Influence of Delay on Cancer Stage Among Patients With Kaposi Sarcoma in Uganda

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Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science
in the Duke Global Health Institute
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ABSTRACT

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Abstract

The incidence of Kaposi sarcoma (KS) has increased rapidly since the advent of the HIV epidemic. Although patient outcomes have improved significantly in high-income countries after the introduction of highly-active antiretroviral medication (HAART), incidence and mortality of KS still remain high in low-incomes countries, such as Uganda, which has one of the highest incidence rates of KS in the world. Poor coverage with HAART, high seroprevalence of human herpes virus type 8 (HHV-8), the causative agent of KS, nutrition, and gender have been attributed for these poor outcomes, but other factors remain unexamined. Delaying treatment may be one of these factors that could explain poor outcomes, but there exists no empirical evidence measuring the association between delay and patient prognosis for KS patients. In response, a prospective, cross-sectional study was conducted at the Uganda Cancer Institute (UCI) among 161 HIV positive patients to measure the association between delay and overall stage risk from June-October 2012. Standardized interviews were conducted to measure delay and chart data were abstracted to obtain the cancer stage the patient received during their initial physician consultation upon admission to the UCI. In multivariate analysis after adjusting for gender, age, income, and exposure to HAART, patients who experienced delay were nearly three and a half times as likely to have an overall poor diagnosis compared to those who did not delay (OR: 3.41, p=0.002, 95% CI: 1.46-7.45). In addition, results indicate that patients who visit traditional healers

are more likely to delay treatment than those who do not delay (OR: 2.69, p=0.020, 95%CI: 1.17-6.17), and patients already in HIV care were no less likely to delay treatment than those who were not in HIV care (OR: 1.76, p=0.128, 95% CI: 0.85-3.66), despite already interacting with the health system. Eliminating harmful delays can be an important factor to intervene upon to improve patient prognosis and outcomes among HIV-associated KS patients in Uganda, and possible solutions may lie in addressing factors of the cancer care referral system.

Contents

Abstract iv

List of Tables ix

List of Figures x

Acknowledgements xi

1. Introduction 1

1.1 Global Burden of Cancer and the Cancer Divide 1

1.2 Burden of Cancer in sub-Saharan Africa 2

1.3 HIV-Associated Malignancies 3

1.3.1 AIDS-Associated Kaposi Sarcoma 5

1.3.2 Disease Progression 6

1.3.3 The Role of Delay to Treatment in KS Disease Progression 8

1.3.4. Defining Delay 9

1.3.4 Delay in Uganda: Examining KS in Context 11

1.5 Study Rationale 13

1.6 Study Aims and Hypotheses 15

2. Materials and Methods 17

2.1 Study Site 17

2.2 Study Population 19

2.2.1 Inclusion and Exclusion Criteria 19

2.4 Measuring the Independent Variable: Delay 19

2.5 Measuring the Dependent Variable: Cancer Stage 20

2.6 Statistical Methods 22
2.6.1 Sample Size 24
2.6.2 Missing Data and Misclassification 24
3. Results 26
3.1 Patient Demographics 27
3.1.1 Socioeconomic Status 29
3.2 Previous Health System Exposure 31
3.3 Previous HIV Experience 31
3.4 Patient Delay 32
3.4.1 Secondary and Tertiary Delay 34
3.5 Cancer Stage 35
3.6 Logistic Regression 36
3.6.1 Univariate Analysis: Association between Primary Delay and Overall Poor Stage Risk 36
3.6.2 Multivariate Analysis: Fully Adjusted Model 37
3.6.3 Secondary Aim: Characteristics Associated with Primary Delay 37
4. Discussion 41
4.1 Delay and Cancer Stage 42
4.1.2 Cancer Stage 44
4.1.3 Association between Primary Delay and Cancer Stage 45
4.2 Patient Characteristics 47
4.2.1 Gender 47

4.2.2. Previous HIV Care 48
4.2.3. Traditional Healers 50
4.3 Previous Exposure to HAART 51
4.3.1 Lack of Association between HAART Exposure and Cancer Stage 51
4.3.2 Leveraging HIV Care for Earlier KS Detection 53
4.3.3. Study Limitations 54
5. Conclusion 55
Appendix A: Background Information 57
A.1 Epidemiology 57
A.2 Pathogenesis and Tumor Formation 58
Appendix B: Survey 60
References 73

List of Tables

Table 1: Cancer Staging Form Adapted from the AIDS Clinical Trials Group staging for AIDS-associated Kaposi Sarcoma.. 22

Table 2: Patient Characteristics by Patient Status as Delayer or Non-Delayer 29

Table 3: Primary Findings: Distribution of Primary Delay, Overall Stage Risk, and Age by Patient Gender.. 33

Table 4: Primary,Secondary, and Tertiary Delay by Gender 34

Table 5: Univariate Logistic Regression Measuring the Association between Primary Delay and Overall Poor Stage Risk 36

Table 6: Multivariate Logistic Regression with Selected Covariates Measuring the Association between Primary Delay and Overall Poor Stage Risk 37

Table 7: Univariate Logistic Regression for Variables Associated with Primary Delay… 38

Table 8: Multivariate Logistic Regression with Selected Covariates Measuring the Association between Visitation to a Traditional Healer and Primary Delay. 39

Table 9: Multivariate Logistic Regression with Selected Covariates Measuring the Association between Previous HIV Clinic Attendance and Primary Delay 40

List of Figures

Figure 1: Diagram Describing Different Stages of Delay 11

Figure 2: Breakdown of Participants for Inclusion in the Final Cohort 27

Figure 3: Age Distribution of Men with Normal Curve 28

Figure 4: Age Distribution of Women with Normal Curve 28

Figure 5: Staging Distribution for All Subjects 36

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1. Introduction

1.1 Global Burden of Cancer and the Cancer Divide

Cancer represents a rapidly increasing global concern, as it contributes 12.7 million cases and 7.6 million deaths yearly (1). This represents a 14.2% increase from 2002 and the burden is projected to increase to 15 million annual cases by 2020 (2), making cancer an increasingly relevant disease as a focus of prevention and treatment. Incidence rates of cancer continue to rise in both developed and developing nations with rapid increases expected to continue in the developing world. In addition to the predicted increase in disease burden, cancer faces the challenge of global inequity, referred to as the "Cancer Divide" (3). The divide reflects inequity with respect to the global disparity in cancer incidence, cancer mortality, and access to essential cancer medications between the global North and the global South.

The majority of the global cancer burden already lies in less developed nations, and changing lifestyles alongside infections that cause cancer provide a combination that will result in a continually increasing cancer burden. Developing countries contribute 56% of all cases and 64% of all deaths, despite the fact that the incidence rate in these countries remains half of that compared to developed nations (4). Most of these deaths are due to cancers from infectious agents that can be prevented and controlled. Eighty percent of all preventable deaths from cancer (2.4-3.7 million) occur in low and middle-income countries (LMICs) (5), and this number is expected to grow. This

represents an area where intervention can make a large impact on the global cancer burden by reducing deaths in developing areas.

All of these inequities, however, can be traced to a lack of global funding and the international policy decisions made around cost and cost-efficacy of treating cancer in the developing world. Currently, gross inequalities exist in providing essential medicines, diagnostics, and training to combat cancer in the developing world. Only 5% of the global expenditure on cancer is spent in LMICs, although they represent 80% of the burden, resulting in a 5/80 cancer disequilibrium (3). New research should focus on closing the cancer divide by characterizing the effects of these global inequities, examining the challenges to providing treatment, and offering solutions to reach currently unreached populations with prevention and treatment regimens.

1.2 Burden of Cancer in sub-Saharan Africa

The growing burden of cancer in developing countries is reflected in the indicators of cancer in Africa, as the 715,000 incident cases in 2008 represent an increase from 2002 (1). The World Health Organization estimates that most countries in sub-Saharan Africa have ratios greater than 1:20 million for cancer radiotherapy services to patients, reflecting considerable challenges for cancer patients seeking care that often force them to delay their treatment (2).

Different statistical methods estimate that between 22.9 to 26.3 percent of all cancers in developing countries would be prevented if infectious diseases were controlled, and 32.7 percent of cancer cases in sub-Saharan Africa would be prevented

(6,7). Infectious agents only account for 7.4 percent of cancer cases in developed countries (6), but the rates of these infection-associated cancers, such as cervical, bladder, and stomach cancers, are two to five times that of developed countries, reflecting the overall higher burdens of the communicable pathogens in these countries (7). These statistics underscore the pressing need for prevention and treatment of these cancers and highlight the importance of working to better understand the epidemiology, causality, and patient outcomes concerning these cancers.

1.3 HIV-Associated Malignancies

In addition to the high burden of other infectious agents, HIV/AIDS represents a challenge for the increasing cancer burden particularly among sub-Saharan African countries, as 80% of the global burden of the 33 million total cases occurs within these countries (8). Although HIV has not been shown to be causative with respect to cancer, immunosuppression and HIV interaction with cellular processes have been shown to contribute to the development of a range of malignancies, especially Kaposi sarcoma, cervical cancer, and non-Hodgkin's lymphoma (NHL).

Several population studies help to confirm the linkage between HIV and specific cancers. HIV positive adults in South Africa and Rwanda were between 20 and 50 times more likely to develop KS than HIV-negative adults (21.9 (95% CI 12.5–38.6) to 47.1 (95%CI 31.9–69.8) (9-11). A case-referent study in Uganda found the association to be even stronger in children, as KS among HIV positive children was over 90 times as likely compared to HIV-negative children (11). Studies suggest this association for NHL and

cervical cancer among SSA populations as well. The association between HIV and NHL has been confirmed through several studies with ORs ranging from 5.0-12.6, while another study in Uganda found women with HIV were more than twice as likely to have cervical cancer compared to HIV-negative women (9-12). The association between HIV and cancer represents significant challenges for contexts like SSA that carry the heaviest HIV burden and where access to antiretroviral medication still remains below 50% (13). In fact, three HIV-associated malignancies, cervical cancer, Kaposi sarcoma, and NHL constitute three of the top ten most common cancers in SSA with cervical cancer being the most common (1). In addition, early identification, prevention, and prompt diagnosis create barriers that make controlling cancer particularly difficult.

One of the most difficult HIV-associated malignancies to control has proven to be Kaposi sarcoma. While the incidence of KS among HIV positive individuals in North American and Europe has decreased 24-fold since its peak in the early 1990s due to the advent of highly active antiretroviral therapy (HAART), it continues to rise in developing regions that lack readily available antiretroviral treatment (from 24.7 cases (95% CI 17.2–32.2) per 1000 person-years in 1994 to 4.7 (95% CI 2.7–6.7) per 1000 person-years in 1997 and 1.7 (95% CI 0.7–3.4) per 1000 person-years in recent years among HIV-infected individuals) (14). Over the same period in which the developed West saw 24-fold decrease in KS, Uganda and Zimbabwe experienced a 20 fold *increase* in KS incidence among HIV positive individuals corresponding with the rise of HIV/AIDS and the lack of antiretroviral therapy (15,16). KS is now the most common cancer in HIV

positive men in SSA and the second most common in women after cervical cancer (1). The rapid increase in incidence and heavy burden of this disease reflects the need for more research to understand the progression of the disease and the challenges that health systems face in these countries to properly control the disease.

1.3.1 AIDS-Associated Kaposi Sarcoma

Kaposi sarcoma (KS) is a "multi-centric, angio-proliferative spindle cell tumor of endothelial origin" (17,18). This means KS has no primary tumor with metastases but can spring up at multiple sites on the body with extensive vessel involvement. Tumors present as cutaneous lesions, often on the skin on the hands, legs, genitals, or oral mucosa and are often accompanied by hyperpigmentation and painful lower-limb swelling. Pulmonary and gastrointestinal dissemination can also occur. KS has traditionally been a rare neoplasm, but has become a disease of focus since the advent of the HIV epidemic that caused rapid increases in the prevalence of KS globally. AIDS-associated KS displays the most rapid progression of disease among KS types due to co-infection with HIV and is the most common of the KS types. Intervening on disease progression requires addressing the unique characteristic of KS that separate it from other cancers, namely, the rapid proliferation that occurs alongside angiogenesis and multi-centric nature of the disease, which makes prompt treatment even more important for regression of KS.

1.3.2 Disease Progression

When considering the progression of AIDS-associated KS, numerous factors must be considered. The role of highly-active antiretroviral therapy (HAART) in treating KS has been considered and examined in numerous population-based and clinical studies (19-21) Treatment with HAART is associated with the tumor regression, better patient outcomes, and can help mitigate the mutual enhancement of HIV and HHV-8 co-infection (22-25). In a study of 13 patients with HIV and KS, exposure to HAART over ten weeks corresponded to no tumor growth, and another study showed a cohort of HIV-KS patients that experienced tumor regression and decreased viral loads with HAART treatment. Other studies have found a KS response with decreased viral loads and increased CD4 counts, which can be achieved with HAART (25,26) These results show that prompt and effective treatment with HAART is important for effective disease control and for understanding the disease progression within each patient.

In addition to treatment with HAART, other factors are important to consider in the progression of AIDS-associated KS, such as gender and viral load. A cohort of 197 epidemic KS patients in Uganda revealed that women were more likely to present with lower CD4 counts, were more likely to have lesions on the face and hard palate, less likely to have lesions on the lower limbs, and were less likely than men to display clinical improvement (27). In SSA, women now represent 40% of all incident cases, and incident cases of KS between men and women are equal in Uganda. This is in contrast to the West where incident KS among women remains far below men (12, 28). HHV-8 viral

load may also play a role in the progression of the disease, as research has shown that increased viral load is associated with an increased rate of lesion eruption and later stage disease (29, 30). These results suggest that treatment with an antiviral and risk factors associated with increased HHV-8 viral load must be considered to accurately understand KS disease progression.

Despite these findings, AIDS-associated KS remains a difficult disease to control and understand. While great strides in control and regression of KS have been made with HAART, it is insufficient for complete disease regression and can have unpredictable results. Recently, research has shown persistent KS despite prompt and effective treatment with HAART (31). Other trials suggest that the best patient outcomes occur for those who receive HAART and effective chemotherapy, rather than HAART alone, calling for increased coverage with chemotherapy for KS patients in low-income settings (32). In addition to these concerns, HAART has been shown to play a role in KS proliferation in some patients due to immune reconstitution inflammatory syndrome (IRIS), a condition of intense inflammation that can cause tissue damage after the CD4 count rises too quickly after first exposure to HAART (33). These findings indicate that treatment for HIV-KS with HAART alone is unpredictable and possibly harmful, and research focusing on accessing chemotherapy and outcomes with chemotherapy should be considered. While ensuring effective antiretroviral therapy is important for initial control of KS and in areas where chemotherapy is not available, chemotherapy is believed to be essential for complete recovery (19, 21). The next step in HIV-KS control is

reaching populations with the most effective known therapy, HAART with chemotherapy. (See Appendix A for more background information on KS epidemiology and tumor pathogenesis).

1.3.3 The Role of Delay to Treatment in KS Disease Progression

Given the fact that HAART can be insufficient alone and chemotherapy is required, examining factors that influence access to these treatments must be considered. One aspect of the progression of AIDS-associated KS that remains unexamined in the literature is the role of patient and treatment delays that occur within the health system. Given the aggressive nature of AIDS-associated KS and the positive outcomes associated with prompt and effective treatment, eliminating barriers that prevent patients from accessing this treatment can be an important aspect of controlling KS. While this may not be a factor in developed countries with an infrastructure and referral system, delay must be considered in developing contexts where an increasing cancer burden is relatively new and resources are focused primarily on treatment of communicable disease rather than cancer.

Because of the rapid disease progression that can occur in AIDS-associated KS that remains untreated, it can be hypothesized that delays in receiving treatment can allow for poorer patient outcomes in those who delay treatment than in those who do not delay. Experience from other cancers suggests, however, that this may or may not be true. Apart from breast cancer, few studies have been able to establish a relationship between delay and cancer stage upon diagnosis (34, 35). A systemic review including

over 53,000 breast cancer patients captured in 14 different studies found the adverse impact of delays of 3–6 months was highly significant (odds ratio 1·24 [95% CI 1·17–1·30]) (36). Other studies have suggested, however, that tumor site and other factors are more important than the delay in determining stage and prognosis in other cancers, such as lung, rectal, and stomach cancer (34, 35) Increased survival and disease stage were not found to be associated with delay among a 2006 cohort of bladder cancer patients (37), and delay has been associated with *better* outcomes in colorectal patients in more than one population-based study (38). All this previous knowledge about the effect delays, however, has been performed in high-income countries among cancers that are not really comparable to HIV-associated KS due to their large difference in clinical presentation and progression. To better understand the effect of delay in cancer stage and prognosis, this factor should be examined across multiple types of cancers in multiple contexts.

1.3.4. Defining Delay

While delay and cancer stage or prognosis have been a subject of both empirical studies and theoretical analyses, there exist different definitions to describe delay from first seeing signs and symptoms until treatment is received. A generally accepted label for the delay that occurs from the time when a patient notices signs and symptoms until he or she seeks care is "patient delay", as it depends primarily on patient characteristics. Literature also labels this type of delay as "primary" or "appraisal" delay (39). An accepted value across literature examining cancer defines a cutoff of three months to

denote those who experience primary delay and those who do not. “Delayers” are defined as those who waited longer than three months before seeking care after noticing signs and symptoms, while “non-delayers” are those who present for care within three months of first seeing signs and symptoms (40-42).

Delay that occurs after primary delay has less clear definitions and has not been implemented in many empirical studies. Delay, however, can occur after the patient enters the health system, falling under clinician delay. This can further be broken down into two stages, “secondary”, or “illness”, delay and “tertiary”, or “utilization”, delay (39, 43). Secondary delay refers to the time between initial contact with the patient and the health system and the determination of the diagnosis. Tertiary delay refers the time between diagnosis and the initiation of treatment. It should be noted that delay does not often occur within these boundaries and responsibility for delay can be attributed to both the health system and the patient within all levels of delay. There are still questions surrounding the definition of delay and how to utilize it in empirical analyses, as it has often been used within specific context with specific cancers particularly in high-income countries. This study not only offers an opportunity to test these definitions of delay, but also to do so with a cancer in a context that has not been analyzed in this way before. Figure 1 gives an overview of the different delay stages across the continuum from initial signs and symptoms until initiation of treatment.

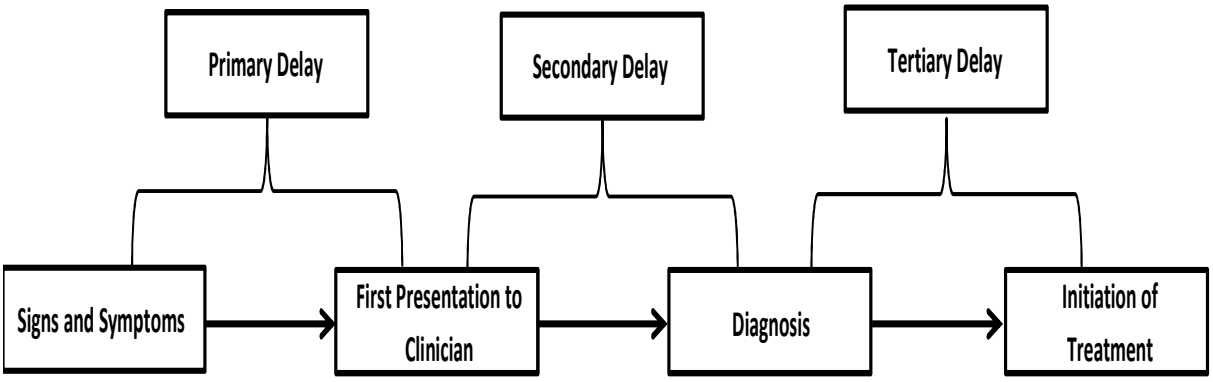


Figure 1. The three stages of delay

1.3.4 Delay in Uganda: Examining KS in Context

There are limitations to current understandings of how delay affects cancer stage upon diagnosis. First, most studies focus on populations in Western Europe or the United States and the cancers that most commonly affect these populations, such as breast cancer, colorectal cancer, and bladder cancer. Limiting delay in order to achieve better patient prognoses and understanding how delay affects cancer stage will mean examining each of these areas.

A literature review reveals that studies performed in areas other than Europe and the United States have examined topics related to delay, but few have examined the impact of delay on cancer stage upon admission or prognosis. Studies, mostly qualitative, have observed the role of stigma and social exclusion in help-seeking

behavior and the influence of traditional healers in possibly creating delay in sub-Saharan Africa, but the effects of these delays are unknown (44-46). In addition, literature that does exist that discusses treatment delay in low and middle-income countries has not empirically measured the association between delay and patient outcomes.

A qualitative study in China found that women who delayed treatment for breast cancer were more likely to experience increased tumor size and have a poorer prognosis than those who did not delay (47). A South African study established a mean delay of cervical cancer patients of 17 months, but did not examine the influence of delay on cancer stage or prognosis (48). Studies that examine the effects of delay are absent from LMICs that consist of different populations and that face unique challenges with respect to cancer awareness and health system capability. Few studies have considered the influence of delay with respect to HIV-associated malignancies, and, in any context, the association between delay and KS stage at diagnosis is yet to be examined.

Uganda provides an example of a setting where each of these factors can be examined. The country has a growing cancer burden, a heavy burden of infectious diseases, and a health system that struggles to treat cancer patients country-wide (WHO 2010). While the yearly burden of approximately 27,100 cancer cases may seem relatively small to the burden of infectious diseases, the mortality rate of those diagnosed with cancer is 79 percent (1). There exists one referral center for the entire population of

cancer patients in the country, the Ugandan Cancer Institute. AIDS-associated Kaposi sarcoma contributes the largest cancer burden in Uganda with 5,200 annual cases (19.2 percent of all cancer) and a mortality rate of 81.5 percent (1). Uganda has hosted numerous studies examining AIDS-associated KS (11, 27, 29, 31), and is now recognized as an important location for examining KS due to its high burden of KS and high sero-prevalence of HHV-8. These factors have come to place Uganda in the middle of the "KS-belt", a geographic region where KS has some of the highest incidence rates in the world.

1.5 Study Rationale

Because of the increasing burden of cancers in Uganda, especially those associated with HIV infection like KS, empirical research is needed to assess the epidemiology, causal linkages, and health outcomes for patients with HIV-associated malignancies. In response to the increasing burden of patients with HIV-associated cancers in Uganda, especially with respect to KS, and the larger questions surrounding the emergence of cancer in sub-Saharan Africa, this study will seek to contribute to the body of empirical literature describing and explaining cancer in SSA. It will also address questions surrounding the role of delay in cancer stage and prognosis, particularly among cancers that are prevalent in developing areas where there exist different health system challenges. Also, it will add to understandings of AIDS-associated KS and the lack of evidence concerning the delays patients with the disease face. Specifically, it will

attempt to examine the prevalence of treatment delays and the effect of those delays in a population of Ugandan patients with AIDS-associated Kaposi-sarcoma.

In addition, the study will address questions surrounding the roles of HAART and chemotherapy in addressing Kaposi sarcoma. While it has been established that HAART reduces the incidence of KS (14), it is unclear to what extent antiretroviral drugs (ARVs) can impede the progression of disease in KS patients or what role ARVs can play as treatment for KS. There are also new questions surrounding the predictability of HAART effectiveness given the poor outcomes in patients who develop immune reconstitution inflammatory syndrome (IRIS) and others who do not respond to HAART at all. In addition, treating KS with HAART alone has been shown to improve outcomes among patients with early stage KS (49), but has been unexamined among patient populations with later stage disease or extensive tumor involvement, which is the case for the majority of patients in Uganda. Examining the association between the duration on HAART before initiation of chemotherapy and the KS stage can lead to conclusions to the efficacy of HAART as treatment for KS in areas without access to chemotherapy.

Finally, the study will contribute to knowledge surrounding the effect of delay on cancer stage for adults with Kaposi sarcoma in developing regions. While middle and high-income countries now enjoy a low incidence of AIDS-associated KS and increased survival, contexts like Uganda still face increasing incidence and poor survival rates. Further, explanations for these poor outcomes, such as delay, have been left unexamined. Poor health systems, a lack of cancer knowledge at the population level,

poor prevention, and a lack of access to drugs are often blamed for delayed treatment and subsequent poor outcomes in these low-income countries, but empirical evidence measuring these associations and the extent of these associations is scarce. By measuring the prevalence of delay and the relationship between delay and KS cancer stage upon admission, this study will add to current understandings of AIDS-associated KS in Uganda and cancer in SSA and serve as an impetus for creating effective healthcare infrastructure to address the rising burden of cancer.

1.6 Study Aims and Hypotheses

KS incidence and mortality is increasing in Uganda, and delays in obtaining treatment have been observed. Delaying treatment may be an important factor to intervene upon, particularly considering that most KS patients are already within the health system as HIV patients. Empirical evidence measuring the association between delay and cancer stage, however, is lacking. In response, this study will seek to answer two questions: What is the effect of treatment delays on patient cancer stage? What factors are associated with delay?

- **Primary Aim**: To measure the association between primary delay and overall poor stage risk
    - *Primary Hypothesis*: Patients who experience primary delay will be more likely to have an overall poor stage risk upon admission to UCI than those who did not experience delay.

- **Secondary Aim**: To determine which patient characteristics are associated with primary delay
    - *Secondary Hypothesis*: Patients who are already interacting with the health system as HIV patients will be less likely to experience primary delay than those who are not already interacting with the health.

2. Materials and Methods

This was a prospective, cross-sectional study of 161 HIV-seropositive patients with histologically confirmed AIDS-associated Kaposi sarcoma; the primary aim was to measure the association between the delay of treatment onset and the cancer stage upon admission to the study site, the Uganda Cancer Institute. Standardized interviews were completed to measure treatment delays, demographic characteristics, and confounding variables, such as socioeconomic indicators and history of HAART (see Appendix B).

Interviews were 30 minutes in length, and all were administered by the primary investigator in English unless the patient was non-English speaking in which case the interview was translated in Luganda by a translator. All translators were trained in ethical considerations regarding patient consent and data collection and performed mock interviews and pilot surveys before actual data collection. Chart data were utilized to gather information on KS stage upon diagnosis.

Per study protocol, verbal consent was obtained for all subjects to undergo the interview and for the release of relevant medical information from the patients' medical records. This study was approved by both the Duke University International Review Board for Research with Human Subjects and the Makerere College of Health Sciences Research Ethics Committee (no.2011-161).

2.1 Study Site

The study was performed at the Uganda Cancer Institute (UCI) at Mulago Hospital in Kampala, Uganda, the only specialized cancer treatment center in the

country. As such, the institute is the starting point for definitive treatment for nearly every case of cancer that is treated with chemotherapy in the country. It is the only location for radiotherapy services, meaning the ratio of radiotherapy centers to population is greater than 1:35 million. While the institute offers many government-subsidized chemotherapy regimens for low cost or free of charge, transport costs for many poor patients coming from around the country and health system failure still constitute significant barriers to accessing the treatment that result in significant treatment delays.

Begun 40 years ago as a collaboration between Makerere University and the National Cancer Institute in the United States, UCI originally focused on Burkitt's lymphoma primarily in children. The institute has grown and is now the primary treatment center for all cancer in Uganda. For East Africa and SSA, UCI represents a significant advancement in cancer care, as the services offered are completely absent in other countries. In addition, a partnership with the Fred Hutchinson Cancer Center from the University of Washington has produced the Uganda Program on Cancer and Infectious Disease (UPCID), which focuses on improving cancer care and research capacity. Despite these advanced, however, significant challenges still remain for achieving cancer control in Uganda.

2.2 Study Population

2.2.1 Inclusion and Exclusion Criteria

The study was performed among adults (≥ 18 years old) who had histologically confirmed Kaposi sarcoma, were HIV seropositive, and had a CD4 count performed within the previous 6 months. Because most KS patients at UCI receive chemotherapy regimens through the out-patients department, most study subjects were out-patients at the Uganda Cancer Institute. Because UCI is the only cancer center in the country, subjects came from various geographic locations across the country. All subjects who received chemotherapy prior to admission to the UCI were excluded from the study to eliminate confounding due to previous treatment.

2.4 Measuring the Independent Variable: Delay

Criteria for determining delay was based on a cutoff of three months between first noticing signs and symptoms and seeking care, which is a widely accepted figure for cancer patients based on numerous population-based studies in the West, but remains relatively unused in LMICs (35, 39-43). Data were gathered for delay at all points in a patient's history from first noticing signs and symptoms until receiving treatment, representing primary, secondary, and tertiary delay (see introduction for definitions). Primary delay and secondary delay were determined through patient interviews and was recorded as a categorical variable. Tertiary delay was determined from chart records using the date of the reported biopsy result for the date of diagnosis

and the date first administration of chemotherapy for the date of treatment and was recorded as a continuous variable.

Patients were categorized by the time delay occurred, rather than attempting to ascertain the responsibility in the delay. For example, a patient who delayed to go to the laboratory for investigations after being seen by a doctor would still be classified as a secondary delayer, despite the fact that he or she played a role in the delay created.

2.5 Measuring the Dependent Variable: Cancer Stage

The cancer stage determined upon admission to the UCI was used to measure the extent of disease and was taken from patient charts from their first visit. These data were recorded after each interview and were obtained from the stage reported by the physician in the patient record. This study used the staging system for AIDS-associated Kaposi sarcoma as designed by the AIDS Clinical Trials Group (ACTG), which is used by physicians at the UCI. Patients were dichotomized as either having "good risk" or "poor risk" based on this system which is described below and in Table 1.

Originally conceived in 1989, the ACTG staging system was designed to determine prognosis for AIDS-associated KS patients based on three risk areas, extent of tumor involvement, immune system status, and presence of systemic illness. A designation of "poor risk" or "good risk" is given for each risk area to give an overall stage.

Poor risk for extent of tumor involvement is described as having any tumor-associated edema, extensive raised KS, oral KS nodules not confined to the palate, or any

KS of the gastrointestinal tract or any other non-nodal viscera. Good risk for tumor extent indicates that all KS nodules, or lesions, are confined to the skin or lymph nodes and any oral involvement is confined to the palate only. The immune system status is measured by CD4 count with a determined cutoff designated as poor or good risk. This study implemented the suggestion of the 1997 ACTG staging validation study that performed a prospective survival analysis (52). The results indicated that the original cutoff set in 1989 of 200 CD4 cells per cubic microliter was too high, as a cutoff of 150 more accurately predicted survival and reflected the patients' disease status. Therefore, this study used a cutoff of 150 cells per cubic microliter.

Good risk for the presence of systemic illness is measured as no history of opportunistic infections, "B" symptoms, or any other HIV-related illness (e.g. neurologic disease, lymphoma). Opportunistic infections are determined by the CDC Clinical Category C, which includes AIDS-defining conditions. B symptoms are defined as the presence of HIV-associated illness by the CDC Clinical Category B, which includes drenching night sweats, greater than 10% body weight loss, unexplained fevers, or diarrhea persisting for greater than two weeks. See table 1 for an overview of the staging system used below.

Table 1. Cancer Staging Form Adapted from the AIDS Clinical Trials Group staging for AIDS-associated Kaposi Sarcoma.

Category	Description	Risk Assessment
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease (non-nodular, confined to palate)	Good Risk = 0 ☐
	Tumor-associated edema or ulceration **OR** Extensive oral KS **OR** KS of GI tract **OR** KS in other non-nodal viscera	Poor Risk = 1 ☐
Immune System (I)	CD4 >150 cells/μL	Good Risk = 0 ☐
	CD4 <150 cells/μL	Poor Risk = 1 ☐
Systemic Illness (S)	No history of opportunistic infection or thrush" **AND** "B" symptoms absent (include unexplained fever, night sweats, >10% weight loss, or diarrhea persisting > 2 weeks) **AND** KPS ≥ 70	Good Risk = 0 ☐
	History of opportunistic infection and/or thrush" **OR** B" symptoms present OR KPS < 70 **OR** Presence of other HIV-related illness (e.g., neurologic disease, lymphoma)	Poor Risk = 1 ☐

2.6 Statistical Methods

Data were stored in Microsoft Excel 2010 and analyzed using Stata/SE v.11.0 (College Station, Texas). Descriptive statistics were measured using means and standard deviations and percentages to obtain prevalence of delay, mean ages, age distribution, and prevalence of different staging criteria. Univariate analyses were performed to measure the association between patient characteristics and cancer stage upon admission (aim 1). Logistic regression implementing a generalized linear model

assumption with binary outcomes was implemented to model all associations and obtain prevalence odds ratios. A multivariate model was created to measure the association between primary delay and an overall poor stage risk ($T_1I_1S_1$), after adjusting for age, gender, income, ability to pay-out-of pocket, and exposure to HAART. Gender and ability to pay-out-of pocket were included in the model because they were significantly associated with overall poor stage risk in the univariate analysis (Table 2) and were determined to qualify as a covariate with direct acyclic analysis. Age, income, and exposure to HAART were anchored in the model based on clinical knowledge and previous literature, which suggests that these variables may be associated with delay and cancer prognosis (22, 27).

To address the second aim, univariate analyses were also completed to measure the association between patient characteristics and having the status a primary delayer. The only statistically significant characteristic, visitation to a traditional healer, was tested in a multivariate model for the association with primary delay, adjusting for age, gender, income, ability to pay-out-of pocket, and exposure to HAART. A third multivariate model was created to test the hypothesis that previous HIV care would be associated with primary delay and measured the association between previous HIV clinic attendance and primary delay, adjusting for age, gender, income, ability to pay-out-of pocket, and visitation to a traditional healer. Covariates for both multivariate models within the second aim were anchored in the model based on clinical knowledge,

analyses with directs acyclic graphing, and previous literature findings, as none of them were significantly associated with delay in the univariate analysis (48, 53)

2.6.1 Sample Size

Using a prevalence estimate for delay of 20%, a sample size calculation that is precise at the 0.05 level, has 80% power, and can detect a nine percent difference in the proportion of outcomes yielded a sample size of 168 study participants, which was the target for this study.

2.6.2 Missing Data and Misclassification

Missing data and misclassification can introduce bias and modify true associations. In our data, three variables, exposure to HAART, distance to the nearest clinic, and income, had missing data. The reason for all missing data points were the because of the patients' inability to recall or decipher an answer. Exposure to HAART had six missing responses and level of income had six missing data points, while distance to a nearest clinic in kilometers had twenty-six missing data points, likely due to an inability to know an exact number of kilometers to the nearest clinic. It was determined that all missing data points were missing at random (MAR) data, as it was determined that their probability of being missing was not associated with their status as a delayer or non-delayer or their status of having good or poor stage risk, the outcome variables of interest. Therefore, no additional analyses were required. Because distance to a nearest clinic was only used as a descriptor and not in any multivariate model, no additional analyses were performed.

Over the course the study it became clear that misclassification may also threaten the validity of the study with respect to correctly classifying the correct staging for each patient. Patients in the study were initially seen and staged by a range of physicians at the UCI, each with their own style of history taking. In particular, the presence of systemic illness, the "S" category, could be subject to variation based on the physician the patient saw, as determining risk in this category relies on a more extensive history, which was not present in some chart data. Again, however, there is no reason to believe that the misclassification that may have occurred was associated with the patient status as either a delayer or having a particular stage risk. Specific physicians did not discriminate the patients that they saw based on their status as a delayer or having a certain stage risk, so one can reasonably infer that any misclassification happened uniformly throughout the cohort, which would not bias the true association between delay status and stage risk.

3. Results

From June 22 to October 30, 2012, 161 consecutive AIDS-associated KS patients were treated at the Uganda Cancer Institute. The survey response rate was 90%, and 265 total files were assessed throughout the course of the study (Figure 2). Among those patients, 73 (45.3%) experienced primary delay longer than three months. Fifty-five (75.3%) of all delayers were men, while 18 were women. Among the 111 men in the study, the percentage experiencing primary delay was nearly equal to those who did not experience delay (49.5 v. 50.5), but the percentage of women who delayed was nearly half that of those who did not delay (36.0 v 64.0), suggesting delay is more likely to occur in men, but this was not significant (p=0.112) (Table 3).

Among all study participants, 46 (28.6%) had an overall poor risk as their KS stage upon admission. Of those, 37 (80.4%) were men, while 9 were women. The percentage of men who had an overall poor stage risk was 33.3% compared to 18.0% for women.

Figure 2. Flow of Participants for Inclusion in the Final Cohort

3.1 Patient Demographics

The ratio of men to women was 2.2:1, which is slightly higher than the traditional literature value of 1.7:1 (Huminer 1989). The mean age was 34.0 years (SD: 7.7) with a slightly lower age distribution for women. Using a Wilcoxan rank-sum test for difference in means revealed that the mean age was not significantly different between men and women (p=0.13; see Table 3). Histograms of age distribution by gender with normal curves are shown in Figure 1 and Figure 2.

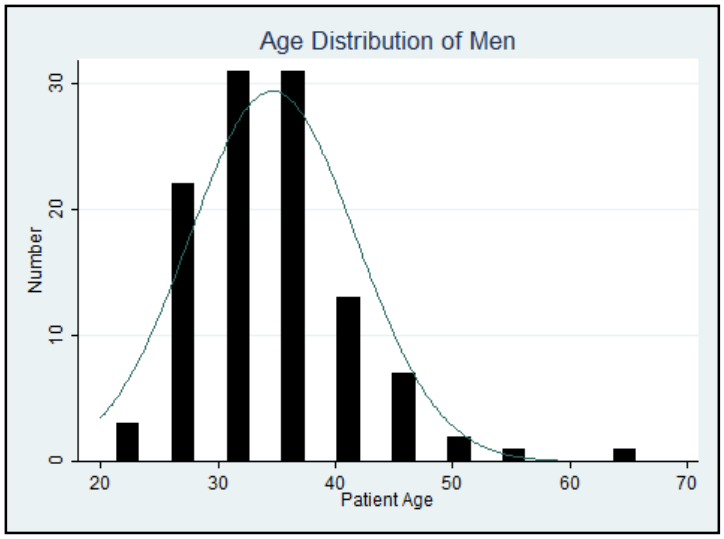


Figure 3. Age Distribution of Men with Normal Curve

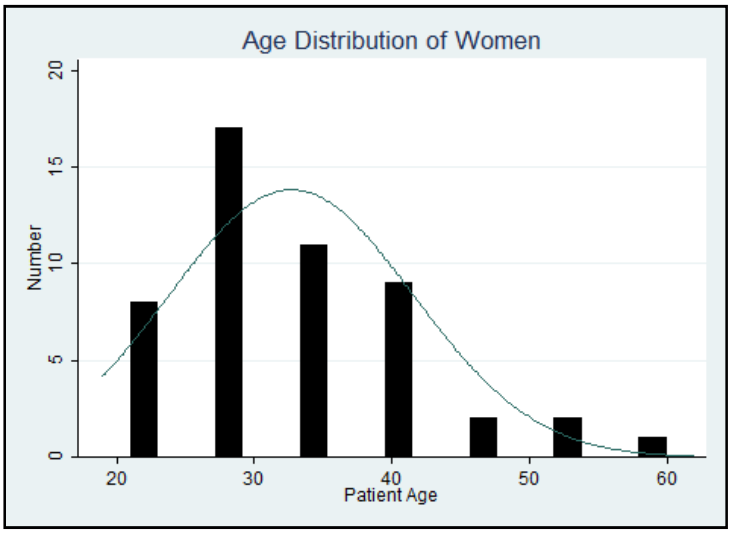


Figure 4. Age Distriubtion of Women with Normal Curve

3.1.1 Socioeconomic Status

Considering socioeconomic status, results reflect the overall low socioeconomic status of patients. Fifty-eight (35.4%) of all subjects were unemployed, and 17 (10.6%) of those unemployed had no income from any source. Fifty-eight percent of all patients who could recall (n=155) earned less than 100,000 UGSH ($40) per month, which is less than two dollars per day, and only 6 (3.9%) earned over 1,000,000 UGSH in one month (range 0-2.5 million UGSH per month). This is also reflected in the level of education, as over half had only completed primary school as their highest level of education (Table 2).

Payment-out-of-pocket for tests or chemotherapy had a protective effect from having an overall poor stage risk in the univariate analysis, as patients with an overall poor stage risk were more than three times less likely to have to pay out of pocket than those with an overall good stage risk (Table 2). Other Socioeconomic characteristics are displayed by status as having poor or good overall risk in Table 2.

Table 2. Patient Characteristics by Patient Status as Delayer or Non-Delayer

Characteristic	**Overall Stage Risk**						
	Good Risk		Poor Risk		Total		**P-Value**
	No.	Col %	No.	Col %	No.	Col %	
Patient Gender							
Male	74	64.3	37	80.4	111	68.9	
Female	41	35.7	9	19.6	50	31.1	0.050*
Total	115	100.0	46	100.0	161	100.0	
Patient Age							
<30	35	31.3	9	20.0	44	28.0	
31-40	59	52.7	26	57.8	85	54.1	

>40	18	16.1	10	22.2	28	17.8	0.143*
Total	112	100.0	45	100.0	157	100.0	
Monthly Income							
<100,000 UGSH	63	57.3	27	60.0	90	58.1	
100K-500K UGSH	45	40.9	14	31.1	59	38.1	
>500,000	2	1.8	4	8.9	6	3.9	0.667
Total	110	100.0	45	100.0	155	100.0	
Level of Education							
Primary	57	49.6	26	56.5	83	51.6	
Secondary	44	38.3	14	30.4	58	36.0	
Tertiary or Degree	14	12.2	6	13.0	20	12.4	0.617
Total	115	100.0	46	100.0	161	100.0	
Paid Out-of-Pocket for Tests or Chemo							
No	57	49.6	36	78.3	93	57.8	
Yes	58	50.4	10	21.7	68	42.2	0.001
Total	115	100.0	46	100.0	161	100.0	
Distance to Nearest Government Clinic							
<5km	46	47.4	18	47.4	64	47.4	
6-10km	20	20.6	7	18.4	27	20.0	
11-30km	22	22.7	6	15.8	28	20.7	0.578
>30km	9	9.3	7	18.4	16	11.9	
Total	97	100.0	38	100.0	135	100.0	
Visited Traditional Healer							
Yes	30	26.1	11	23.9	41	25.5	
No	85	73.9	35	76.1	120	74.5	0.775
Total	115	100.0	46	100.0	161	100.0	
Referred From Another Clinic							
No	23	20.0	16	34.8	39	24.2	
Yes	92	80.0	30	65.2	122	75.8	0.051
Total	115	100.0	46	100.0	161	100.0	
Previous HIV Clinic Attendance							
<3 Months	27	24.3	13	29.5	40	25.8	
>3 Months	84	75.7	31	70.5	115	74.2	0.504
Total	111	100.0	44	100.0	155	100.0	
Exposure to HAART							
No	27	24.8	17	37.0	44	28.4	
Yes	82	75.2	29	63.0	111	71.6	0.127 *
Total	115	100.0	46	100.0	155	100.0	

*Indicates variable was included in multivariate model

3.2 Previous Health System Exposure

For 112 patients (69.8%), KS was their first hospital admission. Among those who had been previously admitted (n=48), tuberculosis and malaria were the most common reasons for a previous admission, accounting for 18.6% of all previous admissions. In the univariate analysis, being referred from an outside clinic showed to have a protective effect, as the odds of having an overall good stage risk were 53.1% lower for those who were not referred compared to those who were referred from an outside clinic (OR: 0.47, see Table 2). This may suggest a first contact from a referral unit is important in obtaining prompt care.

In addition to visiting referral units, 41 (25.5%, n=161) visited a traditional healer prior to seeking care from a physician. Among those visiting a traditional healer, six (14.6%, n=41) reported that they were satisfied with their consultation with the traditional healer, and eight (19.5%) reported that they were referred to a hospital by the traditional healer after treatment failure. Health system characteristics are displayed by status as having poor or good overall risk in Table 2.

3.3 Previous HIV Experience

Data reveal that the majority of this cohort was already engaged in the health system through various forms of HIV care. Among all subjects, 149 (92.6%) had previously received some form of treatment at an HIV clinic upon admission to the Uganda Cancer Institute. The majority of patients were already enrolled in HIV care with over 75% reporting enrollment at an HIV clinic before admission to the UCI

(Table 2). In addition, 106 (73.1%) of all subjects were taking highly-active antiretroviral medication (HAART) upon admission with 77 of those being exposed to HAART for greater than 3 months. Thirty-nine (25.8%) reported being on antiretroviral medication (ARVs) when they first noticed signs and symptoms of KS, indicating possible unresponsiveness to HAART. Patient compliance may have also played a role, as 49 (46.2%, n=106) of those on HAART admitted non-adherence to their ARV regimens, although only 13 (26.5%) reported missing greater than 5 doses in the last month.

Results suggest stigma was not a factor in seeking care. Sixty-two (38.5%, n=161) reported feeling stigma from the HIV positive serostatus, but only 22 (13.8%) reported that stigma forced them to delay going to the hospital or to conceal their symptoms. Previous HIV characteristics are displayed by status as having overall poor or good risk with associated P-values in Table 2. Gender, payment out-of-pocket for tests and chemotherapy, referral from another health clinic, and exposure to HAART were significantly associated with an overall poor stage risk in the univariate analyses.

3.4 Patient Delay

Nearly half of all patients reported that they delayed greater than three months before seeking care after first noticing signs and symptoms of KS (Table 3). Among those who delayed, 26 (35.6%, n=73) waited for more than 6 months, while 18 (24.7%) waited for more than 12 months. Most reported that upon seeing

symptoms, they knew they were sick but suspected another illness (99 individuals, 61.5%). The most commonly cited noticeable symptom was having skin lesions (130 individuals, 80.8%). Also cited were oral lesions (24, 14.9%), lower limb swelling, and hyperpigmentation. Among those who delayed, when asked the reason for the delay, 35 (47.9%) reported that they felt no pain, 23 (31.5%) cited a lack of money, six (8.2%) said the distance to the hospital was too far with the remaining reporting other reasons.

Table 3. Primary Findings: Distribution of Primary Delay, Overall Stage Risk, and Age by Patient Gender

	Male		**Female**		**Total**	
	No.	Col %	No.	Col %	No.	Col %
Primary Delay						
<3 Months	56	50.5	32	64.0	88	54.7
>= 3 Months	55	49.5	18	36.0	73	45.3
Total	111	100.0	50	100.0	161	100.0
Overall Stage Risk						
Good Risk	74	66.7	41	82.0	115	71.4
Poor Risk	37	33.3	9	18.0	46	28.6
Total	111	100.0	50	100.0	161	100.0
Patient Age						
<30	25	23.1	19	38.8	44	28.0
31-40	65	60.2	20	40.8	85	54.1
>40	18	16.7	10	20.4	28	17.8
Total	108	100.0	49	100.0	157	100.0

	Male		Female		Total		**P-Value**
	Mean	SD	Mean	SD	Mean	SD	
Mean Age	34.6	7.1	32.7	8.9	34.0	7.7	0.134

3.4.1 Secondary and Tertiary Delay

In addition to patient delay, data were collected on the secondary delay and tertiary delay that was experienced by subjects. Forty-seven (29.2%, n=161) patients experienced secondary delay longer than one month, while 26 (16.1%) experienced delay less than one week. Twenty-one (13.0%) patients experienced tertiary delay greater than 90 days, and the median delay time was 23 days (IQR: 11-47) with a mean delay of 42.7 days (SD: 53.1). Characteristics of all delay types of gender are displayed in Table 4 below.

Table 4. Primary, Secondary, and Tertiary Delay by Gender

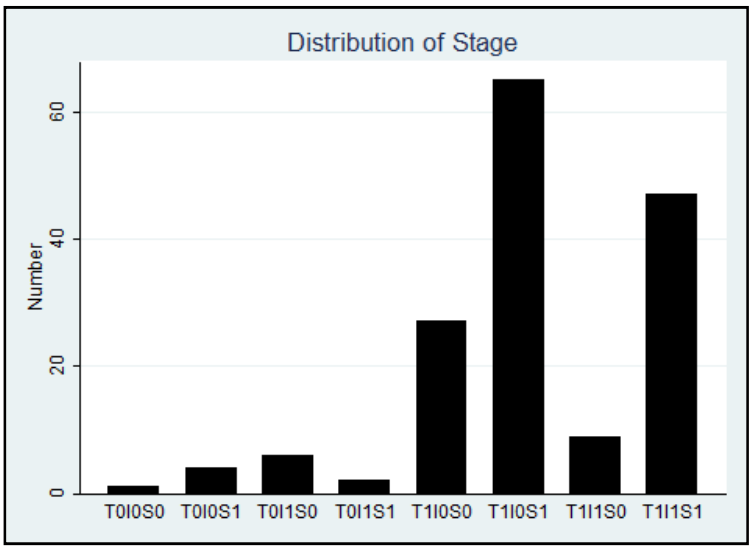
Delay Type	**Gender**					
	Male		**Female**		**Total**	
	No.	Col %	No.	Col %	No.	Col %
Primary Delay						
<3 Months	56	50.5	32	64.0	88	54.7
>= 3 Months	55	49.5	18	36.0	73	45.3
Total	111	100.0	50	100.0	161	100.0
Secondary Delay						
>1 Week	17	15.3	9	18.0	26	16.1
2 Weeks - 1 Month	63	56.8	25	50.0	88	54.7
>1 Month	31	27.9	16	32.0	47	29.2
Total	111	100.0	50	100.0	161	100.0
Tertiary Delay						
0-7 Days	13	11.7	7	14.0	20	12.4
8-30 Days	49	44.1	24	48.0	73	45.3
31-90 Days	35	31.5	12	24.0	47	29.2
>90 Days	14	12.6	7	14.0	21	13.0
Total	111	100.0 5	0	100.0	161	100.0

3.5 Cancer Stage

One hundred forty-eight (91.9%) patients were assessed as having poor risk with respect to the extent of tumor involvement (T). Sixty-four (39.8%) had poor risk considering their immune system function, and 118 (73.3%) had poor risk in the systemic illness category. Forty-seven (29.2%) patients had an overall poor stage risk ($T_1I_1S_1$) for KS upon admission to the Uganda Cancer Institute. Thirty-seven were men and nine were women, which was a significant difference for the association between gender and an overall poor stage risk ($p=0.050$) in the univariate analysis, suggesting a possible protective effect for female gender.

The most common stage was poor risk in both the tumor (T) and systemic illness categories (S) and good risk in the immune system category (I), as 65 (40.4%) patients were admitted with this stage ($T_1I_0S_1$). Twenty-seven (16.8%) had poor risk in the tumor category with good risk with respect to immune system function and systemic illness ($T_1I_0S_0$), and nine (5.6%) individuals had poor risk in the tumor and immune system categories with good risk with respect to systemic illness ($T_1I_1S_0$). The remaining individuals were spread evenly across the remaining staging combinations.

Figure 5. Distribution of Staging for All Subjects



3.6 Logistic Regression

3.6.1 Univariate Analysis: Association between Primary Delay and Overall Poor Stage Risk

An unadjusted measure of the main association of interest reveals that patients who experienced primary delay were 3.59 times as likely to have an overall poor stage risk upon admission than those who did not experience primary delay (Table 5).

Table 5. Univariate Logistic Regression Measuring the Association between Primary Delay and Overall Poor Stage Risk

Variable	Odds Ratio	Std. Err	P>|0.05|	[95% Conf Interval]
Primary Delay	3.59	1.33	0.001	1.74 - 7.41

3.6.2 Multivariate Analysis: Fully Adjusted Model

After adjusting for selected covariates and implementing logistic regression, patients who experienced delay were still 3.41 times as likely to have an overall poor stage risk than those who did not experience primary delay (Table 6). Selected covariates included gender, age, income, and exposure to HAART.

Table 6. Multivariate Logistic Regression with Selected Covariates Measuring the Association between Primary Delay and Overall Poor Stage Risk

Variable	Odds Ratio	Std. Err.	P>|0.05|	[95% Conf. Interval]
Primary Delay	**3.41**	**1.36**	**0.002**	**1.46 - 7.45**
Selected Covariates				
Gender	0.50	0.23	0.144	0.19 - 1.27
Age	1.64	0.50	0.102	0.91 - 2.97
Income	1.00	0.35	0.992	0.51 – 1.99
Exposure to HAART	0.60	0.25	0.216	0.26 - 1.35

3.6.3 Secondary Aim: Characteristics Associated with Primary Delay

In addition to measuring the primary association between primary delay and overall stage risk, univariate analysis was completed in an attempt to ascertain statistically significant characteristics associated with those who experienced primary delay. In univariate analysis, only visitation to a traditional healer was significantly associated with primary delay (Table 7).

Table 7. Univariate Logistic Regression for Variables Associated with Primary Delay

Variable	Odds Ratio	Std. Err	P>|0.05|	[95% Conf Interval]
Gender	0.57	0.57	0.112	0.29 – 1.14
Age	0.76	0.18	0.266	0.48 – 1.23
Income	1.17	0.33	0.584	0.67 – 2.03
Education	0.98	0.22	0.921	0.63 – 1.53
Payment out-pocket	0.61	0.20	0.123	0.32 – 1.14
Distance to clinic	0.88	0.14	0.414	0.64 – 1.20
Visited Trad. Healer	**2.56**	**1.01**	**0.017**	**1.19 – 5.54**
Referred patient	1.45	0.54	0.323	0.69 – 3.03
Previous HIV Clinic	1.55	0.51	0.128	0.82 – 2.96
Exposure to HAART	0.90	0.32	0.763	0.45 – 1.81

One variable, enrollment in an HIV care clinic, was of particular importance because of its implications for improving patient care. It was hypothesized that those who were already enrolled in HIV care before noticing signs and symptoms would be less likely to delay because of their involvement in the health system. Measuring this association in multivariate analysis, however, revealed a trend that patients who were enrolled for at least six months in HIV care before admission to the UCI may *more* likely to experience primary delay than those who were not enrolled in HIV care, although this was not statistically significant (Table 8). Covariates adjusted for included patient gender, age, income, payment out of pocket for tests and chemotherapy, and visitation to a traditional healer.

The only patient characteristic that was significantly associated with primary delay in the univariate analysis was visitation to a traditional healer. After adjusting for gender, age, income, payment out-of-pocket, and previous HIV clinic attendance, this association was still significant, indicating that patients who visited a traditional were more than two and a half times as likely to experience primary delay than those who did not visit a traditional healer (Table 9).

Table 8. Multivariate Logistic Regression with Selected Covariates Measuring the Association between Visitation to a Traditional Healer and Primary Delay

Variable	Odds Ratio	Std. Err.	P>|0.05|	[95% Conf. Interval]
Visitation to traditional healer	**2.69**	**1.14**	**0.021**	**1.17 – 6.17**
Selected Covariates				
Gender	0.91	0.42	0.835	0.37 – 2.25
Age	1.03	0.32	0.909	0.56 – 1.19
Income	0.50	0.21	0.092	0.23 – 1.11
Pay out-of-pocket	0.96	0.40	0.923	0.43 – 2.17
Exposure to HAART	0.79	0.34	0.581	0.34 – 1.84

Table 9. Multivariate Logistic Regression with Selected Covariates Measuring the Association between Previous HIV Clinic Attendance and Primary Delay

Variable	Odds Ratio	Std. Err.	P>|0.05|	[95% Conf. Interval]
Previous HIV clinic attendance	**1.76**	**0.66**	**0.128**	**0.84 – 3.66**
Selected Covariates				
Gender	1.08	0.43	0.843	0.49 – 2.37
Age	1.89	0.53	0.022	1.09 – 3.27
Income	0.54	0.18	0.064	0.28 – 1.03
Pay out-of-pocket	1.19	0.44	0.634	0.58 – 2.46
Exposure to HAART	0.97	0.42	0.946	0.41 – 2.29

4. Discussion

Early diagnosis of cancer is an aim of cancer care and control programs worldwide, especially among LMICs that are experiencing an increasing cancer burden. This is particularly true among HIV-associated malignancies that can leverage current HIV programs to detect cancer faster. Despite the fact that it is often difficult to define and measure delay, as there are many conflicting methods and theories, this can be an important factor to better understand how delay affects patient outcomes, particularly in contexts with struggling health systems. While numerous studies have offered theoretical frameworks for understanding delay, few have measured these delays across the entire continuum from first notice of signs and symptoms until treatment (39, 40, 51). Moreover, to the best of our knowledge, none have examined delays and their influence on cancer stage or patient outcomes in developing areas or delays with respect to HIV-associated malignancies in any context.

In response to this gap in understanding, this study measured the association between primary delay and the cancer stage upon admission among a cohort of 161 Kaposi sarcoma patients in Uganda. Kaposi sarcoma patients who experienced primary delay were nearly three and a half times as likely to present with an overall poor risk cancer stage compared to those who did not experience delay. As KS staging has been shown to be an effective predictor of survival and disease regression, our results indicate that addressing delay might be key to improving patient outcomes (52, 54). Some of our results, however, differ from previous findings and are reflective of the unique

challenges of treating cancer in Uganda, particularly HIV-associated KS,. Overall, delay may be an important factor upon which healthcare providers and public health initiatives can intervene to improve patient outcomes for KS patients in Uganda.

4.1 Delay and Cancer Stage

The prevalence of overall primary delay (Table 1) is higher than previous research examining delay among Kaposi sarcoma patients at UCI, which found that approximately 27% of patients delayed (53). This difference may be attributed to the variance among cohorts or the delivery of the question by interviewers. A literature review did not yield any previous study which has measured delay among KS patients anywhere, but a South African cohort of cervical cancer patients had a much longer mean delay time of 17 months, which could be attributed to the more rapid progression observed in KS as compared to cervical cancer (48). More research should be completed in other contexts and with other cancers to determine the relative severity of delay in this cohort as well as to better understand the unique challenge KS patients face in seeking treatment.

In addition to primary delay, data were taken for secondary and tertiary delay to determine how delay occurs across the entire symptoms-to-treatment continuum. The data are also useful for determining appropriate benchmarks for determining delay at these levels, as there are no generally accepted values in the literature. Previous studies performed with other cancers, primarily in developed contexts, have found median primary delay to range from 21 to 900 days, depending on the type of cancer (55, 56).

The median primary delay for other types of cancer has been measured as ranging from 9-35 days in breast cancer, 10-46 days in thoracic cancer, 8-157 days for cancer of the gastrointestinal tract, and 10 days-14.8 months for soft tissue sarcoma patients (39).

While this study did not measure primary or secondary delay as a continuous variable due to difficulty with patient recall, 39.8% experienced delays greater than 90 days, which suggests that this cohort of KS patients experienced primary delays which are greater than other measured cancers. The same may be true of secondary delay, as this study found only 16.2% experienced delays less than 21 days, while 29.2% experienced delays greater than 60 days. These results seem to be more consistent than other literature values that found median secondary delay to range from 36 days for head and neck cancer to 65 days for cancer of the thorax, but it is still unclear how secondary delay for KS patients in Uganda compares to other cancers given the dearth of data and inadequacy of comparing studies assessing these types of cancer in high-income countries only (57, 58).

When examining tertiary delay, which was recorded as a continuous variable due to the availability of admission and treatment chart data, this study found a median tertiary delay of 23 days (IQR:11, 47). Compared to other studies performed in high-income countries, this is delay is greater than that of gastric cancer (7 days), but less than that of GI and genitourinary cancer, which had median delays of 47 and 70, respectively (39). It appears KS patients in Uganda experience tertiary delay at a rate that is between the extremes found for other cancers, although data from comparable studies is scant.

Given these data, it appears that primary delay and possibly secondary delay remain the greatest challenge to achieving prompt care for KS in Uganda. Interventions should target factors which can be barriers to primary delay, such as education on cancer and improving, and secondary delay, such as prompt diagnosis and efficient referral.

4.1.2 Cancer Stage

This study found that 46 (28.6%) patients had an overall poor stage risk, which is a slightly greater proportion than other literature values that found 22.7% (n=211) with an overall poor risk (54). In addition far more patients (91.9%) presented with poor risk in the tumor extent category than previous values that found only 64.0% (n=289) and 64.5% (n=211) to have poor risk in this category (52, 54). This difference may be attributed to the higher rates of delay also noted in this population, which can allow for greater tumor progression, although these studies also lack comparative power due to their location in high-income settings.

Regarding the other two categories, however, a smaller percentage of patients were found to have poor risk with respect to immune function and the presence of systemic illness than previous literature values. Only 39.8% of patients in this study had a CD4 count less than 150 cells/microliter, while previous studies found 70.1% and 71.4% had poor risk with respect to immune system, although these studies utilized a benchmark of 200 cells/microliter, which may explain the difference (52, 54). Regarding systemic illness, this study found 73.3% had poor risk, which falls between previous findings with the 1997 ACTG study finding 81.9% having poor risk and a later study

performed in the HAART era finding 59.2% having poor risk with respect to systemic illness (52, 54). These differences can most likely be attributed to better results being achieved with more widespread HAART usage. While this cohort seems to be healthier than the 1997 study with respect to immune system function and the presence of systemic illness, most likely due to exposure to HAART, this may not be true when comparing to the 2003 Italian study. With both, it may be inaccurate to closely compare results due to the great differences in the study population demographics and the contexts in which the studies were performed.

These poor outcomes are most likely reflective of the delay experienced that allows tumor progression as well as the poor coverage of HAART, which remains below 45% in some areas of Uganda (13). Much of the success in treating KS in developed countries has been attributed to effective HIV referral systems that recognize KS signs and symptoms and the wide availability of HAART, but these factors are not present in Uganda, possibly explaining the higher rate of poor risk patients, especially with respect to tumor extent. These findings underscore the severity of KS in Uganda and at the UCI and call for a greater understanding of delay so that more favorable cancer stage prognoses can be achieved when KS patients reach the UCI.

4.1.3 Association between Primary Delay and Cancer Stage

Our findings suggest that there is not only an association between primary delay and the KS cancer stage upon admission to a cancer referral center, but also that this can be an important factor upon which intervention can occur to achieve better patient

prognoses. In this study, HIV positive KS patients who experienced primary delay were more than three times as likely to have an overall poor stage risk than those who did not experience primary delay (Table 6), which represents a larger risk compared to other cancers in other contexts. Literature has established the effect of delays on poor prognoses and outcomes in breast cancer patients, finding delays of 3-6 months to be significantly associated with increased risk for tumor progression and mortality, and this link has also been established in cervical cancer and acute myeloid leukemia (36, 59). The opposite, however, has been shown to be true in some populations of bladder cancer and colorectal cancer patients, as delay was associated with slightly better outcomes for these patients (37, 38). It should not be assumed, then, that delay is necessarily associated with poorer prognosis or outcome, and each cancer should be evaluated individually within its own context.

Given these findings, our results underscore the specific need to address primary delays for HIV-associated KS patients who can experience rapid tumor proliferation, especially in the absence of consistent HAART. As an HIV-associated malignancy, limiting delay is particularly important and has been recognized as an important factor in addressing the increasing burden of HIV-associated malignancies in SSA (12). This study represents new data that examines empirically the link between delay and cancer stage among HIV-associated KS in Uganda and underscores the delays that occur for these patients and the subsequent challenges they pose for ensuring better patient outcomes. Other studies should seek to examine this association for other cancers in

Uganda and SSA where health system challenges and local knowledge about cancer can be barriers to providing prompt and effective treatment.

4.2 Patient Characteristics

4.2.1 Gender

Previous literature regarding HIV-associated KS in the West suggested better outcomes for women, but literature regarding KS in SSA shows worse outcomes for women (27, 60). KS has been primarily thought of a disease of men, and incident KS is still nearly two times as likely in men than women, even in the HIV era (51). Recently, however, studies examining gender differences in KS have found that women may experience more rapid disease progression (28). This has been particularly true in SSA where 40% of all incident KS cases are in women, and is the leading malignancy among women in Uganda, even passing cervical cancer (12, 27). These studies have shown that women are more likely to have lower CD4 counts upon admission and are less likely to show clinical improvement, suggesting that new considerations should be taken for KS management in women (27)

Conversely, this study found a protective effect for women as compared to men for the association with an overall poor stage risk ($p=0.050$, OR: 0.43). Women were less likely to have poor risk in each of the categories, tumor extent, immune system function, and systemic illness, than men in this study. For example, women were about equally likely to have poor risk with respect for systemic illness, but men were four times as

likely to have poor risk in this category. If women have a better prognosis upon admission, why are they less likely to have better outcomes than men?

An explanation for this may be some sampling bias due to getting patients primarily from the out-patients department. While patients who were admitted on the ward were included in the study, severely ill patients who were directly admitted to the ward may have been missed. If these patients were primarily women, gender selection bias may have been introduced.

These findings, however, may also be reflective of using the cancer stage as a prognosis. While women may appear better upon staging at diagnosis and admission, there may be additional factors to achieving better outcomes during the course of treatment and management. If this is true, it may suggest that additional factors, such as gender, must be considered when staging a patient. More research is needed to examine the gender differences in managing HIV-associated KS patients.

4.2.2. Previous HIV Care

The second aim of the study hypothesized that patients within the health system in HIV care would be less likely to delay, but results indicate that this association needs to be further explored. In multivaraite anlaysis, attendance in an HIV clinic for more than 3 months before admission to the UCI was not associated with primary delay (Table 9), which suggests that patients already within the health system were no less likely to delay than those who were not in care. Further, the multivariate model revealed a trend that patients in HIV care may be more at risk for delay, although this

hypothesis would need to be further tested, as this association was not statistically significant (Table 6, Table 9). If this association does exist, however, it may suggest that an important opportunity for cancer prevention through HIV care is not only missed, but may be actively overlooked, resulting in worse outcomes for these patients.

Results suggest a possible explanation for this may be a lack of knowledge of signs and symptoms of KS in the patient population, as over 60% of patients thought their symptoms were reflective only of their HIV or were side-effects of HAART, and none identified cancer as their initial perception of their signs. If patients were unable to recognize their signs and symptoms as indicative of KS and confused them for symptoms of HIV, they may have continued with care without bringing their new signs and symptoms to the attention of the care provider until extensive tumor involvement or increased pain.

Another explanation could be failure of the HIV clinical healthcare professionals to recognize or screen for signs and symptoms of KS. If HIV clinics do not include cancer screening or questions which ask about KS-associated signs and symptoms, patients can go through the system without getting the appropriate referrals to investigate the possibility of KS. A third reason could be that healthcare providers in HIV clinics were aware of KS symptoms and were attempting to treat the KS with HAART only initially, although this seems unlikely as the majority of patients had spent more than three months in HIV care before admission to the UCI, and many had spent more than six months in care.

4.2.3. Traditional Healers

Visitation to traditional healers has long been chronicled in the literature, and it is widely acknowledged that these are often a competing source of healthcare, particularly within African settings (44-46). We found this to be true, as visitation to a traditional healer was significantly associated with primary delay in this cohort. Previous literature supports this association. A 2003 study examining the usage of alternative medicine among a cohort of Pakistani breast cancer patients found that a traditional healer was often the first point of care, creating delays. Patients in the study that visited places of alternative medicine were five times more likely to delay in seeking medical care than those who did not visit a traditional healer and were twice as likely to present with more advanced disease (61). Other studies have also shown this association, indicating that patients often first seek care from traditional healers and that this creates delays (44-46). In order to achieve faster referrals into the healthcare system for KS, health systems should seek to integrate traditional healers into the referral system for detecting cancer at the local level. Traditional healers remain an important part of Ugandan societal norms, and results from this study suggest that cancer care and control must work within these norms to address the needs of the KS patient population to reduce delay. Future research and interventions should examine the possible education of traditional healers on signs and symptoms of cancer so that they can be utilized to decrease patient delay.

4.3 Previous Exposure to HAART

This is a population where nearly all were in some sort of HIV care before admission to the UCI. Among 161 individuals, 149 had attended an HIV clinic with 109 in care for longer than 3 months. 106 had been exposed to HAART with 77 of those for longer than 3 months. From these findings, one would expect that this HIV care would be associated with the staging prognosis that a patient received upon admission to the UCI. Despite this extensive previous HIV care, however, we did not find this to be true.

4.3.1 Lack of Association between HAART Exposure and Cancer Stage

Previous literature would suggest that those with longer exposure to HAART would be less likely to have an overall poor stage risk. The advent of antiretroviral medication has long been attributed for decreases in incidence of KS in United States and has been regarded as essential for KS treatment. Treatment with HAART is associated with the regression of KS, better patient outcomes, and can help mitigate the mutual enhancement of HIV and HHV-8 co-infection (22-25).

In this cohort, however, neither exposure to HAART (OR: 0.49, p=0.072) nor the duration of exposure to HAART (OR: 0.87, p=0.691) was associated with the cancer stage upon admission in the univariate analysis. A possible explanation for this may be that treating KS with HAART may not be as effective in Uganda as previously thought. Another study in Uganda found persistent KS despite prompt and effective treatment with HAART (31), and other studies have shown that HAART has been shown to play a

role in KS proliferation in some patients due to immune reconstitution inflammatory syndrome (IRIS) (33). Our study was not powered to examine this association, but results found only a slight trend the HAART was protective for overall poor stage (Table 6). New examinations of the role of HAART in treating KS should be considered.

While HAART has been long regarded as effective treatment for controlling KS, literature reveals that best patient outcomes occur for those who receive HAART and effective chemotherapy, rather than HAART alone (32). This is difficult to achieve in resource-limited settings where chemotherapy is not available, but our results suggest that HAART may not be as effective as previously thought and chemotherapy should be administered when a response to HAART is not achieved.

Finally, other considerations from the literature may help explain the lack of association between HAART exposure and KS cancer stage. A 2003 Italian study suggested that there may be inefficiencies in the ACTG KS staging system for patient populations with high exposure to HAART, such as the population in this study (54). That study found that increased CD4 counts and less systemic illness rendered the staging system less effective, and their results suggested that more categories for determining good and poor risk ought to be added. Taking this into consideration, our failure to find an association between HAART exposure and cancer stage may be due to the inefficiencies of the staging criteria to reflect disease prognosis within this specific population, rather than the ineffectiveness of HAART.

4.3.2 Leveraging HIV Care for Earlier KS Detection

These results show that there is an important opportunity for early KS detection that may be overlooked. A large proportion of this cohort was already enrolled in healthcare through HIV care prior to admission to the UCI, and many of them developed signs and symptoms within HIV care but still experienced primary delays. As those patients enrolled in HIV care were no less likely to delay, there may be an opportunity for intervention. Various HIV/AIDS programs have already begun to strategically target HIV care to be leveraged for non-communicable diseases, and this may be an important opportunity for change within this cohort of KS patients in Uganda (62).

The linkage between HIV and certain cancers has been established, but research examining cancer and how it ought to be treated and controlled has still lagged far behind HIV research, despite the co-morbidity that is increasingly seen. Additionally, the resources for early detection of HIV-associated malignancies have already been established in many cases, as patients are already entering care through HIV clinics. This "resource-focused approach" would be to utilize already existing networks and clinic linkages for cancer care (63). The UCI could embody this approach by working with and encouraging HIV clinics to more closely monitor for signs and symptoms of KS and limit delay.

4.3.3. Study Limitations

This study had some limitations that may have influenced the true association between primary delay and the KS cancer stage in our cohort. Selection bias in using patients primarily from the out-patients department may have had a selective effect for enrolling men in the study. This selection bias may have also underestimated the overall health of the study population, as severely sick patients may have been missed. Recall bias may have also been present through interviews for determining delay, as patients may have been unwilling to admit their own role in creating primary delay. Additionally, it is likely that patients could have underestimated or overestimated total delay time due to poor recall. This recall bias may have also played a role in the accuracy of data regarding previous HIV treatment and adherence.

As noted above, there are also concerns about the legitimacy of using the ACTG KS staging as a proxy for patient prognosis and outcome, as there may be limitations in the staging criteria. A prospective study using survival analysis would better establish the association between delay and patient outcomes, rather than the cross-sectional design implemented in this study, which has limited power to determine causation.

5. Conclusion

As cancer incidence increases worldwide, prevention and control programs continually look for ways to detect cancer earlier to obtain better patient outcomes through prompt delivery of treatment. This is an especially important for LMICs within SSA that experience the double burden of HIV and cancer and face significant health system challenges and a lack of awareness surrounding cancer among patient populations. Delay of treatment is often cited as a factor within these health systems, although empirical evidence is lacking that describes how often delay occurs and what effect it has on patient outcomes. As a response to this gap in knowledge, this study measured the association between primary delay and an overall poor cancer stage risk for HIV-associated Kaposi sarcoma patients in Uganda and found that those who experienced primary delay were over three times as likely to have an overall poor stage risk, or prognosis, upon admission to a cancer treatment center than those who did not delay. Our data suggests that decreasing primary delays may have a significant influence on improving patient outcomes.

In addition, results indicate that there exist new considerations with respect to the care patients receive before admission to the UCI. Visitation to a traditional healer was found to increase delay, and patients already in HIV care were no less likely to experience delay than those already not in care, despite already interacting with the health system. These factors within the health system can be addressed to further achieve better patient outcomes.

Greater advocacy for treatment of KS with chemotherapy should be promoted in Uganda, as results of this study indicate that HAART may be inefficient in achieving KS control. Patients exposed to HAART did not have a better overall cancer stage than those who were not exposed and duration on HAART had no association with overall stage prognosis. Literature has shown that HAART alongside chemotherapy has achieved the best patient outcomes, and the UCI should follow this suggestion to improve outcomes for KS patients across the country. While there exist significant challenges for KS control in Uganda and delay has been shown to be a barrier to achieving this control, these results also indicate that possible solutions are attainable by targeting inefficiencies in the health system, increasing local knowledge of cancer, and promoting prompt treatment with HAART and chemotherapy for KS patients.

Appendix A: Background Information

A.1 Epidemiology

The epidemiology of KS has always been suggestive of an etiology from an infectious agent due to exclusivity within certain populations, but the emergence of AIDS-associated KS nearly exclusively in gay men in New York and San Francisco led researchers to believe that the answer to causation was in some unknown mechanism of HIV. In 1994, however, Chang and Moore demonstrated that spindle cells in lesions of AIDS-associated KS patients contained genomic fragments suggestive of a new human herpesvirus (64). This discovery revealed that the rise of KS in HIV positive patients was due to infection with a co-factor, although transmission, risk factors, and pathogenesis remained unknown.

Because of its association with gay men, transmission of the new herpesvirus was thought to be associated with sexual behavior. Early studies found seroprevalence of this new virus, now called HHV-8, or Kaposi sarcoma herpesvirus (KSHV), to be higher among gay men and associated with sexual behaviors, but later results found no difference in seropositivity between different groups in the same geographic area (65, 66). In addition, studies uncovered the virus in HIV positive KS patients and Classic KS patients, confirming that HHV-8 is a necessary, although not completely sufficient, factor in the etiology of Kaposi sarcoma that is not exclusive to individuals with certain sexual behavior.

Seroprevalence studies have found the virus in children and heterosexual couples, indicating transmission is most likely through saliva, confirming that certain sexual behaviors are surrogate markers for transmission (67-71). The KS burden seems to follow HHV-8 seroprevalence, as studies have shown that in some places with a heavy burden of KS, such as SSA, greater than 50% of individuals randomly tested contained the virus (72). Questions surrounding HHV-8 remain, but it is now understood that transmission is not exclusively associated with sexual behavior, and populations with higher seroprevalence of HHV-8 who are more susceptible to infection with HIV are at the most at risk.

A.2 Pathogenesis and Tumor Formation

HHV-8 primarily infects B cells and endothelial spindle cells, and its genome encodes proteins that block apoptosis and stimulate proliferative growth that causes tumorigenesis (73). Cancer-causing gene expression is believed to mostly occur in the latent cycle, as most HHV-8 viral DNA isolated from spindle cells is in this stage (ibid). Most discoveries to date attribute tumor growth to HHV-8 gene expression that utilizes host cell genetic material that maintains the cell growth cycle (74). The latency-associated nuclear antigen (LANA) is responsible for integration of viral DNA to the host cell genome, viral replication, inhibition of tumor suppressor genes within host cells, and plays a role in activating proto-oncogenes (71). The v-FLIP gene promotes resistance to apoptosis, and the kaposin locus promotes a pro-inflammatory environment that is necessary to viral replication and the KS pathogenesis that leads to

tumor formation (75). In addition, one lytic cycle cascade protein, v-IL-6, has also been shown to play a role in initiating a signal pathway that promotes the gathering of cytokines that also play a role in increasing inflammation at the site of infection (76). In most individuals, these cellular processes are blocked by the immune defense, which makes HIV seropositive individuals more susceptible to the disease.

The higher risk for developing KS in HIV-infected individuals occurs both through decreased immune system function and possible mutual enhancement of gene expression in both viruses when in the presence of the other. The regression of KS in patients receiving HAART suggests that T-cells play a role in controlling KS, indicating that infection with HIV can lead to more rapid progression of KS (32). This observation is further supported by studies that have shown low T-cell responses to HHV-8 and low levels of HHV-8 specific T-cell levels in HIV positive individuals (77-79). In addition to T-cell deficiency, experimental models suggest that HIV, specifically HIV Tat, the positive feedback protein product responsible for rapid HIV transcription, interacts with HHV-8 to cause increased KS cell growth (80, 82). Mice models show the development of KS-like lesions and tumors when injected with subcutaneous Tat (81). These factors create an environment that promotes KS progression and help explain the more rapid progression of the disease in HIV positive individuals. They underscore the need for prompt diagnosis and treatment for HIV-associated KS patients to slow the progression of the disease.

Appendix B: Survey

THE EFFECT OF PATIENT DELAY ON CANCER STAGE IN PATIENTS WITH KAPOSI SARCOMA IN UGANDA

Date:
Hospital/site:
Interviewer:
Interview code:

INFORMED CONSENT

You've been selected to participate in a survey for research conducted by Duke University that will be shared with your physician at UCI, and we wish, with your permission, to interview you. Be assured we want to learn from your experience, and all the information we collect will be used to help us fight against cancer in your community, country and region. Some of the questions asked are of a sensitive nature; however your name will not be recorded. That means we will not take your name or any information that could identify you. This interview will be completely confidential and all information will be secure and only accessible to the researchers. We ask you to answer our questions honestly and to the best of your ability. At any point you can refuse to answer a question or stop the interview without giving any reason. You can also contact myself or your physician if you have any questions about this research after you complete this survey. Your participation in this survey is important and we rely on you to provide us with accurate information that will help us to develop important information on the delay that cancer patients may face and how we can work to limit them to help you and others with cancer get treatment faster. The interview will take approximately 30 minutes, and with your cooperation it can be done quickly. May I have your permission to undertake this interview?

Yes □ **No** □

In addition, we would like your physician to provide us with information on the extent of your sickness, called the cancer stage, which he will collect or has already collected during your normal consultation. May I have your permission to ask your physician to collect this information, or may I collect this information from your file?

Yes □ **No** □

Interviewer signature confirming verbal consent was obtained:

_____ |__|__| |__|__| 2012

Signature of interviewer (witness): Day Month

No.	Question:	Response	Skip:
	Patient Meets Inclusion Criteria?	☐ > 18 yrs of age ☐ Diagnosis of KS confirmed by biopsy ☐ Patient at UCI ☐ HIV positive	
A. Demographics 1. Sex	Sex:	1= ☐ Male 2= ☐ Female	
2. page	Age:	☐	
3. educ	Highest Education level	1= ☐ Primary School 2= ☐ O'level 3= ☐ A'level 4= ☐ Tertiary 5= ☐ Other 98= I don't know 99- Missing	
4.emp	Current Occupation	1= ☐ In formal employment 2= ☐ Casual Laborer 3= ☐ Unemployed 4= ☐ Other_____ 98= I don't know 99= Missing	
5. inco	During the last 12 months, what was your average monthly income from all sources?	1= ☐ Ug Shs. 100,000 or less 2= ☐ Ug Shs. 100,000 to 500,000 3= ☐ Ug Shs.500, 000-1,000,000 4= ☐ over Ug Shs. 1,000,000 5= No income 98 = I don't know 99 = Missing	
6. semp	Spouse's Occupation	1= ☐ In formal employment 2= ☐ Casual Laborer 3= ☐ Unemployed 4= ☐ Other …… 98 = I don't know 99= Missing	If no spouse, **SKIP**
7. relig	Religion?	1= ☐ Catholic 2= ☐ Anglican 3= ☐ Muslim	

		4= ☐ Orthodox 5= ☐ Pentecostal 6= ☐ Other_____ 98= I don't know 99= Missing	
B. Health System 1. Hs1	What prompted you to go to the hospital/clinic?	1= ☐ I had lesions on my skin 2= ☐ I had a lot of pain 3= ☐ I knew I had cancer 4= ☐ My family/friends 5= ☐ Other_____ 98= I don't know 99= Missing	
2. Distc	How far is the nearest clinic to your home?	1= ☐ Very near (within the sub county) 2= ☐ Near (in another sub county) 3= ☐ Distant (at the district) 4= ☐very distant (other district) 98= I don't know99 = Missing	
3. Distkm	How many kilometers is the nearest clinic to your home?	☐	
4. Hs4	How did this affect your going to hospital?	1= ☐ Increased delay 2= ☐ had no effect 3= ☐ Don't know 4= ☐ Other_____ 98= I don't know 99= Missing	
5. Hs5	Were you referred to another health center?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to #8
6. Hs6	Did you go?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **yes**, SKIP to # 8
7. Hs7	Why not?	1= ☐ The hospital is far 2= ☐ I did not have money to go 3= ☐ I went to the traditional healer 4= ☐ Others_____ 98= I don't know 99= Missing	
8. Distru	How far is the referral unit from your home?	1= ☐ Very near (within the sub county) 2= ☐ Near (in another sub county)	

		3= ☐ Distant (at the district) 4= ☐ very distant (other district) 5= ☐ Other_____ 98= I don't know 99= Missing	
9. Hs9	Would you have gone sooner if it was nearer?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
10. Hs10	When you went to the clinic, did you tell the doctor about your symptoms?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
11. Hs11	Do you feel the doctor investigated them thoroughly?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
12. Pay	Did you have to pay for any of the tests or drugs?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to C.
13. Payq	Do you think if they were free you would have started treatment earlier?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
C. Determing Delay 1. Dd1	How did you know you had Kaposi sarcoma?	1= ☐ I had skin lesions 2= ☐ the doctor told me 3= ☐ Other_____ 98= I don't know 99= Missing	
2. Kssigns	Did you have any signs that led you to think you had Kaposi sarcoma?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
3. Kssingssp	What were the signs?	1= ☐ Skin lesions 2= ☐ oral lesions 3= ☐ other_____ 98= I don't know 99= Missing	
4. kssignstime	When did you notice these	1= ☐ < 1 month ago 2= ☐ 4-5 months ago	

	symptoms?	3= ☐ 1 – 3 months ago 4= ☐ 6-12 months ago 5= ☐ More than 12 months ago 98= I don't know 99= Missing	
5. dd5	What did you think about the symptom(s)?	1= ☐ I knew I had cancer 2= ☐ I knew I was sick but did not knowthe disease 3= ☐ Nothing 4= ☐ other disease_____ 98= I don't know 99= Missing	
6. patdelay	Did you seek care immediately you noticed symptoms?	1= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
7. primdelay	How long did you wait after noticing symptoms before going to the hospital?	1= ☐ 1 – 3 months 2= ☐ 4 – 5 months 3= ☐ 6 – 12 months 4= ☐ More than 12 months 98= I don't know 99= Missing	
8. biop	When did youreceive the biopsy results?		
9. secdelay	How long did it take before they told you the diagnosis of cancer?	1= ☐ Within 1 week 2= ☐ In 2 – 3 weeks 3= ☐ After 1 month 4= ☐ In 2 to 3 months 5= ☐ < 3 months 98= I don't know 99= Missing	
10. chemo	When did you begin chemotherapy?		
11. prevtreat	Have you received any previous treatment for the Kaposi sarcoma?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to #12
12. treaty	What was the treatment?	1= ☐ Radiotherapy 2= ☐ Antibiotic	

		3= ☐ Chemotherapy 4= ☐ I do not know 98= I don't know 99= Missing	
13. dd13	Why did you not immediately go to the hospital?	1= ☐ I did not feel any pain 2= ☐ the hospital is far 3= ☐ I did not have money to go 4= ☐ other_____ 98= I don't know 99= Missing	
14. dd14	What does a diagnosis of cancer mean to you?	1= ☐ can't be cured 2= ☐ I am going to die in a few years 3= ☐ Long stay in the hospital 4= ☐ some cancers can be treated 5= ☐ Other 98= I don't know 99= Missing	
15. **FOR INTERVIEWER ONLY**	Is this patient a delayer?	0= ☐ Yes 1= ☐ No	If **no**, SKIP to D.
D. HIV Knowledge and Use of ART and adherence 16. **Hivstat**	Were you told about your HIV status before or after you had been diagnosed with Kaposi sarcoma?	1= ☐ Before 2= ☐ After 98= I don't know 99= Missing	
1. Hivstatime	How long ago were you told you had HIV/AIDS?	1= ☐ 1 month ago 2= ☐ 5 – 6 months ago 3= ☐ 6 – 12 months ago 4= ☐ More than a year ago 98= I don't know 99= Missing	
2. Hivclin	Are you attending an HIV/ART care clinic?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
3. Hivclintime	How long have you been attending the clinic?	1= ☐ 1 – 3 months 2= ☐ 4 – 5 months 3= ☐ 6 – 12 months 4= ☐ More than 12 months 98= I don't know 99= Missing	

1. hivclinhist	Were you attending an HIV/ART clinic before you had been diagnosed with Kaposi sarcoma?	1= ☐ Before 2= ☐ After 98= I don't know 99= Missing	
2. haart	Are you on ARVs?	0= ☐ Yes 1= ☐ No 98= Don't Know 99= Missing	
3. haartime	For how long have you been taking the ART?	1= ☐ 1 – 3 months 2= ☐ 4 – 5 months 3= ☐ 6 – 12 months 4= ☐ More than 12 months 98= I don't know 99= Missing	
4. arv	Were you on ARVs at the time you first noticed symptoms?	0= ☐ Yes 1= ☐ No 98= Don't Know 99= Missing	
5. adherence	Have you ever missed a dose?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to #12
6. adhweek	How many doses/treatments have you missed in the last week?	1= ☐ 1 – 3 doses 2= ☐ 4 – 5 doses 3= ☐ > 5 doses 98= I don't know 99= Missing	
7. adhmnth	How many doses have you missed in the last month?	1= ☐ 1 – 5 doses 2= ☐ 6 – 10 doses 3= ☐ 10 - 15 doses 4= ☐ > 15 doses 98= I don't know 99= Missing	
8. adhreason	Why have you missed doses?	1= ☐ I run out of drugs 2= ☐ just won't take the drugs 3= ☐ I feel fine 4= ☐ Side effects 5= ☐ Other_____ 98= I don't know 99= Missing	

9. hivstatknow	How did you learn about your HIV status?	1= ☐ VCT[1] 2= ☐ when I was ill with this disease 3= ☐ My husband/wife died fromHIV/AIDS so I knew I also had HIVAIDS 4= ☐ The doctor told me 5= ☐ Other_____ 98= I don't know 99= Missing	
E. Social Support Systems/ Social Capital 10. Home#	How many people do you live with in your home?	1= ☐ I live alone 2= ☐1 – 2 people 3= ☐ 3 – 5 people 4= ☐ 6 – 10 people 5= ☐ More than 10 people 98= I don't know 99= Missing	
1. Sssc2	Did you tell anyone about the symptoms of Kaposi sarcoma	0= ☐ Yes 1= ☐ No	If **yes**, SKIP to #4
2. Sssc3	If no, why not?	1= ☐ I was embarrassed about my condition 2= ☐ I was scared they would think Ihave HIV 98= I don't know 99= Missing	SKIP to #6
3. Sssc4	If yes, who did you tell?	1= ☐ Sister/brother 2= ☐ Husband/wife 3= ☐ friend 4= ☐ Other relative_____ 98= I don't know 99= Missing	
4. Sssc5	Did they know about your HIV status?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
5. Sssc6	Did you tell anyone about your HIV status?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If no, SKIP to #8

[1] VCT- Voluntary Counseling and Testing, this is a ountrywide program to promote HIV testing. It is offered at almost all hospitals countrywide

6. Sssc7	If yes, who did you tell?	1= ☐ Sister/brother 2= ☐ Husband/wife 3= ☐ friend 4= ☐ Other relative_____ 98= I don't know 99= Missing	
7. Sssc8	When did you first tell them about the symptoms of Kaposi sarcoma after noticing them?	1= ☐ Within 1 month 2= ☐ After 1 – 3 months 3= ☐ After 4 – 5 months 4= ☐ After 6 – 12 months 5= ☐ Other_____ 98= I don't know 99 = Missing	
8. Sssc9	How did they help?	1= ☐ Took me to the hospital 2= ☐ Advised me to go to hospital 3= ☐ Told me not to worry 4= ☐ Took me to a traditional healer 5= ☐ Did not help at all 6= ☐ Other_____ 98= I don't know 99= Missing	
F. Stima and Social Exclusion 9. Stigmaks	Did you feel people would discriminate against you if they knew you had Kaposi sarcoma	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missin	
1. stimahiv	Did you feel people would discriminate against if they knew your HIV status?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to G.
2. stigmadelay	How did this discrimination affect your decision on when to seek care?	1= ☐ I was afraid to go to the hospital 2= ☐ I concealed my symptoms fromanyone 3= ☐ Did not affect me at all 4= ☐ Other_____	
3. stigma4	What could have changed for you to go to the hospital immediately?	1= ☐ If the hospital was near 2= ☐ If they could cure cancer 3= ☐ If I had the money to go to hospial 4= ☐ If treatment ws free 5= ☐ Other_____	

		6 = Education 98= I don't know 99= Missing	
G. Previous Delay 1. Previll	Have you suffered any other illness that required admission to hospital?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to section H
1. Prevdelill	What illness was it?	1= ☐ Malaria 2= ☐ Tuberculosis 3= ☐ Surgical condition;name…… ……. 4= ☐ Don't Know 5= ☐ Other_____ 98= I don't know 99= Missng	
2. Prevdel3	Did you go to the hospital immediately when you noticed symptoms?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	If **no**, SKIP to #5
3. Prevdel4	If yes, why did you go immediately?	1= ☐ The disease is curable 2= ☐ I was near a health center 3= ☐ Had money to go 4= ☐ Acute illness 5= ☐ Other_____ 98= I don't know 99= Missing	
4. Prevdel5	If no, why not? Give reason		
5. Prevdeltime	From when you knew you were sick, how long did it take you before you went to hospital?		
6. **FOR INTERVIEWER ONLY**	Is this patient a previously delayer? Prevdel	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
H. Tradtional	Did you visit a	0= ☐ Yes	If

7.	Healers Tradheal	traditional healer?	1= ☐ No 98= I don't know 99= Missing	**no**, SKIP to section I.
1.	Tradheal2	Did the traditional healer offer you any treatment?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
2.	Tradheal3	Did the traditional healer tell you what you were suffering from?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
3.	Tradheal4	Do you think the traditional healer was helpful?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	
4.	Tradheal5	Did the traditional healer refer you to hospital?	0= ☐ Yes 1= ☐ No 98= I don't know 99= Missing	

I. PAIN/PAIN CONTROL

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these every day kinds of pain during the past week?

☐ Yes ☐ No

2. Did you take pain medications in the last 7 days?

☐ Yes ☐ No

3. Do you feel you have some form of pain that requires medication every day?

☐ Yes ☐ No

4. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last week.

0 1 2 3 4 5 6 7 8 9 10

No Pain Worst pain imaginable

5. If you are taking pain medication, do you feel you need a stronger type of pain medication? ☐ Yes ☐ No

6. Do you feel that you need to take more of the pain medication than your doctor has prescribed? ☐ Yes ☐ No

7. Are you concerned that you use too much pain medication?
   ☐ Yes ☐ No
8. Are you having problems with side effects from your medication?
   ☐ Yes ☐ No
9. I believe my pain is due to :
   ☐ Yes ☐ No a.) The effects of treatment (for example, medication, surgery).
   ☐ Yes ☐ No b.) My primary disease (HIV/AIDS)
   ☐ Yes ☐ No c.) A medication condition unrelated to my HIV/AIDS.
   Please describe condition:_____

Date:
Hospital/site:
Interviewer:
Interview code:

HIV/AIDS-ASSOCIATED KAPOSI SARCOMA STAGING [2]

Instructions: Based on physical exam and diagnostic tests indicate either "Good" or "Poor" Risk for each category. Only check on box per stage category.

Category	Description	Risk Assessment
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease (non-nodular, confined to palate)	Good Risk = 0 ☐
	Tumor-associated edema or ulceration **OR** Extensive oral KS **OR** KS of GI tract **OR** KS in other non-nodal viscera	Poor Risk = 1 ☐
Immune System (I)	CD4 >150 cells/μL	Good Risk = 0 ☐
	CD4 <150 cells/μL	Poor Risk = 1 ☐
Systemic Illness (S)	No history of opportunistic infection or thrush" **AND** "B" symptoms absent (include unexplained fever, night sweats, >10% weight loss, or diarrhea persisting > 2 weeks) **AND** KPS $\geq$ 70	Good Risk = 0 ☐
	History of opportunistic infection and/or thrush" **OR** B" symptoms present OR KPS < 70 **OR** Presence of other HIV-related illness (e.g., neurologic disease, lymphoma)	Poor Risk = 1 ☐

OVERALL STAGE (e.g. $T_0 I_1 S_1$): _____

[2] The Staging From is adapted from the AIDS Clinical Trials Group staging form for AIDS-associated Kaposi Sarcoma. Taken from:
Krown SE, Testa MA, Huang J. AIDS-related Kaposi's sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. *J Clin Oncol.* 1997;15:3085–3092.

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