A THESIS SUBMITTED AS PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN CLINICAL MEDICINE, UNIVERSITY OF NAIROBI

A STUDY TO DETERMINE THE INFLUENCE OF CHEMOTHERAPY ON OUTCOMES OF AIDS-ASSOCIATED MUCO-CUTANEOUS KAPOSIS' SARCOMA AT KENYATTA NATIONAL HOSIPITAL

DR AYORO C OMONDI

JUNE 2014

DECLARATION

I certify that this dissertation is my original work and has not been presented for a degree at any other university or previously published.

í í í í í í í í í í í í í

Dr Ayoro, Charles Omondi, MBChB

SUPERVISORS

N.A. OTHIENO-ABINYA, MBChB, MMED, FRCP

Professor of Medicine and Medical Oncologist

Department of Clinical Medicine and Therapeutics, University of Nairobi

í í í í í í í í í í í í ..Dateí í í í í í í í í í

G.N. LULE, MBChB, MMED, FRCP

Professor of Medicine and Consultant Physician/Gastroenterologist

Department of Clinical Medicine and Therapeutics, University of Nairobi

í í í í í í í í í í í í í í í Dateí í í í í í í í í í

Dr. D. Zuriel, MBChB, MMED (Path.)

Lecturer and Consultant Pathologist (Derm. Path)

Department of Pathology, University of Nairobi

í í í í í í í í í í í í í í í .Dateí í í í í í í í í í í í í

Dr. L. Achieng, MBChB, MMED

Lecturer and Consultant Physician

Department of Clinical Medicine and Therapeutics, University of Nairobi

í í í í í í í í í í í í í í ...Dateí í í í í í í í í í í í í í .

DEDICATION

This study is dedicated to all HIV and cancer caregivers who strive to give the best possible care.

ACKNOWLEDGEMENT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AIDS…………..Acquired Immunodeficiency Syndrome

CD……………..Cluster Differentiation

CHOP………….Cyclophosphamide, Adriamycin, Vincristine, Prednisone

DNA…………… Deoxyribonucleic acid

EBV…………....Epstein Barr Virus

FLIP…………… Flice Inhibitory Protein

HHV…………… Human Herpes Virus

HAART………… Highly Active Antiviral Therapy

HIV……………...Human Immunodeficiency Virus

IL………………...Interleukin

JAK…………… Janus Associated Kinase

KS……………..Kaposi's sarcoma

KSHV………… Kaposi's sarcoma associated herpes virus

LANA………… Latency associated nuclear antigen

LTc……………….Latency associated nuclear antigen promoter

LTd……………….Kaposin promoter

MCD…………..Multicentric Castleman's disease

MSM…………..Men who have sex with men

NFkB………….Nuclear factor kappa beta

ORF…………...Open reading frames

PEL…………… Primary Effusion Lymphoma

STAT………… Signal transducer and activator of transcription

ABSTRACT

Background: Kaposiøs sarcoma is the most common tumor in HIV infected patients in Africa. In Kenya over the last five years, there have been few studies which have investigated the treatment outcomes KS in HIV positive persons. This study investigated the treatment outcomes of AIDS-associated KS among patients attending KNH.

Objectives: To determine the treatment outcomes of patients with AIDS-associated muco-cutaneos KS at KNH.

Study Design: Retrospective chart review

Materials and Methods: Records of patients with histology confirmed KS and who are HIV positive and had undergone treatment for KS were reviewed. Data collected included: socio-demographic, clinical, treatment modality and treatment outcomes. The treatment outcomes had been defined in this protocol.

Data Management: Data was entered continuously into a secure database and analyzed using SPSS version 18. Continuous data was presented as mean and median. Categorical data was presented as proportions. Cox proportional hazard model was used to determine association of sex, HAART use and outcomes.

Results: Females represented 53% of the study population. The median age of the study subjects was 35.3 years. There was a response rate of 16.5% to KS treatment. The difference in outcomes between males and females was insignificant ($p=0.693$). In addition, the outcomes between those on HAART and those not on HAART was also insignificant ($p=0.557$).

Conclusion: The short term outcome of patients with HIV-associated muco-cutaneous KS receiving chemotherapy was unfavourable.

1.0 LITERATURE REVIEW

Introduction

Kaposiøs sarcoma is a vascular tumour commonly associated with HIV. KS affects both visceral organs and the skin. The skin form can present as patch, nodule or ulcer. The visceral form can present in various patterns depending on the system affected for instance cough, dyspnea, hemoptysis in the respiratory system. KS is not a sarcoma in nature. The word õsarcomaö is a misnomer since it is not mesenchymal in origin. Four distinct epidemiologic forms of KS have been elucidated:

(a) The classic form which occurs in older men of Mediterranean or Jewish background. This presents with few cutaneous lesions on the lower limbs and has an indolent nature.

(b) The equatorial Africa form that occurs in all age groups (endemic KS). This is usually aggressive in nature affecting both adults and children.

(c) The form associated with organ transplantation and its immune suppression. This was first noted in renal transplant patients and has been described in other transplant recipient patients.

(d) The HIV-1 associated KS (epidemic). This is an aggressive form of KS which presents in many forms: cutaneous and visceral. Its association with HIV-1 suggests a synergistic effect between HIV-1 and KHSV.

In the latter two forms, KS is an opportunistic malignancy.

Epidemiology and clinical features of KS

KS was initially described as an uncommon tumor occurring in elderly Mediterranean men and was later reported in African children in the 1960s (1). KS associated with immunodeficiency was first reported in patients undergoing solid-organ transplantation. (2)

In 1981, an epidemic of KS was described in young men who had sex with men (MSM) in the United States (US). This served as an alert of a new immunodeficiency syndrome later identified to be caused by HIV (3). The HIV epidemic evolved and KS was found commonly in MSM (4). KS is the most common tumour in HIV-infected individuals in Africa. (5)

KS was relatively common in South Africa before the HIV/AIDS epidemic with 5 per 1000 population at risk of developing KS (6). However, the incidence increased dramatically as the HIV epidemic worsened (7).

In Kenya, a study by Onyango et al (2004) at Kenyatta National Hospital showed that mucocutaneus KS had a relative frequency of 2 to 5% of all malignancies with a male to female ratio of 2 to 1. The most common site of occurrence of cutaneous KS was in the lower limbs at 45% (8). Data from another Kenyan study by Senba et al (2001) showed that the incidence of KS had increased in the post AIDS era and they suggested that endemic cases had changed to epidemic forms (9). In another study at Kenyatta National Hospital, the highest prevalence of cutaneous KS was found in the 31 to 40 year age group. The ratio of HIV seropositivity to seronegative was 8.5 to 1 and peripheral lymphadenopathy in KS was associated with underlying HIV infection (10).

Oral lesions were more prevalent amongst females in a study done in Uganda. They also had lower CD4 count at diagnosis compared to men. Males at presentation had a mean CD 4 count of 124 cells per millimeter while females presented with a mean CD 4 of 58 cells per millimeter. Females were reported to have had a poor clinical improvement after treatment (11). It has also been noted that KS is rarely reported in Asian countries despite the relatively high prevalence of

HIV infection (12). The incidence of KS has decreased in US and Europe with the introduction of HAART (13, 14).

Pathogenesis of KS

Etiologic role of KSHV

The causative agent of KS had been sought since 1980s. In 1994, Chang and Moore identified KSHV DNA fragment from KS tissue samples (15). KSHV was later identified in samples of patients with Primary effusion lymphoma (PEL) and Multicentric Castleman disease (MCD) (16, 17).

KSHV is a member of the herpes virus family whose prototype human member is EBV. KSHV's primary target in vivo is the B cell, and in healthy seropositive hosts viral DNA is usually found in these cells (18). KSHV also infects the endothelium as evidenced by the presence of viral DNA in KS spindle cells (19). In vitro, KSHV infects many cell lines: epithelial cells, fibroblasts, keratinocytes as well as endothelial cells (20). KSHV, like all herpes-viruses can express its genes either in latency or active states.

In latency state, gene expression is restricted with only a few viral genes being stably expressed. Primary B cells infected with KSHV are neither immortalized nor transformed (21). This is in marked contrast to EBV where latency is usually immortalized. Primary endothelial cells when infected with KSHV undergo morphological changes characterized by rearrangement of the actin cytoskeleton .This produces an elongated morphology strongly similar to the spindle cell (22).

In the human host, the principal site of lytic virus replication is the oropharynx .This could be in B cells of tonsillar or other pharyngeal lymphoid tissue or in pharyngeal epithelium (23).

Role of cytokines

KSHV encodes for a human IL-6 homologue, viral IL-6. This stimulates the known human IL-6 induced signaling pathways via the shared cytokine signaling receptor gp130 coupled to endogenous JAK-STAT pathway (24). KSHV-infected cells induce and secrete viral IL-6 and can retain some potion of viral IL-6 intracellularly. This binds to gp130 and activates STAT3 in an autocrine fashion (25) v-FLIPøs pro survival activity is linked to its ability to activate NF-kB (26).

NF-kB is maintained in cells in an inactive cytoplasmic form, bound to the inhibitor IKB. v-FLIP binds and activates the gamma subunit of IKB kinase-(IKK) (27).

The resulting IKB phosphorylation displaces IKB from NF-KB releasing the active transcription factor to the nucleus where it activates a large panel of proinflammatory and antiapoptotic genes.

KSHV interaction with HIV

The exact mechanisms by which HIV increases KS risk during KSHV infection remains unclear. However, there are other direct mechanisms as suggested by laboratory experiments. Laboratory experiments indicated that HIV can augment KSHV replication both in cell autonomous and paracrine fashions (28, 29). Soluble HIV tat protein can serve as growth factor for cultured KS spindle cells in vitro (30).

The Oncodrug hypothesis

Many investigators have suggested that particular drugs could induce the development of KS. In 2011, Quinine and its derivatives were suggested as possible triggers of KS especially in Africa (31). The search for other drugs that could trigger KS still continues.

Treatment of KS in HIV infected persons

It has been noted that HAART alone improves the outcome of HIV associated KS (32, 33). There are few prospective clinical trials in Africa for Kaposi's sarcoma treatment (34). In South Africa, HAART plus chemotherapy showed higher KS response over 12 months compared to HAART alone (35).

Patients with aggressive forms of KS are treated with combined chemotherapy ABV-adriamycin, bleomycin and vinblastine (vincristine) in our setting. This ABV regimen showed a better response rate than BV (Bleomycin, vinblastine / vincristine) alone (36). Gemcitabine monotherapy has been suggested as a second line option in patients previously treated with ABV (45). Paclitaxel is considered the most attractive agent since it is effective and tolerable over long term administration especially when combined with growth factors (38, 39).

Liposomal anthracyclines do not have a greater efficacy than conventional ABV, but have a better toxicity profile. Alpha interferon and radiotherapy have also been used in the management of AIDS-associated KS. Their use has been limited by the toxicity profile. Rapamycin was noted to be õsafe in HIV infected individuals with KS and can in some cases induce tumour regressioní ö (40).

The Aids Clinical Trials Group uses a CD 4 count of less than 200cells/ml as a poor prognostic factor in the staging of Aids-associated KS (41). Prospective validation of the staging system showed that a CD 4 count of less than 150cells/ml was a better prognostic factor than a CD cell count of 200/ml (42).

The preferred regimen for KS at Kenyatta National Hospital is ABV, although many oncologists are shifting towards using BV. This shift is to avoid the hematologic and cardio-toxicity associated with doxorubicin especially in patients with cardiac disease or dysfunction. HIV may cause cardiomyopathy hence more caution is required while using doxorubicin. Some oncologists also avoid using bleomycin in pulmonary KS since it is associated with pulmonary fibrosis.

There have been few prospective studies done to compare the efficacy of various treatment regimes in Aids-associated KS at Kenyatta National Hospital. Most retrospective studies have also focused on the clinical and socio-demographic factors and not the treatment outcomes. There is a need to perform more studies focusing on treatment outcomes.

2.0 STUDY JUSTIFICATION AND RESEARCH QUESTION

Study Justification.

KS remains an important co-morbidity in persons infected with HIV with a high morbidity and mortality. The rate of mortality in our Kenyan setting has not been clearly documented. The mortality rate of HIV patients with KS in Uganda was found to be 30% (43). The high mortality rate in Africa suggests more attention for Aids-associated KS is warranted.

Data on clinical outcomes of Aids-associated KS in Africa is generally sparse with a few studies originating in East and Southern Africa. Most of the KS outcome studies originate from United States of America. In Kenya, there have been no studies on clinical outcomes of HIV patients with KS given chemotherapy. It would be important to investigate the short term outcomes of such patients.

In addition the clinical characteristics of KS at the time of diagnosis, the treatment regime for the KS and the treatment outcomes have not been clearly correlated. Secondly, the impact of HAART on outcomes of Aids-related KS in our setting has not been studied.

This study was deemed useful in that it would shed light on the issues discussed above and provide baseline data for future studies. In addition, this study could act as a clinical audit on the management of Aids-associated KS at KNH.

Research Question

What are the one year treatment outcomes for persons receiving chemotherapy for Aids-associated KS at KNH?

3.0 OBJECTIVES.

Broad Objective

To determine the treatment outcomes of persons with HIV-associated muco-cutaneous KS at week forty eight from the first course of chemotherapy

Primary Objectives

1. To determine the treatment outcomes of persons with HIV-associated muco-cutaneous KS given chemotherapy.

2. To describe the clinical features and determine the CD 4 cell counts at diagnosis of KS.

3. To describe the various chemotherapeutic regimen used in the above mentioned persons.

Secondary Objectives

1. To determine the association between treatment outcome and gender.

2. To determine the association between treatment outcome and HAART use.

4.0 METHODOLOGY.

Study Design

This was a retrospective chart review of patients given chemotherapy for Aids-associated muco-cutaneous KS during the period 2004-2013 at KNH.

Study Population

Patients with HIV and KS who had attended the various units of KNH including medical wards, surgical wards, Comprehensive Care Clinic and the Hemato-Oncology Clinic had their records retrieved and reviewed by the principal investigator and his assistant.

Screening and Recruitment

A computer generated list of patients with both HIV and KS was printed by Hospital Records Department staff for each year of the study period. The patient files were then extracted and sampled consecutively following the list. Those with complete data and documentary evidence of histologically confirmed KS were included into the study. Care was taken to ensure that pathology records had been signed by a qualified pathologist. CD 4 counts were not more than three months from the date of the histology report. This was so since it is internationally accepted to do serial CD 4 counts after every six months for those receiving HAART. Subjects were excluded if they were solid organ recipients, even if they had HIV. They were also excluded if they had biopsy proven evidence of visceral KS elsewhere.

Sample size calculation

This was a whole population survey and every person who met the inclusion criteria was enrolled into the study.

Data collection and Analysis

Data was collected using a predetermined data tool. The tool was pretested to ensure data clarity. Sampling was through the consecutive sampling method. The tool was then used by the principal investigator and his trained assistant to collect data. The data was entered into a secure Microsoft Access database continuously. The study variables were: Socio-demographic (age, sex, marital status) and clinical (site of KS occurrence, HAART use or not, duration of HIV since diagnosis, CD 4 count at KS diagnosis, treatment regime for KS and treatment outcome). The primary site of KS in case of multiple site involvement was the one the patient noticed first.

Data was analyzed using SPSS software version 18. Descriptive analysis methods including mean or median and standard deviation or inter-quartile range were used to summarize continuous variables for example age. Categorical variables for example sex, site of KS occurrence, duration of HIV since diagnosis, treatment outcomes were summarized using percentages and presented as frequency tables. The relationship between HAART use on non HAART use, sex and treatment outcome was examined in bivariate analysis using Cox proportional hazard. All p-values were two-sided and a cut-off of 0.05 was used for statistical significance.

Study Defined Treatment Outcomes

Treatment outcomes were assessed 48 weeks after the first course of chemotherapy. The treatment outcomes were based on predetermined criteria as follows:

Category I (Failure)-This referred to KS progression as documented in the patient notes, initiation of new chemotherapy agent or change of modality, for example addition of

radiotherapy or surgery. In the patients notes we looked for words such as: õenlargingö, õworseningö, õnot improvingö, õpoor responseö among others phrases to denote failure. Patients who had received at least one course of chemotherapy and could not be traced on their telephone numbers or on their next of kinøs phone number were also categorized as failure.

Category II (Stable)-This referred to continued follow-up at week 48 with no KS progression (as documented on the patientsø notes) nor response without initiation of new chemotherapeutic agent or change in treatment modality. Words and phrases such as õstableö, õstatus quoö, õsame sizeö, õunchangedö were used to define a stable state. Patients who had missed clinic visits but were available on phone or next of kinøs phone and reported no worsening of condition were also classified as stable.

Category III (Response)-This referred to continued follow-up at week 48 with KS partial or complete response as documented by the clinicianøs notes. Words and phrases such as õimprovingö, õreducingö, õdiminishingö, õgood responseö in the patients notes denoted response.

Category IV (Transferred)-This referred to patients who had been transferred from the hospital to another hospital officially as documented by the cliniciansø notes.

It is important to note that categories I, II, and III have been borrowed and modified from the Aids Clinical Trials Group Criteria.

Ethical Consideration

The study was only initiated after approval by the KNH/UON Ethics and Research Committee. Results were disseminated to Department of Clinical Medicine and Therapeutics, UON and Department of Medicine, KNH. The data collecting tool did not contain any patient name and patient records were handled in strict confidentiality.

5.0 RESULTS

Eight hundred and one (801) patient records with clinical diagnosis of KS and HIV between the years 2004-2013 were reviewed. One hundred and forty six (146) records representing eighteen percent (18%) met the inclusion criteria. Thirty one (31) records were excluded for various reasons as shown in the flow chart below (Fig 1).

The final analysis had 115 persons.

```
┌─────────────────────────────────────────────────────┐
│ 801 files reviewed, exclusions:                       │
│                                                       │
│ 612 no histology                                      │
│                                                       │
│ 24 non KS histology, 19 KS histology HIV -ve          │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────┐
│ 146 patients                              │
│                                           │
│ With confirmed KS + HIV                   │
└─────────────────────────────────────────┘
       │   11 excluded since not started KS treatment
       ▼
┌─────────────────────────────────────────┐
│ 135 on KS treatment                       │
└─────────────────────────────────────────┘
       │   8 excluded, incomplete records
       ▼
┌─────────────────────────────────────────┐
│ 127 with complete records                 │
└─────────────────────────────────────────┘
       │   12 excluded, not finished 48 weeks follow up
       ▼
┌─────────────────────────────────────────┐
│ Final analysis 115                        │
│                                           │
└─────────────────────────────────────────┘
```
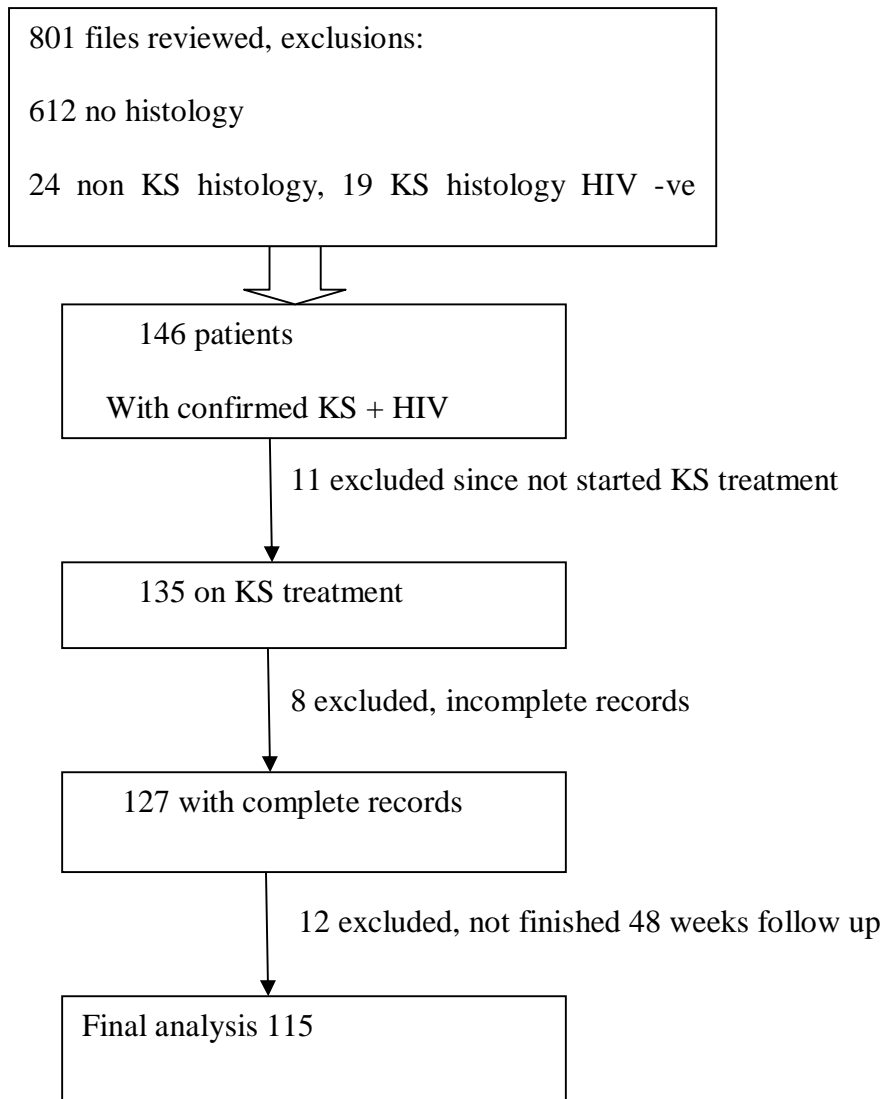
Fig 1: Flow chart of review of records for analysis.

Socio-demographic characteristics

The mean age of the population studied was 35.3 years. The subjects had an age range of twelve to seventy six years (12-76). Females accounted for sixty one subjects (53%) of the total population (table 1).

VARIABLE	FREQUENCY	PERCENTAGE
Age		
Mean (SD)	35.3(11.4)	
Min-max	12-76	
Gender		
Female	61	53.0
Male	54	47.0
Marital status		
Single	34	29.6
Married	67	58.3
Widowed	11	9.6
Separated	3	2.5

Table1: Socio-demographic characteristics of the population.

Clinico-pathological characteristics

A majority of the population (89%) were diagnosed with KS within 4 years of HIV diagnosis while 10.4 % were diagnosed with KS after that period (table 2). The median CD 4 at diagnosis of KS was 217 cells/ ml. The two most common sites of KS presentation were: lower limbs at 63.5% and palate at 17.4%. The least likely recorded site for KS presentation was the groin

(0.9%). The mean CD 4 cell count at diagnosis between males and females was 212/ml versus 231/ml (table 3).

VARIABLE	FREQUENCY	PERCENTAGE
Duration of HIV since diagnosis		
<1 yr	49	42.6
1-4 years	54	47.0
5-10 years	12	10.4
CD 4 count		
Median	217 (IQR 88-326)	
Min-max	2-2251	
Primary Site of KS		
Tongue	5	4.3
Palate	20	17.4
Neck	5	4.3
Face	6	5.2
Upper limbs	2	1.7
Lower limbs	73	63.5
Torso	3	2.7
Groin	1	0.9

Table 2: Clinico-pathological characteristics of KS /HIV

Variable	Female	male	P value
Mean CD 4 count/ml	231	212	0.525
	On HAART	Not on HAART	
Mean CD 4 count/ml	219	210	0.547

Table 3: Mean CD 4 count in various groups

Use of HAART and HAART regimes in KS patients

71% of patients with KS and HIV were on HAART at six weeks of initiation of first chemotherapy course (table 4). The three most common HAART regimes were D4T/3TC/EFV (23.2%), D4T/3TC/NVP (18.3%) and AZT /3TC/EFV (18.3%). Second line regimes accounted for less than 5% of the HAART regimes.

KS treatment modalities and outcomes

The most common chemotherapeutic regime was Bleomycin + Adriamycin (53.1%) other regimes accounted for 7.9% (table 5). The median number of cycles given was 4. The treatment outcome according to the protocol was as follows: Failure (64.3%), response (16.5%) and stable (17.4%). Only 1.75% of patients were transferred to other facilities.

VARIABLE	FREQUENCY	PERCENT
HAART Use		
On HAART	82	71.3
Not on HAART	33	28.7
HAART regime (n=82)		
D4T/3TC/NVP	15	18.3
D4T/3TC/EFV	19	23.2
AZT/3TC/EFV	15	18.3
TDF/3TC/NVP	4	4.9
TDF/3TC/EFV	15	18.3
AZT/3TC/NVP	8	9.8
ABC/3TC/EFV	2	2.4
ABC/3TC/EFV	1	1.2
A2T/3TC/LPVr	1	1.2
OTHER	2	2.4

Table 4: Use of HAART and HAART regimes in KS /HIV patients

KS treatment outcomes and gender

The treatment outcomes between males and females were compared as shown in table 6.

Females generally had a better response rate than the males. However, there was no statistical

significant difference in outcomes between the two sexes (p=0.693).

VARIABLE	FREQUENCY	PERCENTAGE
Chemotherapy Regime		
Vincristine Alone	12	10.4
Vincristine+Adriamycin	5	4.3
Bleomycin+Vincristine	61	53.1
Bleomycin+Vincristine+Adriamycin	28	24.3
Other	9	7.9
Number of courses given		
Median(IQR)	4 (1-6)	
Min-Max	1-20	
Treatment Outcomes		
Failure	74	64.3
Stable	20	17.4
Response	19	16.5
Transferred	2	1.7

Table 5: KS treatment modalities and outcomes

KS treatment outcome	Female	Male	P value
Failure	38(62.3%)	36(66.7%)	
Stable	10(16.4%)	10(18.5%)	
Response	11(18.0%)	8(14.8%)	0.693
Transferred	2(3.3%)	0(0.0%)	

Table 6: Treatment outcomes between gender

KS treatment outcome and HAART use

Table 7 below summarizes the outcomes between patients on HAART and those not on HAART. There was no statistical significant difference between the two groups (p= 0.557). It was quite unusual that those on HAART seemed to have a low response rate than those not on HAART. This has been discussed in detail in the discussion chapter.

KS Treatment Outcome	ON HAART	Not on HAART	P Value
Failure	55(67.6%)	19 (57.6%)	
Stable	13 (15.9%)	7 (21.2%)	
Response	12 (14.6%)	7 (21.2%)	0.557
Transferred	2 (2.4%)	0 (0.0%)	

Table 7: Treatment Outcomes and HAART use

Chemotherapeutic Regime	Frequency	Percentage
Vincristine Alone	8	10.8
Vincristine+ Adriamycin	6	8.1
Vincristine + Bleomycin	36	48.6
Vincristine+Adriamycin+Bleomycin	19	25.7
0ther	5	6.8

Table 8: Stratification of failure by Chemotherapeutic Regime

Table 8 above illustrates the contribution of various chemotherapeutic regimes to the failure outcome. The Vincristine + Bleomycin regime represented the largest proportion of failure. It was followed by Vincristine+Adriamycin+Bleomycin (25.7%).

6.0 DISCUSSION

This was a retrospective study on the short term outcomes of patients with HIV-associated muco-cutaneous KS who had received chemotherapy at a tertiary health facility affiliated to a medical school in Nairobi, Kenya. Arguably, it is the first treatment outcome study on patients with HIV/AIDS and KS at the institution. Hopefully it will provide useful baseline data for future studies.

Females formed a slight majority of patients at 53% and the mean age of patients with KS was 35.3 years. This contrasts and compares with studies by Mwanda et al (10) and Phipps et al (11) who also found a female proportion of 42% and 55% respectively. The mean age of our population was in the age bracket 31-40 years described by Mwanda et al (10).

Most patients were diagnosed with KS within 4 years of HIV/AIDS diagnosis. This would suggest that KS occurs early in the course of HIV. However, this study was not designed to investigate when KS occurs in HIV. In addition, it is difficult to ascertain the accurate duration of HIV infection in any person. The most common site of KS presentation was the lower limbs (63.5%). This correlates with a study by Onyango et al who found the lower limbs the most common site at 45% (8). Why KS occur mostly in the lower limbs is still unclear. Stasis of blood in the lower limbs could play a major role in increasing KSHV interaction with co-factors and vascular endothelium (44).

The goals of HIV-associated KS treatment are mainly palliation of symptoms and improvement in the quality of life (44). HIV-associated KS chemotherapy treatment is hardly ever intended to

eradicate the disease because of toxicity concerns and the fact that failure to eradicate the underlying cause makes it difficult to permanently eradicate KS. Palliation of symptoms includes reduction in lesion sizes, reduction in pain and swelling. The treatment outcomes in this study were assessed using a predetermined protocol.

The treatment outcomes according to the protocol were: failure 64.3%, stable 17.4%, response 16.5% and transferred (1.7%). Other studies in Africa with a different design to this study have yielded different results. In Malawi, a study to determine the outcomes of AIDS-associated KS 12 months after 6 weekly cycles of vincristine showed a mortality of 22% and a default rate of 15%, n= 488 (45). Our study was not designed to estimate mortality. In Uganda, a study of HIV infected patients with KS receiving non nucleoside reverse transcriptase inhibitors without chemotherapy showed that 72% (n=18) had complete regression(43). However, this was a small study. A prospective study from South Africa on treatment outcomes with ABV regime showed a high response rate of 66% (46).

The low response rate in our study could be due to the definition of our outcomes. In our study, the high failure rate could be due to: patients who defaulted (received at least one cycle of chemotherapy and dropped from follow-up), patients who had radiotherapy or surgery as adjuvant to chemotherapy and those who died from other causes. The following six factors have been identified as possible contributors to the low response rate: adherence to antiretroviral therapy, advanced KS presentation, KS immune reconstitution syndrome, other HIV-associated co-morbidities in KS patients, inadequate treatment for KS and possibility of a more aggressive KS in African blacks.

High level adherence (> 95%) to antiretroviral therapy is a major factor in immune reconstitution. Mills et al, in a meta-analysis found the combined continental adherence for Africa and North America to be 77% and 55% respectively (47). In Kibera, Nairobi various adherence rates have been reported ranging from 48% to 89% (48, 49, 50). Wakibi et al found that younger respondents below the mean age of 39 years were more likely not to adhere to antiretroviral therapy. In our study, the median age of persons with KS was 35.3 years and in the age bracket of those likely not to adhere to therapy. Clearly the adherence rates above are sub-optimal which could contribute to poor immune reconstitution and hence poor response rates. However, in our study we did not check for antiretroviral adherence.

Advanced KS presentation could have also contributed to the low response rate. Chu et al showed that advanced KS was associated with high mortality (51). We could not stage the study subjects since it was a retrospective study and some of the data was not available. It would have been pertinent to have had the information since we think advanced disease presentation may have contributed to the low response rate. However, Nguyen et al demonstrated that measured baseline characteristics: tumour stage, CD 4 T-cell count, HIV viral load, prior active antiretroviral therapy did not predict improvement or resolution (52).

Patients on HAART in our study had poorer outcomes compared to those not on HAART. We think KS immune reconstitution syndrome (IRIS) may have contributed to this outcome.
KS IRIS is a relatively less known occurrence of antiretroviral therapy. The incidence of KS-IRIS has been estimated to range from 6.6% to 14.3% (53, 54, 55). One study showed that

Africans had an incidence rate 2.5 times of the European cohorts largely explained by advanced disease and lower chemotherapy availability (54). Part of the low response in our study could be due to KS-IRIS which we could not exclude due to our study design.

The low treatment response in our study could be due to mortality by other HIV-associated conditions. Patients with HIV-associated KS can also be afflicted with other HIV-associated opportunistic or defining conditions. We did not check the cause of mortality for the subjects in our study who died. It would have been important to categorize the cause of death as either KS related or not. However, this was not possible. Martin-Carbonero et al showed that the cause of death in KS patients (n=9) was related to the appearance of other tumours including lymphomas, gastrointestinal adenocarcinoma and tongue epidermoid cancer (56). Our low response late due to mortality could be due other common HIV-associated opportunistic conditions in our setting including tuberculosis, cryptococcal meningitis, pneumocystis jirovecii pneumonia among others.

Inadequate treatment could also have led to a low response rate. Ten percent of the study subjects were on vincristine monotherapy. In addition, another 7.8% were on other therapies including cyclophosphamide and adriamycin monotherapy. Monotherapy has been associated with poor outcomes (36). It is also difficult to determine non-hematological toxicities in our settings since echocardiograms, computed tomograghy, pulmonary function tests though available may not be affordable. These toxicities may have influenced the outcomes.

The low treatment response rate led us to query the possibility of a more aggressive KS in African black population. High treatment response rates for KS have been been reported in the Western Europe and North America: Cattelan et al, 86% n=10 (57); Pellet et al, 85% n=22 (58); Bower et al, 74% n=254 (59); and Cooley et al, 80% n=60 (60). In Africa, the response rates to Aids-associated KS treatment have been low. In Johannesburg, South Africa the complete remission on chemotherapeutic drugs was 4/17; while 10/17 had partial remission. The investigators concluded that:ö . . . the response rate to chemotherapy was very low and of brief durationö (61). Maskew et al found that patients with Aids-associated KS were over three times more likely to die at any time after HAART initiation compared to non- KS patients (62). Our study yielded a response rate of 16.5% comparable to Maskew et al.

One of the highest KS treatment response rate was recorded in Cape Town, South Africa at 66% (51). Arguably, the University of Cape Town is the equivalent of Europe in terms of medical resources and personnel; and therefore it would not be surprising to record such a high rate. We think the disease could be less aggressive in the west; however the better treatment response rates could be due to better patient selection and better medical support. Exclusion of patients with other co-morbidities could account for the better response rates. In most parts of Africa it is financially challenging to do endoscopy to rule out visceral KS while investigating muco-cutaneous KS. We also faced the same handicap. In addition, the west preference for liposomal anthracyclines which have less toxicities could also contribute to the better rates. It would be interesting to do a comparative study on treatment outcomes for KS with the same patient selection methodology and chemotherapeutic agents in both Africa and Europe.

Could it be that that the Aids-associated KS in Africa is more aggressive than in the West?

CONCLUSION

1. Poor short term outcomes of patients with HIV-associated muco-cutaneous KS offered chemotherapy.

2. Relatively poor outcomes of patients with HIV/AIDS with KS on HAART.

2. Relatively poorly kept patient records.

RECOMMENDATIONS

The investigators faced some hurdles in determining the treatment outcomes since the records were not standardized, and therefore recommend:

1. Do a prospective study which might be more objective in estimating outcomes and defining factors associated with poor outcomes.

2. Standardization of recording of KS treatment outcomes among patients attending KNH.

STUDY LIMITATIONS

This was a retrospective study and had the inherent weakness of such studies. First, there was selection bias in that only patients who had KS histology were selected for the study. Secondly, information bias was expected in that the investigators depended on the data previously recorded. Thirdly, it was difficult to control outcome assessment. In our case, we tried to mitigate this by having categorical outcomes. In addition, the study subjects were not on protocol based management but case-based management. We could not rule out visceral Kaposi's sarcoma in our study subjects due to the financial challenges our patients experience in doing endoscopies. Finally, as in other retrospective studies the temporal relationship in observed outcomes was difficult to assess.

REFERENCES

1. Taylor JF, Templeton AC, Vogel CL, et al. Kaposi's sarcoma in Uganda: a clinico-pathological study. Int J Cancer 1971; 8: 122-35.

2. Stribling J, Weitzner S, Smith GV. Kaposi's sarcoma in renal allograft recipients. Cancer 1978; 42:442-46.

3. Hymes KB, Cheung T, Greene JB, et al. Kaposi's sarcoma in homosexual men-a report of eight cases. Lancet 1981; 2:598-600.

4. Beral V, Peterman TA, Berkelman RL, et al. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet 2000;335:123-28

5. Whitby D, Howard MR, Tenant-Flowers M, et al. Detection of Kaposi's sarcoma associated herpesvirus in peripheral blood of HIV infected individuals and progression to Kaposi's sarcoma. Lancet 1995, 346: 799-802.

6. Cook-Mozaffari P, Newton R, Baral V, et al. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. Br J Cancer 1998, 78:1521-28.

7. Del Maso L, Serraino D, Franceschi S. Epidemiology of AIDS related tumours in developed and developing countries. Eur J Cancer, 2001, 37:1188-1201.

8. Onyango JF, Njiru A. Kaposi's sarcoma in A Nairobi Hospital. East Afr Med J 2004 Mar 81(3) : 120-25

9. Senba M, Buziba N, Mori N, et al. Increased prevalence of Kaposi's sarcoma associated herpesvirus in the Kaposi's sarcoma endemic area of Western Kenya in 1981-2000. Acta Virol 2001; 55(2): 161-64.

10. Mwanda OW, Fu P, Collea R, et al. Kaposiøs sarcoma in patients with and without immunodeficiency virus infection in a tertiary centre in Kenya. Ann Trop Med Parasitol 2005 Jan; 99(1):81-91.

11. Phipps W, Ssewankabo F, Nguyen H, et al. Gender differences in clinical presentation and outcomes of epidemic Kaposiøs sarcoma in Uganda. Plos One 2010 Nov 12; 5 (11): e 13936.

12. Thomas S, Sindhu CB, Sreekumar S, et al. AIDS associated Kaposisø Sarcoma. J Assoc Physic India 2011 June 59; 387-89.

13. Jacobson LP, Yamashita TE, Detels R, Multicenter AIDS Cohort Study et al. Impact of potent antiretroviral therapy on the incident of Kaposiøs sarcoma and non Hodgkinøs lymphoma among HIV 1 infected individuals. J Acquir Immune Def Syndr 1999, 21 (suppl 1):S 34 -41.

14. Ledergerber B, Telenti A, Egger M, Swiss HIV Cohort Study. Risk of HIV related Kaposiøs sarcoma and non-Hodgkinøs lymphoma with potent antiretroviral therapy: prospective cohort study. Br Med J 1999; 319:23-24.

15. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposiøs sarcoma. Science 1994; 266:1865-9.

16. Cesarman E, Chang Y, Moore MS, et al. Kaposiøs sarcoma-associated herpesvirus-like DNA sequences in AIDS ó related body ó cavity ó based lymphomas. N Eng J Med 1995; 332:1186-91.

17. Soulier J, Grollet L, Oskenhendler E, et al. Kaposiøs sarcoma ó associated herpes virus ó like DNA sequences in Multicentric Castlemanøs disease. Blood 1995; 86: 1276-80.

18. Ambroziak JA, Blackbourn DJ, Herndier BG, et al. Herpes - like sequences in HIV ó infected and uninfected Kaposiøs sarcoma patients. Science 1995; 268 (5210): 582-83.

19. Parravicini C, Chandran B, Corbellio M, et al. Differential viral protein expression in Kaposiøs sarcoma ó associated herpesvirus- infected diseases: Kaposiøs sarcoma, primary effusion lymphoma, and Multicentric Castlemanøs disease. Am J Pathol. 2000; 156(3):743-49.

20. Vieira J, OøHearn PM. Use of the red fluorescent protein as a marker of Kaposiøs sarcoma ó associated herpesvirus lytic gene expression. Virology 2004; 325(2):225-40.

21. Kliche S, Kremmer E, Hammerschmidt W, et al. Persistent infection of Epstein-Barr human herpesvirus 8. J Virol 1998; 72(10): 8143-49.

22. Grossmann C, Podogrobskina S, Skobe M, et al. Activation of NF-kB by the latent v-FLIP gene of KSHV is required for the spindle shape of virus-infected endothelial cells and contributes to their pro-inflammatory phenotype. J Virol. 2006; 80(14):7179-85.

23. Duus KM, Lentchitsky V, Wagenaar T, et al. Wild-type Kaposiøs sarcoma-associated herpesvirus isolated from the oropharynx of immune-competent individuals has tropism for cultured oral epithelial cells. J Virol. 2004; 78(8): 4074-84.

24. Stebbing J, Pantanowitz L, Dayyani F, et al. HIV-associated Multicentric Castlemanøs disease. Am J Hematol 2008; 83: 498-503

25. Sullivan R, Dezube BJ, Koon HB. Signal transduction in Kaposiøs sarcoma. Curr Opin Oncol 2006; 18:456-62.

26. Matta H, Chaudhary PM. Activation of alternative NF-kappa B pathway by human herpesvirus 8-encoded Fas-associated death domain-like IL-1 beta converting enzyme inhibitor (v-FLIP). Proc Natl Acad Sci USA.2004; 101(25): 9399-9404.

27. Liu L, Eby MT, Rathore N, et al. The human herpes virus 8-encoded viral FLICE inhibitory protein physically associates with and persistently activates IKB kinase complex. J Biol Chem. 2002; 277(6): 13745-51.

28. Varthakavi V, Smith RM, Deng H, et al. Human immunodeficiency virus type-1 activates lytic cycle replication of Kaposiøs sarcoma-associated herpesvirus through induction of KSHV Rta. Virology, 2002; 297(2): 270-80.

29. Mercader M, Taddeo B, Panella JR, et al. Induction of HHV-8 lytic cycle replication by inflammatory cytokines produced by HIV-1-infected T-cells. Am J Pathol. 2000; 156(6):1961-71.

30. Barillari G, Ensoli B. Angiogenic effects of extracellular human immunodeficiency virus type 1 Tat protein and its role in the pathogenesis of AIDS-associated Kaposiøs sarcoma. Clin Microbiol Rev. 2002; 15(2):310-26.

31. Ruocco V, Ruocco E, Schwartz RA, et al. Kaposiøs sarcoma and quinine: a potentially over looked trigger factor in millions of Africans. J Am Acad Dermatol 2011 Feb 64(2):434-36.

32. Dupin N, Rubin de Cervens V, Gorin I, et al.The influence of HAART on AIDS-associated KS. Br J Dermatol 1999; 140:875-81.

33. Mosam A, Uldrick TS, Shaik F, et al. An evaluation of the early effects of a combination antiretroviral therapy programme on management of AIDS-associated Kaposiøs sarcoma in Kwa Zulu Natal, South Africa. Int J STD AIDS 2011; 22(11):671-73.

34. Krown SE. Treatment Strategies for Kaposiøs sarcoma in Sub-Saharan Africa: Challenges and opportunities. Curr Opin Oncol 2011 Sept; 23(5):463-68.

35. Mosam A, Shaik F, Uldrick TS, et al. A randomized controlled trial of HAART and chemotherapy in therapy-naive patients with HIV-associated Kaposiøs sarcoma in South Africa. J Acquir Immune Defic Syndr 2012, Mar 19(e-published ahead of print).

36. Gill PS, Rarick M, McCutchan JA, et al. Systemic treatment of AIDS-related Kaposiøs sarcoma: results of a randomized trial. Am J Med 1991; 90: 427-33.

37. Strother RM, Gregory KM, Pastakia SD, et al. Retrospective analysis of the efficacy of gemcitabine for previously treated AIDS-associated Kaposiøs sarcoma in Western Kenya. Oncology 2010 Mar 78(1):5-11.

38. Gill PS, Tulpule A, Espina BM, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposiøs sarcoma. J Clin Oncol 1999; 17:1876-83.

39. Saville MW, Lietzan J, Pluda J et, al. A phase ll trial of Paclitaxel (Taxol) in patients with HIV-associated Kaposiøs sarcoma. AIDS Res Hum Retrovirol 1994; 10(suppl.): S103.

40. Krown SE, Roy D, Lee JY, et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposiøs sarcoma: An AIDS Malignancy Consortium Study. J Acquir Immune Defic Syndr 2012 Apr 15; 59(5):447-54.

41. Krown SE, Metroka C, Wernz JC. Kaposiøs sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1989 7(9):1201-7

42. Krown SE, Testa MA, Huang J. Aids-related Kaposiøs sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1997 15(9):3085-92

43. Asiimwe F, Moore D, Were W, et al. Clinical Outcomes of HIV-infected patients with Kaposiøs sarcoma receiving non-nucleoside reverse transcriptase inhibitors-based antiretroviral therapy in Uganda. HIV Med 2012 Mar; 13(3):166-71

44. Ruocco E, Ruocco V, Tornesello ML, et al. Kaposiøs saroma: etiology and pathogenesis, inducing factors, causal associations, and treatments: facts and controversies. Clinic Dermatol. 2013 Jul-Aug;31(4):413-22

45. Makombe SD, Harries AD, Yu JK, et al. Outcomes of patients with Kaposiøs sarcoma who start antiretroviral therapy under routine programme conditions in Malawi. Trop Doct 2008 38:5

46. Mosam A, Shaik F, Uldrick TS, et al. Randomised Controlled trial of HAART versus HAART and chemotherapy in therapy-naïve patients with HIV-asssociated Kaposiøs sarcoma in South Africa. J Acquir Immune Defic Syndr 2012 June 1; 60(2):150-57

47. Mills EJ, Nachenga JB, Buchan I, et al. Adherence to Antiretroviral Therapy in Sub-Saharan Africa and North America. JAMA. 2006;296(6):679-90

48. Ellis AE, Gogel RP, Roman BR, et al. A Cross-Section Study of Adherence to Short Term Drug Regimens in Urban Kenya. Soc Work Heal Care. 2006;42(3-4):237-50

49. Wakibi SN, Ngøangøa ZW, Mbugua GG. Factors associated with non-adherence tohighly active antiretroviral therapy in Nairobi, Kenya. AIDS Res Ther. 2011;8:43

50. Unge C, Sodergard B, Marrone G, et al. Antiretroviral Treatment and Program Drop-out in a High Risk Urban Setting in Sub-Saharan Africa. A prospective Cohort Study. Plos One. Oct 2010;5(10):e13613

51. Chu KM, Mahlangeni G, Swannet S, et al. AIDS-associated Kaposi's sarcoma is linked to advanced disease and high mortality in a primary care HIV programme in South Africa. J Int AIDS Soc. 2010 Jul 8;13:23

52. Nguyen HQ, Margaret AS, Kitahata MM, et al. Persistent Kaposi's sarcoma in the era of highly active antiretroviral therapy: characterizing the predictors of clinical response. AIDS 2008 May 11(8):937-45

53. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 2005 Aug 1;23(22):5224-8

54. Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma: higher incidence and mortality in Africa than in the UK. AIDS 2013 June 19:27(10)1603-13

55. Haddow LJ, Moosa MS, Mosam A, et al. Incidence, Clinical Spectrum, Risk Factors and Impact of HIV-associated Immune Reconstitution Inflammatory Syndrome in South Africa. Plos One 2012; 7(11)e40623

56. Martin-Carbonnera L, Palacios R, Valencia E, et al. Long term prognosis of HIV infected patients with Kaposi's sarcoma treated with pegylated liposomal doxorubicin. Clin Infect Dis 2008 Aug 147(3):410-17

57. Cattelan AM, Calabro ML. Gasperini P, et al. Acquired immunodeficiency syndrome-related Kaposi's sarcoma regression after highly active antiretroviral therapy: biologic correlates of clinical outcome. J Natl Cancer Inst Monogr 2001;(28)44-9

58. Pellet C, Chevret S, Blum L, et al. Virologic and immunologic parameters that predict clinical response of AIDS-associated Kaposi's sarcoma to highly active antiretroviral therapy. J Invest Dermatol 2001 Oct; 117(4):858-63

59. Bower M, Weir J, Francis N, et al. The effect of HAART in 254 consecutive patients with AIDS-related Kaposiøs sarcoma. AIDS 2009 May 24;23(13):17101-6

60. Cooley T, Henry D, Tonda M, et al. A randomized, double blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposiøs sarcoma. Oncologist 2007 Jan; 12(1):114-23

61. Stein ME, Lachter J, Spencer D, et al. Chemotherapy for AIDS-related and endemic Kaposiøs sarcoma in Southern Africa. Int J Dermatol 1995 Oct; 34(10):729-32

62. Maskew M, Fox MP, van Cutsem G, et al. Treatment response and mortality among patients starting anti-retroviral therapy with and without Kaposiøs sarcoma: a cohort study. Plos One 2013 Jun 5; 8(6):e64392

Appendix 1: Study Questionnaire

TREATMENT OUTCOMES OF AIDS-ASSOCIATED KS AT KNH

Subject No. _____

1. The person's age at diagnosis of KS is_____ years.

2. The person's sex is

       0   female

       1 male

3. The person's current marital status is:

1. Single

2. Married

3. Widowed

4. Separated/Divorced

4. What is the duration of the person's HIV status before occurrence of KS?

  1. <1 year   3. 5-10 years

  2. 1-4 years   4. >10 years

5. The person's CD4 count at diagnosis of KS is _____ cells/ml.

6. Is the person on HAART at diagnosis of KS or 6 weeks post 1st chemotherapy course?

     0   Yes

     1   No

7. If on HAART what was the regime?

  1. D4T/3TC/NVP   8. D4T/3TC/ABC

  2. D4T/3TC/EFV   9. D4T/DDI/NVP

  3. AZT/3TC/EFV   10. AZT/3TC/NVP

4. AZT/3TC/D4T   11.ABC/3TC/NVP

5. AZT/3TC/ABC   12. ABC/3TC/EFV

6. TDF/3TC/NVP   13. Other(1st line)í í í í í í í í í í í .

7. TDF/3TC/EFV   14. 2nd lineí í í í í í í í í í í í í

8. What is the primary site of occurrence of KS? (Tick one)

   1. Tongue   4. Face   7. Torso (chest + abdomen)

   2. Palate   5. Upper limbs   8. Groin

   3. Neck   6. Lower limbs

9. What chemotherapy regime is used for treating the KS?

   1. Vincristine alone

   2. Vincristine + adriamycin

   3. Bleomycin+ Vincristine

   4. Bleomycin +Vincristine+ Adriamycin

   5. Other í í í í í í í í í í í í í í í í í

10. What is the number of courses given? í í í í í í í ..

11. What is the treatment outcome according to the protocol?

   1. Failure

   2. Stable

   3. Response   4. Transferred

Appendix 2: KIJITABU CHA MASWALI YA UTAFITI

UTAFITI KUHUSU MATIBABU YA SARATANI YA KAPOSIØS SARCOMA KWENYE WATU WENYE VIRUSI VYA HIV/UKIMWI KATIKA HOSPITALI YA KNH

Nambari ya faili ya mgonjwa ni í í í í í í í í í í í í í .

1. Umri wa mgonjwa wakati wa kupatikana na saratani ya KS ni miaka í í í í í í

2. Mgonjwa huyo ni wa jinsia(gender) gani:

   0 Mwanamke

   1 Mwamume

3. Je hali ya ndoa ya mgonjwa ni:

   1. hajaoa/hajaolewa

   2. Ameolewa/ameoa

   3. Amefiwa

   4. Ametengana

4. Je, umekuwa mgonjwa wa HIV kwa miaka ngapi kabla ya kupata saratani ya KS?

   1.< mwaka 1   3. Miaka 5-10

   2. miaka 1-4   4. Zaidi ya miaka 10

5. Kipimo chake cha cha CD 4 count wakati anapatikana na saratani ya KS ni í í í ....

6. Je, huyu mgonjwa alitumia madawa ya kuzuia makali ya HIV (yaani ARVs) wakati alipopatikana na saratani ya KS?

   0 Ndio

1 Hapana

7. Kama alitumia madawa ya ARVs ni madawa aina gani?

    1. D4T/3TC/NVP   8. D4T/3TC/ABC

    2. D4T/3TC/EFV   9. D4T/DDI/NVP

    3. AZT/3TC/NVP   10. AZT/3TC

    4. AZT/3TC/EFV   11. ABC/3TC/NVP

    5. AZT/3TC/ABC   12. ABC/3TC/EFV

    6. TDF/3TC/NVP   13. Nyingine(1st line)í í í í í í í í í í í .

    7. TDF/3TC/EFV   14. 2nd líneí í í í í í í í í í í í í .

8. Ni sehemu gani ya mwili ambapo saratani ya KS ilitokea kwanza?

    1. Ulimi   4. Uso   7. Kifua/ tumbo

    2. Mdomo   5. Mikono   8. Sehemu nyeti

    3. Shingo   6. Miguu   9. Viungo vya ndani

9. Kama anapata dawa ni madawa yapi?

    1. Vincristine pekee

    2. Vincristine na Adriamycin

    3. Bleomycin na Vincristine

    4. Bleomycin na Vincristine na Adriamycin

10. Amepewa madawa ya kansa mara ngapi? í í í í í í ..(courses)

11. Je mgonjwa amepata mabadiliko gani baada ya matibabu?

    1. Ugonjwa umeendelea

    2. Hakuna mabadiliko

    3. Amepona   4. Amedalisha hospitali