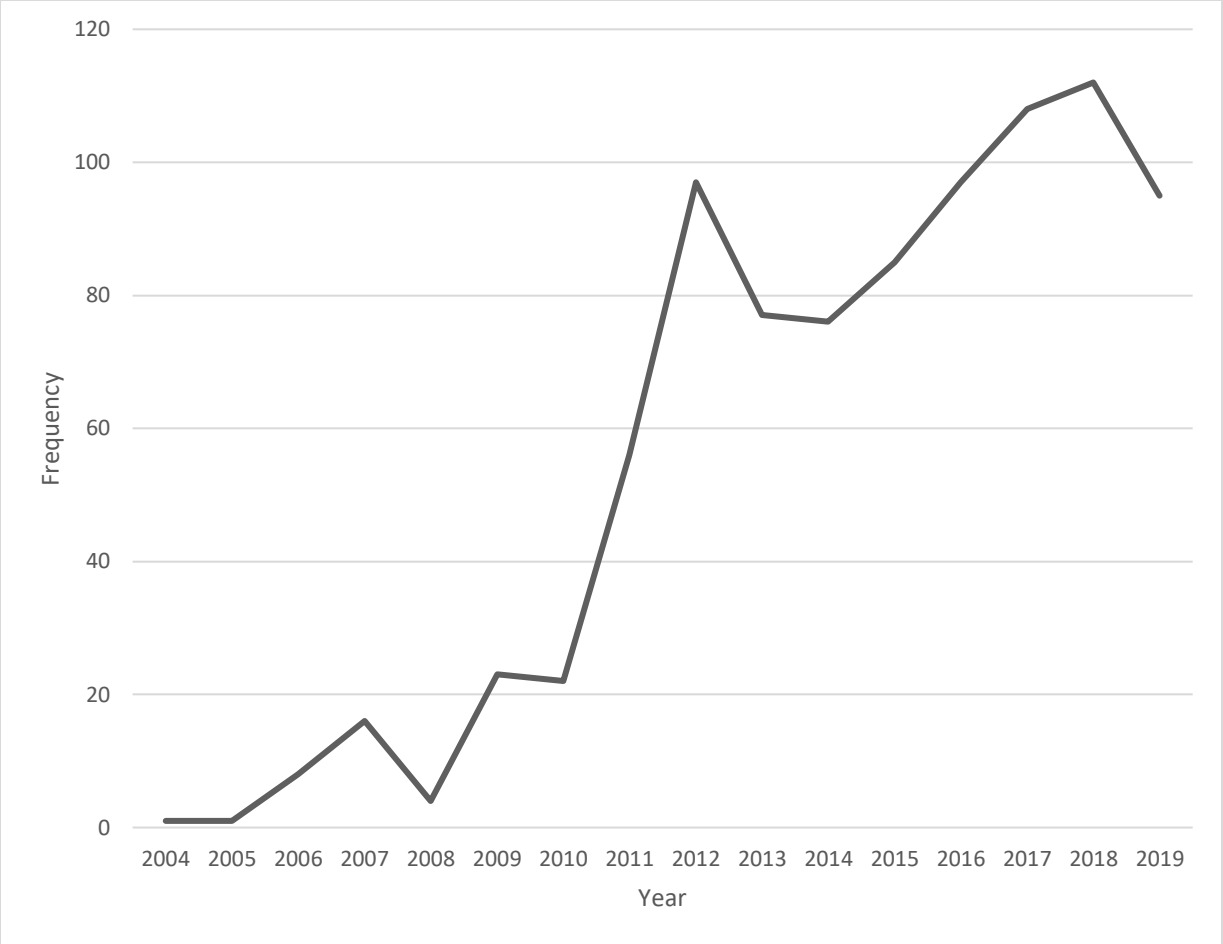


Figure 3: Number of KS cases between 2004 and 2019.

The number of KS patients between 2004 and 2019 is presented in a table on Appendix A.

In general, there is an increasing trend in the number of KS cases over the period 2004 to 2019.The frequency of KS was lowest in 2004(n:1) and highest in 2018

(n :112) (Figure 3)

There was a significant increase between 2010 and 2012 from 22 to 97 respectively. Interestingly between 2012 and 2014, there was a drop in the number of KS patients. Between 2015 and 2018, the number of KS patients showed a steady increase reaching a peak of 112 patients in 2018.

The comparison of CD4 count in KS patients between 2004 and 2019.

A total number of 837 KS patients on HAART were retrieved from patient files for this comparison.

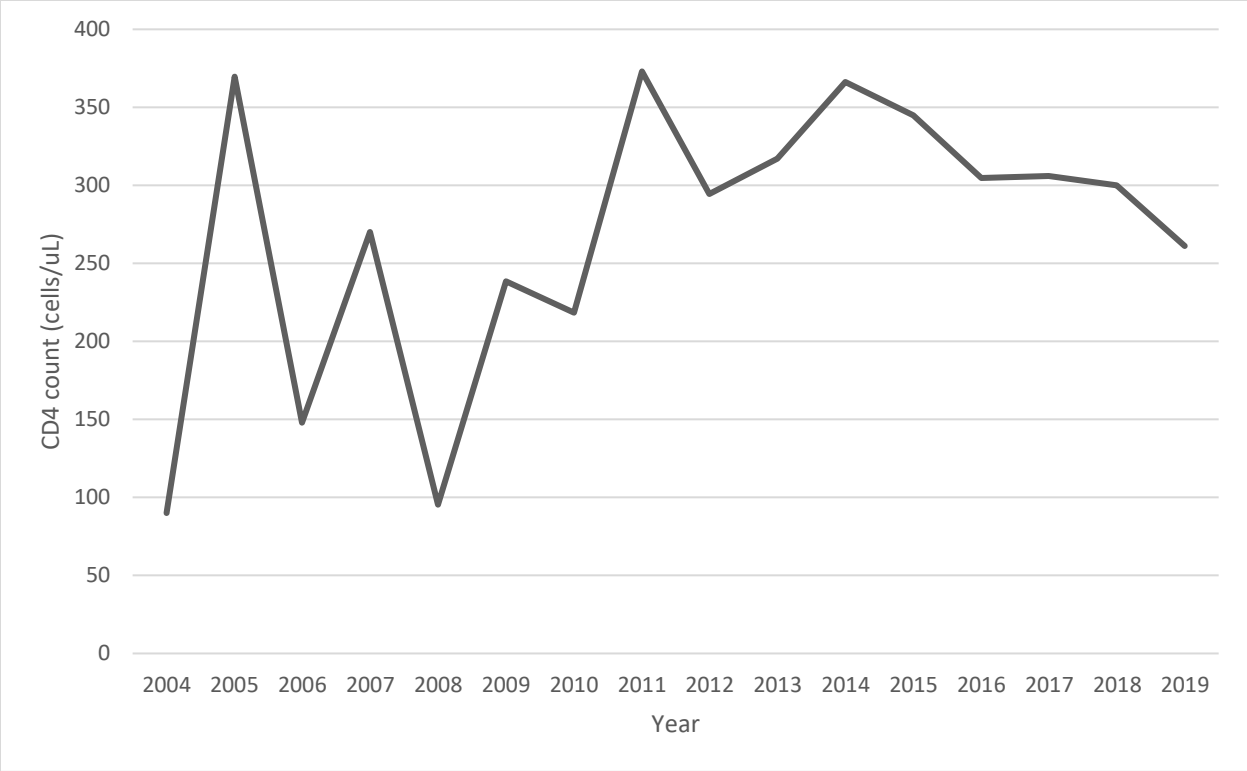


Figure 4: The Average CD4 count of KS patients from 2004 to 2019

The mean ranks of CD4 count in males and females 417, 29 and 420, 10 respectively (*p*: 0,867) (Mann Whitney Test).

The impact of CD4 count on KS frequency between 2004 and 2019 was not statistically significant. This was evidenced by a P value of (*p*: 0,424) using the Kruskal Wallis Test) (Figure 4).The National health guidelines for initiation of HAART were adjusted in the year 2009 and 2014.

A decrease by 9% in the CD4 count of KS patients (Appendix B) was observed between 2009 and 2010.Additionally, there was a 6% decrease in the CD4 count of KS patients between 2014 and 2015(Appendix C).

THE COMPARISON OF VIRAL LOAD IN KS PATIENTS BETWEEN 2004 AND 2019

A total number of 680 KS patients was retrieved from the files for this comparison.

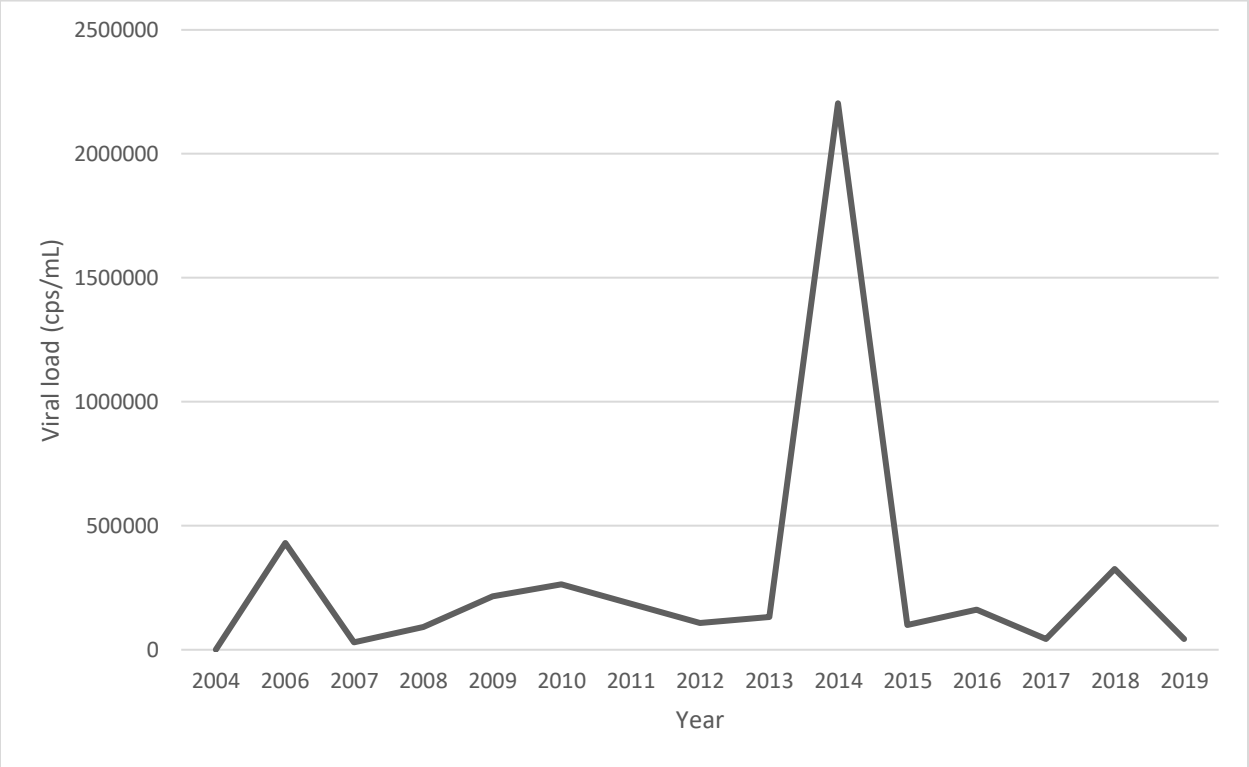


Figure 5: The Average Viral Load of KS patients from 2004 to 2019

The mean ranks of viral loads of KS patients for males and females was 374 and 305 respectively (*p*: 0,203) (Mann Whitney Test)

The viral load of KS patients was highest in the year 2014 with a value of 2 203 940 (p<0, 05) (Kruskal Wallis Test). (Figure 5)

When the effect of changes in the new treatment guidelines were compared, there was a 22% increase in the viral load of KS patients between 2009 and 2010(Appendix D).On the other hand a significant decrease of 95% in viral load of KS patients from 2014 to 2015 was noted with the adjustment of HAART guidelines in 2014(Appendix E).

2.5 DISCUSSION

We report KS trends at the CMJAH after the rollout of HAART in 2004(from December 2004 to December 2019).The periods of HAART initiation guidelines adjustment (2009 – 2010 and 2014-2015) were also closely monitored and the effect of these regulations on the impact of KS frequency was also analyzed.

HAART initiation as a form of AIDS treatment has changed the natural course of HIV KS [35, 36], which by classification has been decreasing as an AIDS defining condition[37].

The majority of KS patients in our study were male, who contributed 57% of the numbers as compared to only 43% of females. This variation is similar to the one seen in a study done in Algeria (1998 to 2010), which had 79% of the population being male [38] coinciding with several other studies done worldwide[39,40].

These differences in gender statistics could be explained by physiological protective factors in women for example beta HCG and menstrual cycle hormones like FSH and

LH which reduce risk of KS development [41].

In our study, 70% of the population (which was the majority) were in the age group range of between 30 to 49 years, with a median age of 37,85 years. This was a similar age distribution to a study done in USA over the period (1994 to 1997) which had a median age of 35 years. This common range of age distribution for AIDS KS is influenced by increased high risk behavior and immunosuppression when people reach that stage of development [42, 43].

Adjustment of treatment guidelines both nationally and internationally by WHO influenced development of KS .Before 2010 ,HAART initiation was guided by CD4<200[44] which was changed to <350 in 2013[45, 46].In September 2015, guidelines were adjusted to allow treatment for everyone with a confirmed HIV diagnosis. Viral load for HAART initiation was introduced in 2012[47].

With the above guidelines taken into consideration, statistical influence of CD4 count and viral load on KS prevalence was also studied, with a special look at the influence of guidelines changing in 2010 and 2014 in South Africa. For both periods, there was insignificant change in the frequency of KS. This conclusion was supported by both *p* values which had values >0,05.

The median CD4 count in our study was similar to the ones of other studies e.g. in Australia was 500[48]. In Tanzania, a lower median of 148, which could have been explained by effective HAART .The increase in median CD4 count was inversely relating to the decreasing numbers of KS cases, whilst cases which had very low CD4 counts were strongly associated to KS[49].

When comparing the variation of CD4 count values (an important parameter for HAART

initiation) between males and females, there was no significant result across gender, with the analytic test having a *p* value of 0,867.This insignificance was similar to a study done in Tanzania which also had a p value of 0,675 between males and females.

The prevalence of KS was 93, 5% after HAART introduction in 2004.This was supported by a gradual increase in the frequency of KS as graphically illustrated, with a numerical rise from 1 to 95 cases in 2019.This rising trend is common in African countries e.g. the Tanzanian study and could be explained by poor social circumstances limiting access to HAART and other methods of prevention[50] and the increased incidence of HHV8 itself [51]. In the Algerian study, the number of KS cases actually tripled after HAART initiation (2004 to 2007)[52,53].This could also be explained by lack of adequate therapy and late stage of diagnosing the disease. One study revealed a plateau in KS incidence values after HAART. The result is different in developed countries e.g. USA [54] and Germany [55] which both showed a decrease in KS after HAART. This was explained by noble HAART guidelines, adequate access to medication and protective effect of HAART[56].

Our study had a continual increase in frequency of KS cases despite the initiation of HAART in 2004.HAART alone can't effectively treat or alter the pathogenesis of KS [57, 58] hence other modalities like chemotherapy have to be introduced guided by the cancer stage. The study of the impact of HAART rollout on the trends of KS alone is limited, [59] this is due to limited available study data and unknown HAART benefits to advanced HIVKS cases.

Conclusion

KS is still an important AIDS defining condition, despite the introduction of HAART. Our study had most of the participating patients being in the immunosuppressed clinical stage of HIV (with CD4 counts of less than 500) on presentation. This observation together with multiple WHO adjusted HAART initiation guidelines contributed to an increase in KS frequency post 2004.Poor development of South Africa contributed to lack of education about HIV and HAART, poor access to treatment and poor adherence to HAART. The influence of HAART on the variety of HIV associated carcinomas is still unknown [60].However, further studies are still recommended to improve HIVKS prevention and management which can lead to a KS free generation.

Recommendations

Further prospective studies and data are required to determine the influence of HAART on KS. The pathological response of KS to different HAART regimens also needs to be further evaluated. A national registry of patients with histologically confirmed KS diagnosis before initiation of HAART and after HAART should be maintained and response to these drugs should be closely monitored. In the interim, repeat biopsies should be done to monitor KS response to HAART. Repeated CD4 count and viral load blood tests should also be done frequently, which will assist in monitoring KS response to any WHO implemented HAART guidelines.

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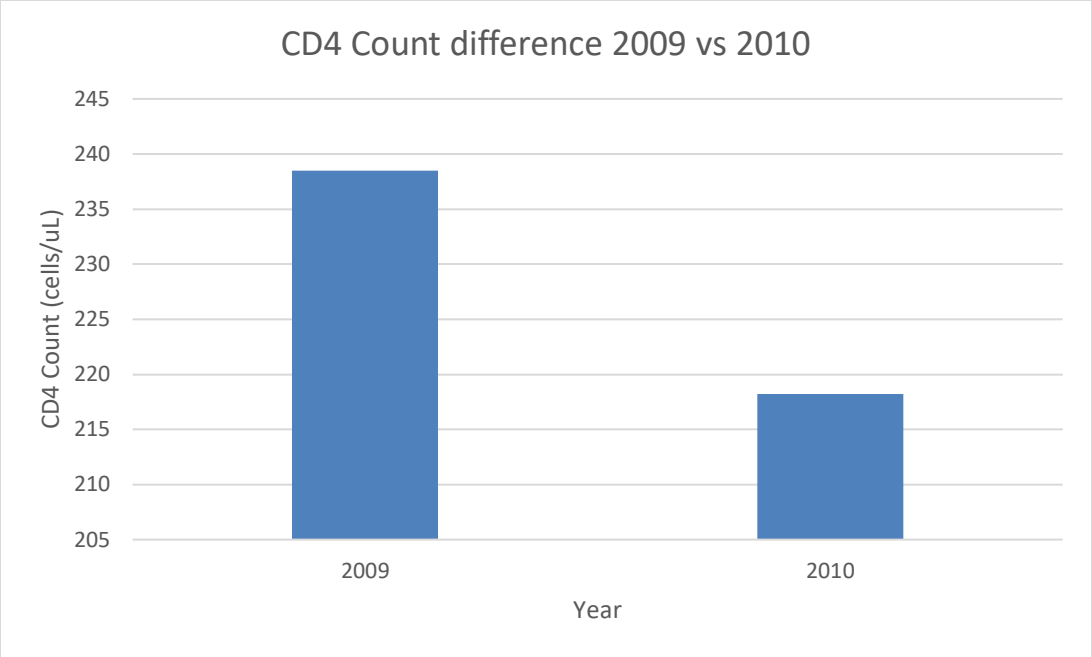
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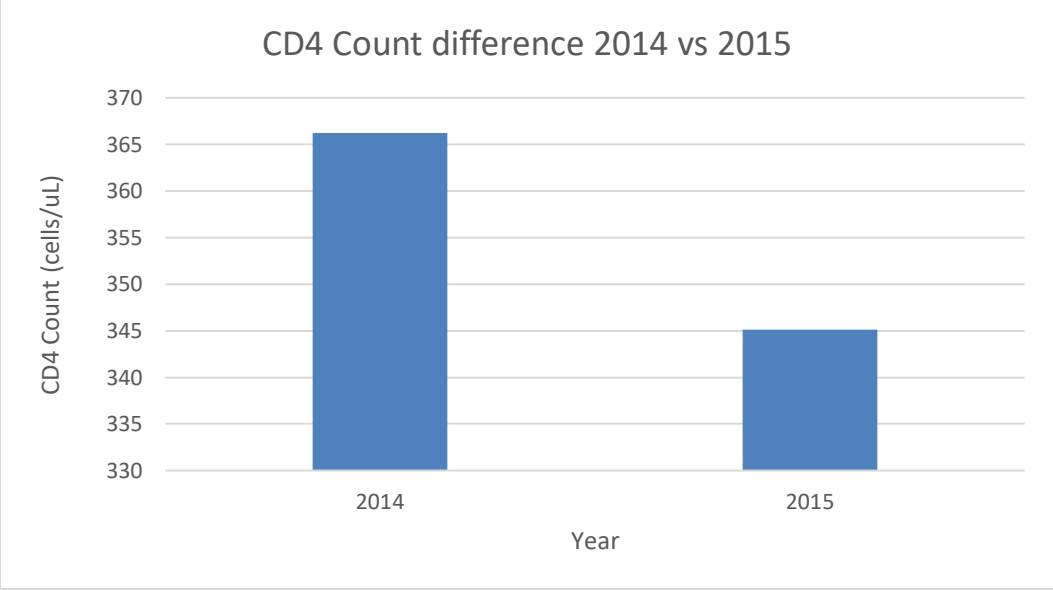
CHAPTER 3: APPENDICES

Year	Numbers
2004	1
2005	1
2006	8
2007	16
2008	4
2009	23
2010	22
2011	56
2012	97
2013	77
2014	76
2015	85
2016	97
2017	108
2018	112
2019	95
Total	**878**

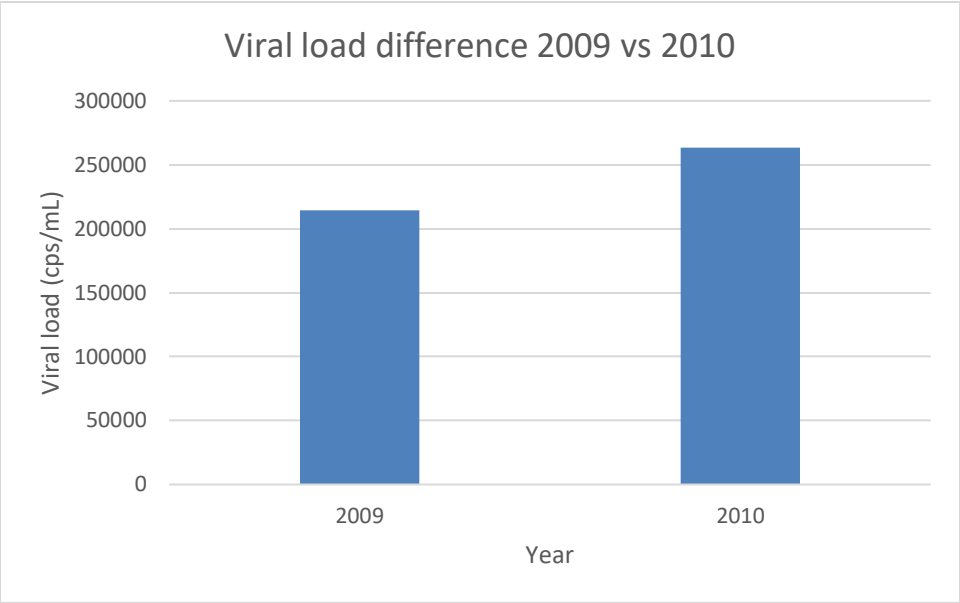
Appendix A: KS numbers from 2004 to 2019



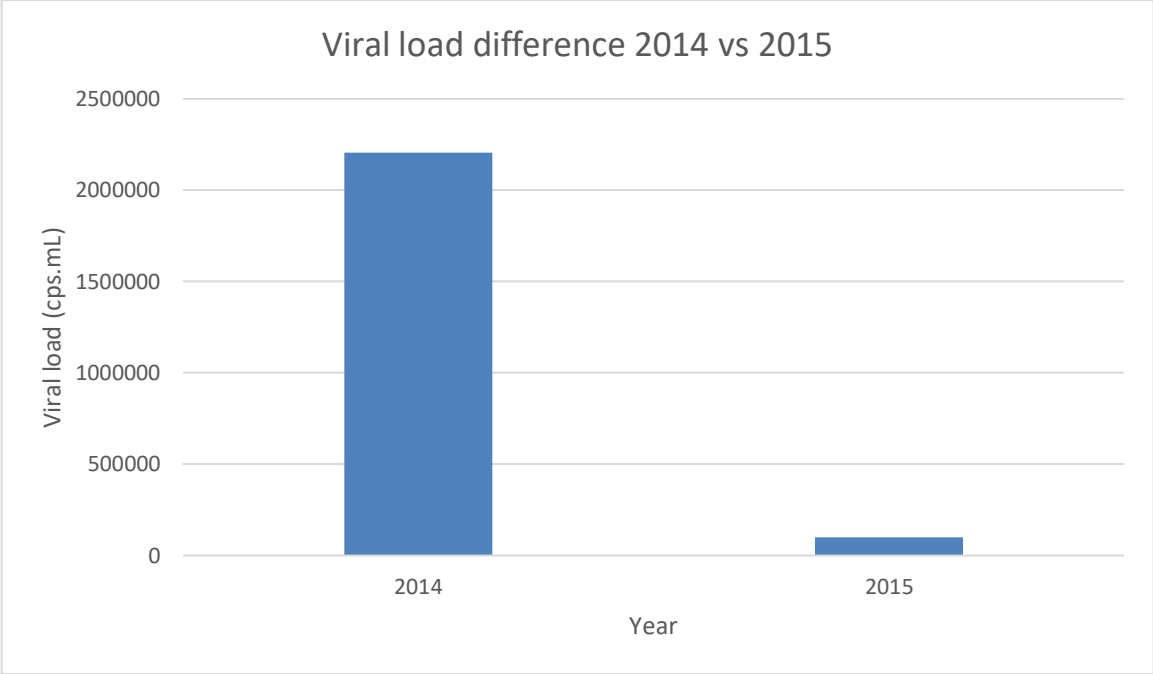
Appendix B: CD4 Count difference between 2009 and 2010



Appendix C: CD4 Count difference between 2014 and 2015



Appendix D: Viral load difference between 2009 and 2010



Appendix E: Viral load difference between 2014 and 2014

APPENDIX F:

UNIVERSITY OF THE WITWATERSRAND
JOHANNESBURG

R49 Dr F Hute

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M190509

NAME: Dr F Hute
(principal Investigator)

DEPARTMENT: School of Clinical Medicine
Department of Medicine
Division of internal medicine- Dermatology

PROJECT TITLE:
Trends in Kaposi Sarcoma at the Charlotte Maxeke Johannesburg Academic Hospital after the antiretroviral drugs rollout in 2004(from December 2004 to December 2019)
Change in study title noted on 2021/02/05

DATE CONSIDERED: 2019/05/31

CONDITIONS:

SUPERVISOR: Professor D Modi

APPROVED BY: Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2019/07/08

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in «Missing mail merge field» and therefore reports and re-certification will be due in the month of «Missing mail merge field» each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date