Role of HIV in Cancer Survival

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Abstract

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Evidence exists for an association between HIV and multiple AIDS-defining and non-AIDS-defining malignancies, resulting in a growing cancer burden that is increasingly recognized to impact resource-limited countries. Despite the consistent evidence for an association between immunosuppression and cancer risk, little is known about how HIV impacts cancer survival. We therefore investigated the role of HIV on survival after a cancer diagnosis in a retrospective cohort from Uganda (N=802). Cancer patients that resided in Kyadondo County, were ≥18 years of age, and were diagnosed from 2003-2010 with one of the following cancers were eligible: breast cancer (N=220), cervical cancer (N=316), Non-Hodgkin lymphoma (N=134), Hodgkin lymphoma (N=63), and esophageal cancer (N=69). Cancer patients were classified as HIV-positive based on a positive HIV antibody lab test, HIV-positive medical history in the clinical notes, or an HIV clinic referral letter. The primary outcome, vital status at 1 year following primary cancer diagnosis, was abstracted from the patient medical record or determined through database linkages to the national hospice system. Cox proportional hazards regression was utilized to evaluate the association between HIV status at the time of primary cancer diagnosis and 1-year case-fatality. HIV-positive cancer patients in Uganda experienced a more than two-fold increase in case fatality during the year following cancer diagnosis compared to HIV-negative patients (HR=2.32; 95% CI 1.64-3.29). This marked inverse association between HIV infection and cancer survival was consistently observed for both cancers with (HR=1.61; 95% CI 1.07-2.43) and without (HR=2.61; 95% CI 1.17-5.84) an infectious

etiology, regardless of the initial cancer stage. This study was the first to date to demonstrate the role of HIV in cancer survival for both AIDS-defining and non-AIDS-defining malignancies in a resource-limited, HIV-endemic region. Our results extend the established relationship between HIV and cancer incidence to also include a role for HIV in cancer patient outcomes, an increasingly important question as the number of patients diagnosed with both HIV and cancer continues to grow.

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DEDICATION

Dedicated to Mama and Dad

Your support has been unwavering since the day that I started asking you to re-read me books for the hundredth time. I will be forever grateful for your love and unconditional support throughout the many years of study and travel that have followed.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure **Page**

Immune Suppression and Cancer Risk. It has long been recognized that immunosuppression is associated with an increased risk of developing cancer, initially noted with congenital immunodeficiency and then corroborated by the increased risk of cancer in iatrogenically-induced immunosuppression in organ transplant recipients (OTR)[1-12] and more recently in patients infected with human immunodeficiency virus (HIV).[13-29] Despite the fact that these immunosuppressed populations have different mechanisms of immunosuppression and distinct sets of potential confounding factors which could contribute to increased cancer risk, OTR studies have observed elevated rates for multiple cancer types that are also increased in the context of HIV. Specifically, cancers attributable to infectious agents are most common and are consistently elevated in immunosuppressed individuals. [30-33]

A 2007 meta-analysis utilizing data from 5 OTR and 7 HIV/AIDS registries highlighted the striking concordance in the incidence and types of cancer for these two populations, each of which was compared to the general population using standardized incidence ratios (SIRs). Rates were significantly elevated in these immunosuppressed populations for a range of infection-related cancers, including both AIDS-defining (ADM) and non-AIDS-defining (NADM) malignancies: (SIRs: Non-Hodgkin lymphoma (NHL): $76.67_{HIV/AIDS}$, 8.07_{OTR}; Kaposi sarcoma (KS): $3640.0_{HIV/AIDS}$, 208.0_{OTR}; cervical cancer: $5.82_{HIV/AIDS}$, 2.13_{OTR}; liver: $5.22_{HIV/AIDS}$, $2.13_{OTR;}$ anal cancer: $28.75_{HIV/AIDS}$, $4.85_{OTR;}$ Hodgkin lymphoma (HL): $11.03_{HIV/AIDS}$, 3.89_{OTR}).[34] Notably, in every instance in this meta-analysis, the SIRs for HIV-positive patients were consistently higher than transplant recipients, potentially due to a more systemic and complete destruction of the immune system in the context of HIV, or possibly due to a tumor-promoting, oncogenic role for HIV itself.

The severity of immune system dysfunction measured in both OTR and HIV-positive patients appears related to the development of cancer. A comparison of cancer incidence in kidney transplant recipients demonstrated that the risk for many infection-related malignancies was elevated to a greater degree during periods of stronger immunosuppression (i.e. transplant function) when compared to periods of reduced immunosuppression (i.e. dialysis, transplant failure). [35] Similarly, HIV/AIDS evaluations have repeatedly demonstrated that higher patient CD4 T-cell count is inversely associated with cancer

incidence. [15,20,21,26,27,29,36,37] Longer exposure to depressed CD4 T-cell counts has been associated with increased risks for both ADMs (CD4 < 200: HR= 1.36 per year) and NADMs (CD4 < 500: HR=1.13 per year), [16] particularly for infection-related NADMs (CD4 < 200: HR=1.16 per year). [24] One notable exception to the relationship between depth of immunosuppression and risk of malignancy is cervical cancer, as discussed in greater detail below.

Decreasing AIDS-Defining Malignancy Risk with HAART. Highly active antiretroviral therapy (HAART) was introduced in 1996. This effective HIV treatment led to marked improvements in immune status and life expectancy for HIV-positive individuals.[38] Comparisons of cancer incidence in the era prior to HAART availability to incidence in the post-HAART era demonstrate striking associations for KS and NHL. Rates of KS and NHL incidence increased dramatically following the onset of the HIV epidemic and subsequently fell after the introduction of HAART.[13,15,20,21,39] For example, rates of KS in white men in San Francisco increased from 0.3 per 1,000 in 1973 to approximately 8.0 in 1989-1991, a more than 25-fold increase, and declined almost 8-fold to 0.9 by 1998, only two years after HAART introduction. [40] Although some earlier reports did not observe the same immediate benefits of HAART on NHL rates, [23] data from 23 international prospective studies comparing rates of various malignancies, including KS and NHL, in pre-HAART (1992-1996) and post-HAART (1997-1999) time points provided evidence of significant declines in incidence for both KS (RR=0.32; 95% CI 0.26-0.40) and NHL (RR=0.58; 95% CI 0.45-0.74). [39] The impact of effective HIV treatment on KS and NHL incidence has also been demonstrated over longer durations of follow-up. NHL rates in the Swiss HIV Cohort declined more than 7-fold, from 13.6 per 1,000 immediately prior to HAART introduction to 1.8 by a decade after HAART, [41] and KS rates in a US military cohort declined 5-fold between pre-HAART and post-HAART years.[20]

The relationship between HIV-induced immunosuppression, HIV treatment, and invasive cervical cancer is not as convincing or consistent as for KS and NHL. Immunosuppression is related to earlier stages of the cervical carcinogenic process, with higher rates of low-grade cervical lesion regression and lower rates of recurrence of abnormal cytology consistently observed among HIV-infected women with

lower CD4 T-cell counts or among those on HAART. [42-47] One investigation of over 50,000 patients from two HIV-infected cohorts (1992-2003) did report an association between cervical cancer and CD4 T-cell count.[27] However, the majority of US-based registry studies report null associations.[15,18,21,26] Furthermore, the 23-cohort international collaboration observed no change in cervical cancer rates according to HAART era (RR=1.87; 95% CI 0.77-4.56), [39] a consistently observed lack of HAART-related trend for cervical cancer. [19,48] Notably, these studies were conducted in resource-rich settings but were not able to account for changes in cervical cancer screening, which may also parallel changes in HAART availability over time and complicate the interpretation of trends.

Despite the lack of a clear link between HIV-related immunosuppression and invasive cervical cancer, data from two of the most recent AIDS registry studies demonstrated an approximately 5-fold increase in rates of cervical cancer among HIV-infected women compared to the general population (SIR=5.0; 95% CI 4.0-6.2; SIR=5.6; 95% CI 4.8-8.5). [18,49]

Elevated Non-AIDS-Defining Malignancy Risk in HAART Era. In the HAART era, the association between HIV and cancer has been extended to include some but not all NADMs.[14,17,48,50,51] Recent registry data reported that the incidence of NADMs is elevated by 70% in HIV-infected patients compared to the general population in the 3-5 years post-AIDS diagnosis and by 60% at 6-10 years post-AIDS diagnosis. [49] Results from a meta-analysis by Shiels and colleagues compiled data from 18 international cancer registry studies and confirmed that HIV-infected patients are at significantly higher risk for NADMs, specifically those with a known viral etiology such as Hodgkin lymphoma (HL), anal, and liver cancer (SIR_{HL}=11.0; SIR_{Anal}=28.0; SIR_{Liver}=5.6). [28]

Of particular public health concern is that improved life expectancy in the post-HAART era in HIV-infected patients has translated into an increased opportunity to develop NADMs, with rates of certain NADMs actually increasing after 1996. [18,22,27,48,52,53] Recent US registry data reported that the SIR comparing anal cancer rates in HIV-infected patients to that in the general population increased nearly 3-fold between the pre- and post-HAART eras (RR=2.9; 95% CI 2.1-4.0). [49] A near doubling of the SIR for HL between the pre- and post-HAART years was also observed (RR=1.9; 95% CI 1.1-3.3). In fact, data

from large HIV-infected cohorts indicate that proportional morbidity has tipped towards NADMs in recent years. A US military cohort of HIV-infected patients over the course of 20 years reported that 71% of cancers in the late HAART era were now NADMs; rates increased from 2.8 per 1,000 to 6.7 in only two decades. [20] Likewise, a comparison of the absolute number of cancers presenting in the US AIDS patients in 1991-1995 versus 2001-2005 revealed that NADMs have significantly increased in absolute number by approximately 3-fold. [54]

Continued Cancer Burden in HIV/AIDS Patients. The increasing occurrence of NADMs adds to the already established burden of ADMs in HIV-infected patients. Despite decreasing incidence in KS and NHL over time, recent data from 15 US cancer registries highlights the important fact that ADMs do still occur at significantly elevated rates in HIV-infected patients compared to the general population, even 6-10 years post-AIDS diagnosis (SIR_{KS}=1347; SIR_{NHL}=15; $SIR_{Cervical}$=3.6). [49] Ultimately, the combination of NADMs and the continued risk for developing ADMs has resulted in elevated co-morbidity between HIV infection and cancer. The increasing survival of individuals diagnosed with both HIV and cancer motivates investigations into the role of HIV in not just cancer risk but also cancer treatment and outcomes in the context of immunosuppression.

HIV and Cancer Risk in Uganda. Cancer as a complication of HIV infection is increasingly recognized to impact not just Western settings but also resource-limited regions.[55] HIV/AIDS registries do not exist in most HIV-endemic regions, making it difficult to do studies comparable to those cited earlier from Western settings. However, there is one study from Uganda that utilized a large HIV clinic (TASO) in the Kampala area to compare cancer rates in HIV-infected patients to those in the general population, as estimated from the Kampala Cancer Registry (KCR).[56] This study observed significantly elevated risks in HIV-infected patients compared to the general population across a range of cancer types after AIDS onset ($SIR_{Kaposi\ Sarcoma}$=5.7; $SIR_{Non\text{-}Hodgkin\ Lymphoma}$=3.6; $SIR_{Cervical}$=2.7; SIR_{HL}=5.7; SIR_{Lung}=5.0). Because the HIV prevalence is much higher in Uganda than in the United States (6.5% versus 0.6% in the US in 2009 as reported by the World Health Organization[57]), the effect estimates from this study are likely underestimates of the true association between HIV and cancer incidence.

Kampala Cancer Registry. The estimates for general population cancer incidence for the study outlined above were generated from the KCR. The KCR is a population-based cancer registry that initiated cancer registration in Kyadondo County (Kampala and surrounding areas) through the Mulago Hospital Department of Pathology in 1953.[58,59] This population-based registry has operated in the Kampala area continuously since the 1950's, with the exception of selected years in the 1970-80's due to political turmoil. Data are ascertained not only from the pathology department but also the four main hospitals in Kampala and the national hospice system. The most current report from the KCR includes incidence rate and incidence trend data through 2006 and utilized the 10th edition of the International Classification of Diseases for Oncology. [60] A histological diagnosis is not required for entry into the registry, and stage of disease has not regularly been recorded to date.

Increasing Cancer Risk in Uganda. Data from the KCR provide evidence of an increasing cancer burden in Uganda. [58,60] For example, KCR-generated incidence rates of Kaposi sarcoma (KS) increased more than 10-fold, from 3.7 per 100,000 in earlier decades (1967-1971) to 39.3 at the peak of the HIV epidemic in Uganda (1991-1994) for men, and from 0.2 to 17.9 during the same time period for women.

Although rates appeared to level off by 2006, incidence remained significantly elevated compared to earlier decades (27.9_{Men} and 20.1_{Women} per 100,000).[58,60]

The introduction of antiretroviral therapy (ART) regimens for HIV-infected patients in Uganda has been delayed compared to Western settings. Nonetheless, a 2010 report demonstrated significant improvements in life expectancy after ART introduction, with greater than 65% reductions in overall mortality for HIV-infected Uganda patients.[61] However, we do not see the same precipitous declines in KS and NHL rates since ART introduction that were noted in resource-rich settings. The KCR reports that incidence continues to increase in Uganda for ADMs such as NHL (Annual Percent Change (APC): +6.7% and +11.0% between 2002-2006 and 1991-1995 in men and women, respectively) and has only recently begun declining (APC: -2.8% between 2002-2006 and 1991-1995) for KS among men, with no significant decline for women. [60] Recent (post-2008) cohort data from both Uganda and Kenya has in fact demonstrated significant declines in the risk of KS in individual HIV-infected patients over time with ART initiation, [62] although the association between HIV treatment and KS risk on a population level is not as clear or consistent as that observed in the Western setting. [63,64] In Uganda, this picture is perhaps altered because ART coverage still had only reached approximately 45% by 2008.[63]

Notably, the elevation in cancer incidence in Uganda has not been limited to traditional ADMs. Among men, the rate of all cancers (minus KS) has increased from 54.2 per 100,000 in 1961-1966 to 166.6 per 100,000 in 1995-1997, although increases in NADM incidence have not been uniform. [58] For example, while esophageal cancer incidence increased from 1.7 per 100,000 in 1961-1966 to 15.4 by 2006, HL rates remained stable over that time frame. [58,65] Among women, incidence rates of not just cervical but also breast cancer doubled between the 1960's and 2000's ($17.7_{CervicalCancer}$ and $11.7_{BreastCancer}$ per 100,000 in 1960-1966; $52.4_{CervicalCancer}$ and $31.0_{BreastCancer}$ per 100,000 in 2000-2006). [58,65]

Study Motivation. Importantly, the increase in cancer burden in Uganda is occurring alongside HIV prevalence rates that are more than 10-fold higher than those observed in the US population. Although the prevalence of HIV has fallen since its 1991 peak in Uganda of 10.7%, the prevalence remained at

6.5% in 2009, at least 10-fold higher than the US (0.6%). The increasing cancer occurrence in the context of a generalized HIV epidemic accelerates a trend towards increasing co-morbidity of these two chronic diseases and necessitates exploration of the role of HIV in cancer outcomes.

KCR data further highlight the extremely poor cancer patient outcomes in this resource-limited setting that warrant further investigation into cancer survival. Five-year absolute survival rates were as low as 3.5% and 15.9% for esophageal and cervical cancer, respectively, and only approximately one third (33.4% and 38.4%) of lymphoma and breast cancer patients survived 5 years after cancer diagnosis.[66] These extremely poor cancer survival rates, high HIV prevalence, and an increasing cancer burden in Uganda motivated our investigation into the potential role of HIV in altering patient survival after a cancer diagnosis in this resource-limited setting. To accomplish this goal, we conducted a retrospective cohort study of cancer patients who were treated at either the Uganda Cancer Institute (UCI) or the national hospital (Mulago) and were followed for survival outcomes.

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INTRODUCTION. Substantial evidence exists for an association between HIV infection and increased incidence for AIDS-defining malignancies (ADMs: Kaposi sarcoma (KS), Non-Hodgkin lymphoma (NHL), and cervical cancer) as well as many non-AIDS-defining malignancies (NADMs: all other cancers). [1-11] Highly active antiretroviral therapy (HAART) was introduced in 1996. This effective HIV treatment led to marked improvements in immune status and life expectancy for HIV-positive individuals.[12] The most striking associations between HIV infection and cancer risk have been demonstrated for KS and NHL, with incidence rates increasing dramatically following the onset of the HIV epidemic and subsequently falling after the introduction of HAART.[1,2,4,7,8] KS incidence fell more than 6-fold, from $1{,}282_{\text{pre-HAART}}$ per 100,000 in the US to $190_{\text{post-HAART,}}$ and NHL rates dropped four-fold, from $1{,}226_{\text{pre-HAART}}$ to $306_{\text{post-HAART}}$.[6] These dramatic changes in cancer incidence in HIV-infected patients are likely explained by a constellation of factors, including immune reconstitution as a result of effective HIV treatment, anti-tumorigenic properties of anti-retroviral medications,[13-17] or changes in risk factor prevalence among HIV-infected patients over time.

Despite reductions in cancer incidence for certain ADMs, immune deficiency remains a risk factor for many cancers, and the association between HIV and cancer risk has been extended in this post-HAART era to include increases for many NADMs.[9,10,18-20] Prolonged exposure to immunosuppression has been associated with elevated NADM incidence in European cohorts, even among HIV-positive patients on stable HAART (HR=1.13 per year CD4 T-cell <500; HR=1.12; 1.03-1.22 per year CD4 T-cell <200). [21,22] An international, 18-study meta-analysis confirmed that HIV-infected patients are at significantly higher risk for NADMs, most notably those with a known viral etiology such as Hodgkin lymphoma (HL), anal, and liver cancer (SIR: 11.0, 28.0, and 5.6, respectively). [11]

Rates of certain NADMs have actually increased in the post-HAART era among HIV-infected patients.[3,19,23-26] Recent US registry data reported that the SIR comparing cancer rates in HIV-infected patients to the general population increased nearly 3-fold between the pre- and post-HAART eras for anal cancer (RR=2.9; 95% CI 2.1-4.0) and doubled for HL (RR=2.0; 95% CI 1.3-2.9).[6] A comparison of AIDS patients diagnosed with cancer in the US in pre- versus post-HAART years revealed that NADMs have

significantly grown in absolute number by approximately 3-fold. [27] This increasing NADM burden has occurred against the backdrop of the continued risk for ADMs; although incidence has decreased over time for KS and NHL, as described above, recent data from 15 US cancer registries highlights the important fact that ADMs do still occur at significantly elevated rates in HIV-infected patients compared to the general population (SIR_{KS}=1347 and SIR_{NHL}=15). [6] The combination of NADMs and the continued risk for developing ADMs has resulted in elevated co-morbidity between HIV infection and cancer, motivating investigations into the role of HIV in not just cancer risk but also cancer treatment and outcomes in the context of immunosuppression

Cancer as a complication of HIV infection is increasingly recognized to impact not just Western settings but also resource-limited regions.[28] HIV/AIDS registries do not exist in most HIV-endemic regions. However, one Ugandan study utilized a large HIV clinic in Kampala and data from the Kampala Cancer Registry (KCR) to compare cancer rates in HIV-infected patients to those in the general population [29] and observed significantly elevated risks for a range of cancers after AIDS onset (SIR_{KS}=5.7; SIR_{NHL}=3.6; $SIR_{Cervical}$=2.7; SIR_{HL}=5.7; SIR_{Lung}=5.0). The association between HIV treatment with anti-retroviral therapy (ART) and KS risk, particularly on a population level, is not as consistent or clear as in the Western setting, [30,31] but recent cohort data from both Uganda and Kenya observed declines in the risk of KS in HIV-infected patients over time with ART initiation.[32]

The onset and trajectory of the HIV epidemic, the introduction of ART in the early 2000's, as well as dramatic improvements in life expectancy over the past 50 years in Uganda, have contributed to increased incidence for many cancers, not just ADMs. [33,34] Importantly, this increasing cancer burden in Uganda and other HIV-endemic settings is occurring in the context of a generalized HIV epidemic, with HIV prevalence rates in Uganda reported by the World Health Organization (WHO) [35] more than 10-fold higher than in the US population, accelerating a trend towards increasing co-morbidity of these two common chronic diseases in this resource-limited setting.

Little is known, however, about how HIV impacts cancer survival. Researchers from the California Cancer Registry examined differences in patient survival after a cancer diagnosis according to

HAART use for common NADMs. They observed significantly lower case-fatality for HIV-positive HL and respiratory cancer patients who reported ≥6 months of HAART use, compared to non-users. [36] However, this study included patients diagnosed with AIDS from 1990-2000; HAART did not become widely available until 1996. HAART users prior to 1996 likely represented a set of patients with different levels of immunosuppression and HIV replication compared to users in the post-HAART era. A more recent study of post-HAART era data from the Center for AIDS Research clinic system investigated differences in survival after cancer diagnosis among HIV-positive patients treated with combination antiretroviral therapy ≥6 months. [37] After accounting for cancer stage and treatment, researchers observed lower case-fatality for cancer patients who achieved HIV viral suppression (≤400 copies/mL) and for each 100-count improvement in CD4 T-cell count. The selection of post-HAART era patients on stable cART increases confidence that the variation in cancer patient survival observed in this more recent report may be due to an association with HIV-related immunosuppression and not differences in other patient characteristics over time.

Only one case-fatality study to date, a New York registry study, directly addressed the question of the difference in cancer patient survival based on HIV status by including an HIV-negative comparison group. [38] This study compared 2-year survival after cancer diagnosis between HIV-negative cancer patients diagnosed with AIDS during the pre-ART (1980-1989), early ART (1990-1995), and HAART (1996-2000) eras. Hazard ratios decreased from the pre-ART to HAART era across a wide spectrum of malignancies. The decreasing survival disadvantage for HIV-infected cancer patients could have been influenced by several factors, including changes in HIV-related causes of death in AIDS patients across different decades, improvements in cancer treatment, or increased uptake of cancer screening over time and diagnosis at earlier stages of disease in. Covariate data for important prognostic factors such as cancer stage were not available for these registry participants, complicating interpretation of the results. Although limited, these studies provide preliminary evidence from a resource-rich setting that HIV may play a role in cancer survival.

Comparable data on cancer survival are not available from resource-limited settings, although extremely poor cancer patient survival in that setting warrants further investigation into factors, including HIV infection, which may alter patient outcomes. Five-year absolute survival rates reported from the KCR were as low as 3.5% and 15.9% for esophageal and cervical cancer, respectively, and only approximately one third (33.4% and 38.4%) of lymphoma and breast cancer patients survived 5 years after cancer diagnosis.[39] These extremely poor survival rates and the growing global health burden of these two chronic diseases motivated us to investigate the role of HIV in survival after cancer diagnosis in Uganda, a resource-poor and HIV-endemic country. We undertook a retrospective cohort study of cancer patients who were treated at either the Uganda Cancer Institute (UCI) or the national hospital (Mulago) in Kampala and were followed for survival outcomes to test the hypothesis that HIV alters cancer survival.

METHODS.

Eligibility. Cancer patients eligible for this cohort study resided in Kyadondo County, were ≥18 years of age at the time of incident, primary cancer diagnosis, and were diagnosed from 2003 to 2010 with one of the selected cancers: breast cancer, cervical cancer, NHL, HL, and esophageal cancer. Cancers were selected based on frequency. From the five most common cancers in Ugandan men, we selected one ADM with a known infectious etiology (NHL), one NADM with a known infectious etiology (HL), and a NADM without an established infectious etiology (esophageal). We selected the two most common cancers in Ugandan women: breast cancer, a NADM without an established infectious etiology, and cervical cancer, an ADM with a known infectious etiology. Patient residence, age at diagnosis, and year of diagnosis were determined from the medical record intake form, and patients with a prior malignancy noted in the medical record were excluded.

Case Ascertainment. Eligibility criteria were used to create lists of potential cohort patients using the Kampala Cancer Registry (KCR) database. The KCR is a population-based registry covering Kampala and the surrounding areas (Kyadondo County) that has been operational since the 1950's.[34,40] The lists were transferred to the Uganda Cancer Institute (UCI) and Mulago Hospital, where records' officers facilitated file retrieval and medical record abstraction. To achieve more complete case ascertainment,

eligibility criteria were also given directly to the records officers at the UCI and Mulago to check against the clinic log books used for patient registration at each department.

Exposure Assessment. A cancer patient was classified as HIV-positive if he/she met any of the following three criteria: (1) positive HIV antibody lab test result included in the medical record, (2) indication of HIV-positive medical history in the clinical notes from the medical record, or (3) evidence of a referral to or ongoing treatment at a local HIV clinic. If a cancer patient did not have specific evidence of HIV infection, the patient was classified as HIV-negative.

Outcome Assessment. The primary outcome was vital status at 1 year following the primary cancer diagnosis, with death from any cause during the first year classified as an event. Vital status information was abstracted directly from the medical record. Three possible vital status outcomes at 1 year existed for each cancer patient. **Alive**: the medical record included at least one clinic visit dated $\geq$1 year after primary cancer diagnosis. **Dead**: the medical record noted that the patient died during the year following cancer diagnosis. **Unknown**: the medical record did not specifically note that the patient died during the year following cancer diagnosis, and the last clinic visit date noted in the medical record was prior to 1 year following primary cancer diagnosis.

For any cancer patient with vital status defined as unknown at 1 year, linkage to the national hospice system (Hospice Africa Uganda) database was conducted. The national hospice system in Uganda conducts active follow-up for enrollees, a crucial resource. Through this source, vital status information was available for 101 cohort patients with initially unknown vital status at 1 year as determined from the medical record.

Survival time for each cancer patient was calculated beginning at the earlier of the two following dates: (1) the date of first presentation, defined as the date listed on the medical record intake form or (2) the biopsy result report date, defined as the date listed on the pathology report in each medical record confirming a histological diagnosis. The survival time end date was the date of death as listed in the medical record for deceased cancer patients. Survival time was censored on the last date of any clinical contact listed in the medical record for cancer patients with alive or unknown vital status.

Covariates and Extent of Disease Assessment. Covariate data were abstracted directly from the medical record for the following patient characteristics measured at the time of primary cancer diagnosis: age, sex, year of diagnosis, duration of symptoms prior to presentation (months), history of smoking, family history of cancer, and prior medical conditions (diabetes, tuberculosis, cardiovascular disease).

A reproductive history, including information on parity, contraception, menarche, and menopausal status was included in the clinical notes for female patients. Information on baseline body mass index (BMI) measured for the purpose of chemotherapy dosage calculations was only uniformly (84%) available for lymphoma patients. Additionally, hemoglobin values measured at primary cancer diagnosis were recorded for >99% of lymphoma and ~70% of cervical cancer patients.

The attending physician recorded the degree of lymph node involvement, including location and spread (local spread: one side of the diaphragm; distant spread: both sides of the diaphragm). The spread of disease to other organs was determined by a set of scans conducted as part of initial patient staging, including an abdominal scan and a chest x-ray. Based on these staging investigations, as well as the size and location of the presenting tumor, the attending physician assigned a cancer stage at diagnosis prior to recommending cancer treatment. If an initial clinical stage was not specifically noted, a consulting physician reviewed the medical record and adjudicated stage at diagnosis based on available data. If a TNM stage was assigned, the T, N, and M values were used to assign a value ranging from Stage I-IV, with Stages I and II considered early stage disease and Stages III and IV considered advanced disease.

Statistical Analysis. Kaplan-Meier product-limit survival estimates were generated comparing differences in vital status at 1 year according to HIV status at the time of cancer diagnosis (HIV-positive vs. HIV-negative). Differences for unadjusted analyses were statistically evaluated using the log-rank test, with p-values <0.05 considered statistically significant. Cox proportional hazards regression was utilized to evaluate the association between HIV status (HIV-positive vs. HIV-negative) and the outcome of 1-year survival after cancer diagnosis in the full cohort (N=802). Multivariable models included the following covariates for all malignancies selected *a priori*: age, sex (lymphoma and esophageal cancer

patients only) year of cancer diagnosis, and cancer stage. Adjusted regression models were also run with the outcome of 2-year survival.

Etiologically meaningful subgroups of cancers were defined as: 1) cancers with a known infectious etiology (NHL, HL, cervical cancer) and 2) cancers without an established infectious etiology (breast and esophageal cancer). Traditional malignancy classifications were also explored: 1) ADMs (cervical cancer, NHL) and 2) NADMs (breast and esophageal cancer, HL). Additional models were run among lymphoma patients with further adjustment for BMI and hemoglobin and among cervical cancer patients with further adjustment for hemoglobin because both BMI and anemia were observed to alter 1-year survival (p-value <0.10) in univariate analyses.

A regression model that subdivided HIV-positive patients according to year of cancer diagnosis, which serves as a surrogate for ART availability in Uganda compared 1-year case-fatality in HIV-negative cases to the following groups: 1) HIV-positive cases diagnosed in 2003-2005 (ART coverage range: 5-25%), 2) HIV-positive cases diagnosed in 2006-2008 (ART coverage range: 30-45%), and 3) HIV-positive cases diagnosed in 2009-2010 (ART coverage estimate $\geq$50%).[30] To avoid over-adjustment, year of diagnosis was not included as a variable in this final regression model. All Cox proportional hazards regression coefficients were statistically evaluated using the likelihood ratio test, with p-values <0.05 considered statistically significant.

Finally, a sensitivity analysis was undertaken to explore parameterization of HIV exposure categories into HIV-positive, HIV-negative, and HIV-unknown. HIV-negative cancer patients were re-classified as HIV-unknown if both of the following were absent: 1) negative result on the HIV antibody lab test result included in the medical record and 2) HIV-negative status recorded in the medical history or clinical notes.

RESULTS. Our retrospective cohort (N=802) included the following distribution of cancer types as described in **Table 1**: breast cancer (N=220), cervical cancer (N=316), NHL (N=134), HL (N=63), and esophageal cancer (N=69). Approximately one third of the cancer patients in our cohort were HIV-positive at the time of primary cancer diagnosis (34%; N=274). This proportion differed depending upon

the cancer diagnosis. (**Figure 1**) Among patients diagnosed with a cancer without an established infectious etiology, prevalence rates were similar to those reported by the WHO for the general Ugandan population (breast cancer: 11%; esophageal cancer: 6%). In contrast, prevalence was higher among patients diagnosed with infection-related cancers (NHL: 57%; cervical cancer: 42%; HL 44%).

Patient characteristics differed by HIV status. The majority of the cohort patients were women due to the inclusion of breast and cervical cancer patients. Among lymphoma patients, females comprised a higher proportion of HIV-positive cases for both NHL and HL (NHL: 51% $_{HIVPositive}$ vs. 37% $_{HIVNegative}$; HL: 66% $_{HIVPositive}$ vs. 39% $_{HIVNegative}$). HIV-positive cancer patients were significantly younger than their HIV-negative counterparts for all cancer types considered, particularly cervical cancer, with 41% of HIV-positive cervical cancer patients diagnosed at 18-35 years of age, compared to only 13% of HIV-negative cervical cancer cases. Esophageal cancer, the malignancy with the lowest proportion of HIV-positive cases, was the only subgroup with the majority of patients (64%) diagnosed at 56-86 years of age, although the small number of HIV-positive esophageal cancer patients (N=4) precluded comparison of age distribution according to HIV status.

The stage of disease assigned at primary cancer diagnosis varied according to cancer patient HIV status, but these differences were driven to a large degree by cancer type. For example, earlier stage at diagnosis in HIV-positive cancer patients compared to HIV-negative cancer patients was largely attributable to cervical cancer. HIV-positive cervical cancer patients were uniformly diagnosed at earlier stages than their HIV-negative counterparts (Stage I/II: 39% $_{HIVpositive}$ vs. 21% $_{HIVnegative}$). In contrast, HIV positivity occurred more frequently among more advanced stage disease for both breast cancer (Stage III/IV: 46% $_{HIVpositive}$ vs. 39% $_{HIVnegative}$) and HL patients (Stage III/IV: 63% $_{HIVpositive}$ vs. 50% $_{HIVnegative}$). No substantive differences in stage at diagnosis were observed for NHL patients, who were uniformly diagnosed with advanced disease: 83% $_{HIVpositive;}$ 81% $_{HIVnegative}$. The majority (74%) of stage information was not recorded in the medical record for esophageal cancer patients.

Only 322 cancer patients were confirmed as alive 1 year after their primary cancer diagnosis, and 262 of the patients in the cohort remained alive and under follow-up after 2 years. Among patients

confirmed as deceased during the first year following cancer diagnosis (N=152), nearly half died within 3 months, and more than two-thirds died by 182 days, only 6 months following cancer diagnosis. For patients with unknown vital status at 1year (N=328), over half were lost to follow-up in less than 3 months (80 days), indicative of loss occurring almost immediately after diagnosis.

The 1-year case-fatality for cancer patients was significantly related to their specific cancer diagnosis (log rank p-value <0.01), regardless of HIV status. Breast cancer patients had the best prognosis, with 63% (N=138) confirmed as alive at 1 year. NHL patients experienced the poorest survival, with only 33% (N=44) patients reported as alive at 1 year.

The HIV status of cancer patients at the time of primary cancer diagnosis was significantly associated with vital status at 1 year (log-rank p-value <0.01) (**Figure 2**). This association between HIV and 1-year cancer survival remained even after accounting for potential outcome differences due to cancer stage at diagnosis (**Table 2**). HIV-positive cancer patients in Uganda were more than twice as likely to die during the first year following primary cancer diagnosis as HIV-negative cancer patients (HR=2.32; 95% CI 1.64-3.29). Importantly, this marked association between HIV-positive status and higher 1-year case-fatality was consistent for both cancers with and cancers without an established infectious etiology. Specifically, HIV-positive cases diagnosed with infection-related cancers had ~60% higher rates of case-fatality during the first year after cancer diagnosis (HR=1.61; 95% CI 1.07-2.43) compared to HIV-negative cases. HIV-positive cases diagnosed with cancers without an established infectious etiology experienced strong and significant elevations in case-fatality during the first year after cancer diagnosis (HR=2.61; 95% CI 1.17-5.84). Notably, results were also consistent according to the traditional classifications: HR_{NADM}=2.49; 95% CI 1.25-4.95; HR_{ADM}=1.63; 95% CI 1.07-2.47.

Results for case-fatality at 1 year among lymphoma patients after further adjustment for sex, hemoglobin, and BMI were consistent with those reported in **Table 2** ($HR_{Model\ 2}$=1.30; 95% CI 0.73-2.32; $HR_{Fully\text{-}adjusted}$=1.28; 95% CI 0.65-2.52). HIV-positive cervical cancer patients experienced higher 1-year case-fatality compared to HIV-negative patients after adjustment for hemoglobin ($HR_{Model\ 2}$=1.77; 95% CI

0.99-3.15; $HR_{Fully\text{-}adjusted}$ =1.77; 95% CI 0.88-3.57), despite decreased study power due to missing hemoglobin values for 30% of these women.

At 1 year following primary cancer diagnosis, a total of 152 cancer patient deaths had occurred. An additional 61 patients died during follow-up over the course of the second year following primary presentation. Utilizing this additional follow-up data to examine the role of HIV in cancer patient survival revealed results for 2-year outcomes (**Table 3**) consistent with those reported for 1-year outcomes. After accounting for age, year of cancer diagnosis, and cancer stage, 2-year case-fatality for HIV-positive cancer patients remained approximately double that of HIV-negative patients (HR=2.10; 95% CI 1.54-2.87). This relationship was consistent for patients diagnosed with infection-related cancers (HR=1.49; 95% CI 1.03-2.15) as well as cancers without an established infectious etiology (HR=2.22; 95% CI 1.10-4.48).

To investigate immunosuppression and 1-year case-fatality, we compared HIV-negative cancer patients to HIV-positive patients diagnosed during different periods of ART coverage (**Figure 3**). Estimates of ART coverage in Uganda increased from 5-25% prior to 2006 to nearly 45% by 2008 [30] and are assumed to have continued to increase in more recent years. Accordingly, we observed that HIV-positive cases diagnosed prior to widespread ART availability, possibly patients with higher levels of immune dysfunction, experienced the poorest 1-year survival compared to HIV-negative patients ($HR_{2003\text{-}2005}$=3.04; 95% CI 1.57-5.89). The 1-year case-fatality remained elevated in HIV-positive patients diagnosed more recent years compared to HIV-negative cancer patients ($HR_{2006\text{-}2008}$=2.40; 95% CI 1.60-3.63; $HR_{2009\text{-}2010}$=2.01; 95% CI 1.25-3.25), but the difference in cancer survival was not as pronounced.

When patients with unknown HIV status (N=212) were separated from confirmed HIV-negative patients (N=316) and comparisons in 1-year survival were made directly between confirmed HIV-positive and confirmed HIV-negative cases only, the findings were consistent with those reported ($HR_{Fully\text{-}adjusted}$=2.24; 95% CI 1.53-3.26). No differences in 1-year survival were observed between HIV-unknown and confirmed HIV negative cases ($HR_{Fully\text{-}adjusted}$ =0.88; 95% CI 0.55-1.43), supporting the contention that

the majority of patients with unknown vital status were correctly classified as HIV-negative at the time of cancer diagnosis.

DISCUSSION. In the first large and comprehensive study of the association between HIV and cancer survival in sub-Saharan Africa, we found that HIV-positive cancer patients in Uganda experienced a more than two-fold increase in case-fatality during the first year following a cancer diagnosis compared to HIV-negative cancer patients for all cancers under study. This marked inverse association between HIV and cancer survival was consistently observed for cancers with and without an infectious etiology, including ADMs and NADMs, regardless of the stage at diagnosis. Importantly, this was the first study with adequate case numbers and data on cancer stage and HIV status to evaluate survival after a breast or esophageal cancer diagnosis and was the largest such study of cervical cancer. These findings extend the established relationship between HIV and cancer incidence to include a role for HIV in cancer outcomes in a resource-limited setting.

Our results build upon the limited data on the interaction between HIV and cancer survival in resource-limited regions, an important public health issue considering the 5-year cancer survival rates in Uganda.[39] A recent study in Uganda of the association between HIV and 1-year survival for NHL patients (N=154) ascertained cases from a similar time frame (2004-2009) but included much younger cases (eligibility $\geq$13 years) than our cohort. [41] HIV-positive patients not on ART experienced significantly worse 1-year survival than both HIV-positive patients on ART and HIV-negative patients, although these results did not account for cancer stage at diagnosis. An earlier study of cervical cancer patients (N=261) diagnosed prior to ART availability in Uganda (1995-1997) examined outcomes at 3 years post-cancer diagnosis in relation to a variety of patient characteristics, including HIV status. [42] Consistent with the current study, HIV-positive patients had marginally poorer survival (p=0.09), although this association did not persist after inclusion of adjustment covariates at 3-years.

It has long been recognized that immunosuppression is associated with an increased risk of developing cancer, initially noted with congenital immunodeficiency and then corroborated by the increased risk of cancer in iatrogenically-induced immunosuppression in organ transplant recipients

(OTR)[43-54] and more recently in patients infected with human immunodeficiency virus (HIV).[2-4,7-11,21,22,25,26,55-59] Specifically, cancers attributable to infectious agents are most commonly elevated in immunosuppressed individuals. [60-63]

The risk for NHL, an EBV-related malignancy, is strongly associated with immune status. Evidence from 23 cohort studies demonstrated lower NHL incidence in the post-HAART compared to pre-HAART period (RR=0.58; 95% CI 0.45-0.74). [1] Studies consistently demonstrated an elevated risk associated not just with HIV infection but also with the severity of HIV disease. [2,4,7,8,19] Immunosuppression is also related to earlier stages of the cervical carcinogenic process, with higher rates of low-grade cervical lesion regression and lower rates of recurrence of abnormal cytology consistently observed among HIV-positive women with lower CD4 T-cell counts or among those on HAART. [64-69] However, US-based registry studies consistently report a null association between CD4 T-cell counts and HAART use in HIV-positive women and the risk of being diagnosed with invasive cervical cancer, [1-3,7,5819,55] although these studies are not able to account for changes in cervical cancer screening that may parallel changes in HAART availability over time.

HL is traditionally classified as a NADM, despite often being caused by the EBV in the context of HIV infection. [70-73] HL risk follows a U-shaped incidence curve; whereas HL rates generally increase in the presence of greater immunosuppression,[59,74] HL rates in HIV-positive persons are actually highest among those with low, but not the absolute lowest, CD4 T-cell counts (e.g. 53.7 per 100,000 at CD4 150-199; 20.7 per 100,000 at CD4 <50). [75] CD4 T-cell surface proteins have the ability to mimic survival signals in HL cells; complete elimination of the CD4 T-cell pool at counts <50 removes these survival signals, [76] and the result is the consistent observation that HL rates peak at CD4 T-cell counts slightly above 50 and actually decline in patients with the most severe immunosuppression.[77]

Our results suggest that a relationship between HIV infection and cancer survival exists not only for infection-related cancers but also for NADMs without an established infectious etiology, suggesting a more uniform association between HIV and cancer outcomes than risk. No cohort study to date has reported on the association between HIV and esophageal cancer. A recent series of 19 cases was

published,[78] with no obvious differences noted between HIV-positive and HIV-negative cases; over 80% of the patients reported at least one known risk factor for esophageal cancer (e.g. heavy smoking or alcohol consumption), suggestive of a consistent risk etiology according to HIV status. Results from the international 18-study meta-analysis did indicate marginally elevated esophageal cancer risk in the HIV-positive population (SIR=1.5; 95% CI 0.99-2.3),[11] although failure to adjust for strong lifestyle risk factors such as smoking and alcohol consumption complicates interpretation.

In contrast, the same meta-analysis reported a marginally decreased risk for breast cancer among the HIV-positive population (SIR=0.7; 95% CI 0.6-0.97). [11] One US-based registry study utilized indirect adjustment to investigate the association between HIV and breast cancer while attempting to account for known risk factors such as age at first birth and parity [79] and observed lower breast cancer risk in HIV-positive women (SIR=0.69; 95% CI 0.62; 0.77), although this reduced risk was only observed for local, potentially screen-detected, disease and was not observed for distant breast cancer (SIR=0.89; 95% CI 0.40-1.68). A recent study reported that significantly fewer HIV-positive women who developed breast cancer harbored CXCR4-tropic HIV compared to HIV-positive women who did not develop breast cancer, [80] hypothesized to be due to apoptosis inducted by interaction between HIV and CXCR4 expressed by breast cells.[81] Although intriguing, this finding necessitates replication with a larger sample of cases and careful adjustment for the duration of HIV infection between cases rand controls, a key determinant of HIV tropism.

Biological mechanisms could help explain a substantive portion of the observed survival disadvantage for HIV-positive cancer patients. For infection-associated malignancies, immune dysfunction in the context of HIV and the resulting inability to control oncogenic viruses alters the risk of tumor development. Both the number and functional capacity of anti-viral, CD8 T-cells specific to EBV antigens are impaired in EBV-infected AIDS patients who progressed to NHL, [82-84] providing a plausible mechanism for the observed association between HIV-related immunosuppression and NHL risk. We also have an example that anti-viral immunity can play a direct role in tumor progression; HIV-positive KS patients with improved disease had lower levels of replicating HHV8 in the peripheral blood, in

parallel with superior function of KS-specific CD8 T-cells, as opposed to KS patients with progressive disease, who experienced higher HHV8 levels in the peripheral blood and poor KS-specific CD8 T-cell responses. [85,86]

Our findings suggest a uniform survival disadvantage for all immunosuppressed cancer patients, consistent with the pathology of HIV and cancer overall. The dysfunction of CD8 T-cell immunity is a hallmark of HIV pathogenesis and occurs as a result of not only the destruction of CD4 T-cells by HIV but also the chronic immune activation that occurs in HIV infected patients. [87,88] Experimental studies have documented a direct correlation between the presence of HIV and CD8 T-cell activation. [89-92] This chronic immune activation stems from both persistent, long-term HIV infection [93,94] as well as prevalent co-infections such as cytomegalovirus.[53,95,96] A key implication of this constant immune activation in the context of HIV infection is a premature ageing of the immune system, or a senescent immune phenotype.[97-99] This immune failure results in the depletion of naïve CD8 T-cells capable of responding to new antigens [100-104] as well as an impaired ability to proliferate and divide in response to prevalent infections and a loss of memory T-cells. [105,106107,108] This pathogenic effects of HIV on CD8 T-cells could have direct implications for anti-tumor surveillance since CD8 T-cells have demonstrated an ability to develop effective cytotoxic responses to proteins on the surface of tumor cells.[109 110] Mouse studies have illustrated the importance of lymphocyte populations, including CD8 T-cells, in the prevention of tumor formation [111-114] and have also documented the importance of cytotoxic, cell-mediated activity in controlling tumor metastasis. [115-117]

This experimental evidence is supported by data from population studies that have repeatedly observed that infiltration of human tumors with CD8 T-cells is associated with improved tumor prognosis and reduced tumor growth.[118-123] As such, this immune dysfunction has broad implications for altering cancer outcomes in HIV-positive patients, not just for tumors arising from ADMs but also NADMs with a non-infectious etiology. Once a tumor has been initiated, HIV could play a role in diminishing the capacity of the immune system to control the growth and metastatic potential of that tumor.

Another direct implication of persistent immune activation in the context of HIV is chronic inflammation.[88,124] Levels of pro-inflammatory cytokines are significantly higher in HIV-positive versus HIV-negative individuals, and population studies have consistently found that inflammation markers correlate with the degree of HIV disease severity.[125-127128,129] This elevated inflammation has direct implications for tumor progression; the potential for inflammation to promote cancer progression has been well described in the literature [130-135] and is considered to be an underlying hallmark of cancer due to its role in multiple processes involved in tumorigenesis.[133] The HIV viral protein Tat plays a direct role in altering cytokine signaling [136-142] and can mimic the activity of extracellular matrix proteins and VEGF-A, promoting angiogenic signaling and vascularization. [143-145] Angiogenesis, both a component of inflammation and another hallmark of cancer, can provide the blood supply necessary for a nascent tumor to grow and metastasize, promoting cancer progression. [146-148]

Ultimately, the tumor environment for both ADMs and NADMs contains lymphocyte populations that can both promote and destroy malignant cells. This balance between anti-tumor and pro-tumor immunity may be dangerously affected by the presence of HIV infection. The depletion and exhaustion of key lymphocyte populations by HIV alters anti-tumor immunity, while chronic immune activation is accompanied by high levels of inflammation, which results in pro-tumor processes such as angiogenesis. The sum of this tumor balance equation is that in an HIV-infected individual, regardless of the etiology of that tumor (i.e. for both infection-related and unrelated cancers), tumor promotion is allowed by both an increase in pro-tumor signaling accompanied by a decrease in anti-tumor immune surveillance.

The limitation of case eligibility for our cohort to the decade post-ART availability increased the likelihood that HIV-positive patients had some level of access to ART and avoided vast differences in HIV-related deaths that would be expected across different decades. Data on stage at diagnosis were collected or adjudicated, decreasing the potential for confounding bias in survival comparisons. Adequate numbers of cancer patients for certain cancer diagnoses were included to estimate stable cancer type-specific effects. Further, the inclusion of HIV-negative cancer patients provided a true unexposed comparison group to investigate our hypothesis. However, this study is not without limitations, the most

important of which was the significant loss to follow-up during the first year following cancer diagnosis. Approximately 42% of patients diagnosed with cancer were lost to follow-up prior to one year (N=339). Reassuringly however, the difference in loss to follow-up did not differ by HIV status, with 43% of HIV-negative patients lost and 41% of HIV-positive patients lost. Differences in loss to follow-up by HIV were inconsistent by cancer diagnosis, with no systematic patterns observed throughout the cohort.

Uganda does not have nationwide death registration that provides cause of death information. This precluded investigation of cancer-specific survival estimates. Instead, overall survival during the first year following cancer diagnosis was used as a verifiable outcome, although it did not reflect death *only* from cancer-related causes. However, our confidence that the survival differences observed in the first year after cancer diagnosis according to HIV status reflected not just HIV-related causes of death but also cancer-related deaths is strengthened by the proximity of the majority of deaths to the date of cancer diagnosis. The timing of deaths was heavily weighted towards the date of cancer diagnosis rather than evenly spaced over the course of follow-up, a trend that was consistent irrespective of HIV status. One final limitation to note was the inability to ensure that case ascertainment was complete for the given cancers and years selected; data were abstracted from records provided with available follow-up data, such that cases who disappeared immediately after presentation (i.e. prior to histological diagnosis) or with lost medical records were not available for the cohort. Although this does not threaten the internal validity of the study or findings, this may limit generalizability.

The next steps for similar research in HIV-endemic regions should include the investigation of cancer-specific outcomes and active mortality follow-up to address the limitations highlighted above. The prospective collection of more sensitive HIV-related measures, such as HIV RNA levels at the time of cancer diagnosis, may also identify characteristics of HIV-positive patients that could explain a portion of the observed survival differences. Epidemiological studies to date have not adequately answered the increasingly important question of whether HIV alters outcomes after a cancer diagnosis, including treatment response and survival. Future work that utilizes patient cohorts with complete stage and treatment data is needed to examine the association between HIV-related immunosuppression and

disease-specific outcomes. Despite the improvements made possible by ART, the number of patients with co-morbidities of both HIV infection and cancer will continue to grow, particularly in resource-limited settings. Understanding their disease course is paramount to improving prognosis.

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TABLE 1. PATIENT CHARACTERISTICS

	Total Cohort (N=802)		HIV Negative (N=528)		HIV Positive (N=274)		Kaplan-Meier log-rank p-values [a]
	N	%	N	%	N	%	
Cancer Type							
Breast Cancer	220	27.4	196	37.1	24	8.8	
Cervical Cancer	316	39.4	182	34.5	134	48.9	
Non-Hodgkin Lymphoma	134	16.7	57	10.8	77	28.1	
Hodgkin Lymphoma	63	7.9	28	5.3	35	12.8	
Esophageal Cancer	69	8.6	65	12.3	4	1.5	<0.01
Sex of Case [b]							
Female	125	47.0	62	41.3	63	54.3	
Male	141	53.0	88	58.7	53	45.7	0.44
Age (years)							
18-35	211	26.3	103	19.5	108	39.4	
36-44	188	23.4	93	17.6	95	34.7	
45-55	210	26.2	159	30.1	51	18.6	
56-86	185	23.1	169	32.0	16	5.8	0.63
Year of Cancer Diagnosis							
2003-2005	120	15.0	81	15.3	39	14.2	
2006-2008	367	45.8	244	46.2	123	44.9	
2009-2010	315	39.3	203	38.5	112	40.9	0.78
Body Mass Index [c]							
< 18.5	73	37.1	34	40.0	39	34.8	
18.5-24.99	66	33.5	23	27.1	43	38.4	
25.0-29.99	20	10.2	12	14.1	8	7.1	
30+	7	3.6	4	4.7	3	2.7	0.08
Missing	31	15.7	12	14.1	19	17.0	
Anemia at Presentation [d]							
No	126	24.6	77	28.8	49	19.9	
Yes: ≤12 g/dL	221	43.1	100	37.5	121	49.2	
Severe: ≤7 g/dL	70	13.6	32	12.0	38	15.4	<0.01
Missing	96	18.7	58	21.7	38	15.4	
Tumor Stage							
Stage I	34	4.2	20	3.8	14	5.1	
Stage II	112	14.0	53	10.0	59	21.5	

Stage III	370	46.1	257	48.7	113	41.2	
Stage IV	183	22.8	113	21.4	70	25.6	<0.01
Missing	103	12.8	85	16.1	18	6.6	
Parity [e]							
Nulliparous	31	4.7	19	4.4	12	5.4	
Parous	537	81.7	350	80.3	187	84.6	0.24
Missing	89	13.6	67	15.4	22	10.0	
Menopausal Status [e]							
Post-Menopausal	184	28.0	166	38.1	18	8.1	
Pre-Menopausal	370	56.3	191	43.8	179	81.0	0.8
Missing	103	15.7	79	18.1	24	10.9	
Vital Status at One Year							
Alive	322	40.2	234	44.3	88	32.1	
Dead	152	19.0	79	15.0	73	26.6	
Lost to Follow-up	328	40.9	215	40.7	113	41.2	

[a] Log-rank p-values from Kaplan-Meier product limit survival estimates for each covariate of interest.

[b] Numbers and percentages for sex restricted to lymphoma and esophageal cancer patients (N=266)

[c] Numbers and percentages for BMI restricted to lymphoma patients (N=197)

[d] Numbers and percentages for anemia restricted to lymphoma and cervical cancer patients (N=513)

[e] Numbers and percentages for parity and menopausal status restricted to female patients (n=657)

TABLE 2. ASSOCIATION BETWEEN HIV AND 1-YEAR CANCER SURVIVAL

			Model 1 [a]		Model 2 [b]	
		Total/Deaths	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All Cancer Patients (n=802)						
	HIV Negative	528/79	1.00		1.00	
	HIV Positive	274/73	2.08 (1.47-2.95)	<0.01	2.32 (1.64-3.29)	<0.01
Breast Cancer (n=220)						
	HIV Negative	196/23	1.00		1.00	
	HIV Positive	24/6	1.98 (0.74-5.27)	0.17	2.02 (0.75-5.43)	0.16
Lymphomas (n=197)						
	HIV Negative	85/22	1.00		1.00	
	HIV Positive	112/31	1.26 (0.71-2.23)	0.43	1.30 (0.73-232)	0.38
NHL (n=134)						
	HIV Negative	57/19	1.00		1.00	
	HIV Positive	77/26	1.16 (0.63-2.14)	0.65	1.31 (0.702.45)	0.39
HL (n=63)						
	HIV Negative	28/3	1.00		1.00	
	HIV Positive	35/5	1.71 (0.36-8.07)	0.50	1.64 (0.34-7.95)	0.54
Esophageal Cancer (n=69)						
	HIV Negative	65/8	1.00		1.00	
	HIV Positive	4/3	4.71 (0.97-22.9)	0.43	5.57 (1.07-29.0)	0.04
Cervical Cancer (n=316)						
	HIV Negative	182/26	1.00		1.00	
	HIV Positive	134/33	1.59 (0.88-2.85)	0.12	1.77 (0.99-3.15)	0.06
Cancers with Infectious Etiology (n=513)						
	HIV Negative	267/48	1.00		1.00	
	HIV Positive	246/64	1.52 (1.01-2.28)	0.04	1.61 (1.07-2.43)	0.02
Cancers without Infectious Etiology (n=289)						
	HIV Negative	261/31	1.00		1.00	
	HIV Positive	28/9	2.63 (1.19-5.85)	0.02	2.61 (1.17-5.84)	0.02

[a] Model includes: age, year of cancer diagnosis

[b] Model includes: Model 1 + stage at presentation (categorical: Stage I/II, Stage III, Stage IV, Stage unknown)

TABLE 3. ASSOCIATION BETWEEN HIV AND 2-YEAR CANCER SURVIVAL

			Model 1 [a]		Model 2 [b]	
		Total/Deaths	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All Cancer Patients (n=802)						
	HIV Negative	528/109	1.00		1.00	
	HIV Positive	274/85	1.89 (1.39-2.58)	<0.01	2.10 (1.54-2.87)	<0.01
Breast Cancer (n=220)						
	HIV Negative	196/34	1.00		1.00	
	HIV Positive	24/8	1.91 (0.84-4.35)	0.12	1.98 (0.87-4.54)	0.10
Lymphomas (n=197)						
	HIV Negative	85/24	1.00		1.00	
	HIV Positive	112/34	1.32 (0.76-2.28)	0.32	1.36 (0.78-2.37)	0.29
NHL (n=134)						
	HIV Negative	57/20	1.00		1.00	
	HIV Positive	77/29	1.30 (0.72-2.35)	0.39	1.46 (0.80-2.67)	0.21
HL (n=63)						
	HIV Negative	28/4	1.00		1.00	
	HIV Positive	35/5	1.21 (0.30-4.95)	0.79	1.14 (0.27-4.80)	0.86
Esophageal Cancer (n=69)						
	HIV Negative	65/13	1.00		1.00	
	HIV Positive	4/3	5.54 (1.14-26.9)	0.32	5.15 (1.00-26.6)	0.05
Cervical Cancer (n=316)						
	HIV Negative	182/38	1.00		1.00	
	HIV Positive	134/40	1.35 (0.81-2.23)	0.25	1.44 (0.87-2.39)	0.15
Cancers with Infectious Etiology (n=513)						
	HIV Negative	267/62	1.00		1.00	
	HIV Positive	246/74	1.42 (0.98-2.05)	0.06	1.49 (1.03-2.15)	0.04
Cancers without Infectious Etiology (n=289)						
	HIV Negative	261/47	1.00		1.00	
	HIV Positive	28/11	2.26 (1.12-4.53)	0.02	2.22 (1.10-4.48)	0.03

[a] Model includes: age, year of cancer diagnosis
[b] Model includes: Model 1 + stage at presentation (categorical: Stage I/II, Stage III, Stage IV, Stage unknown)

Figure 1. Distribution of Cancer Type, according to HIV Status

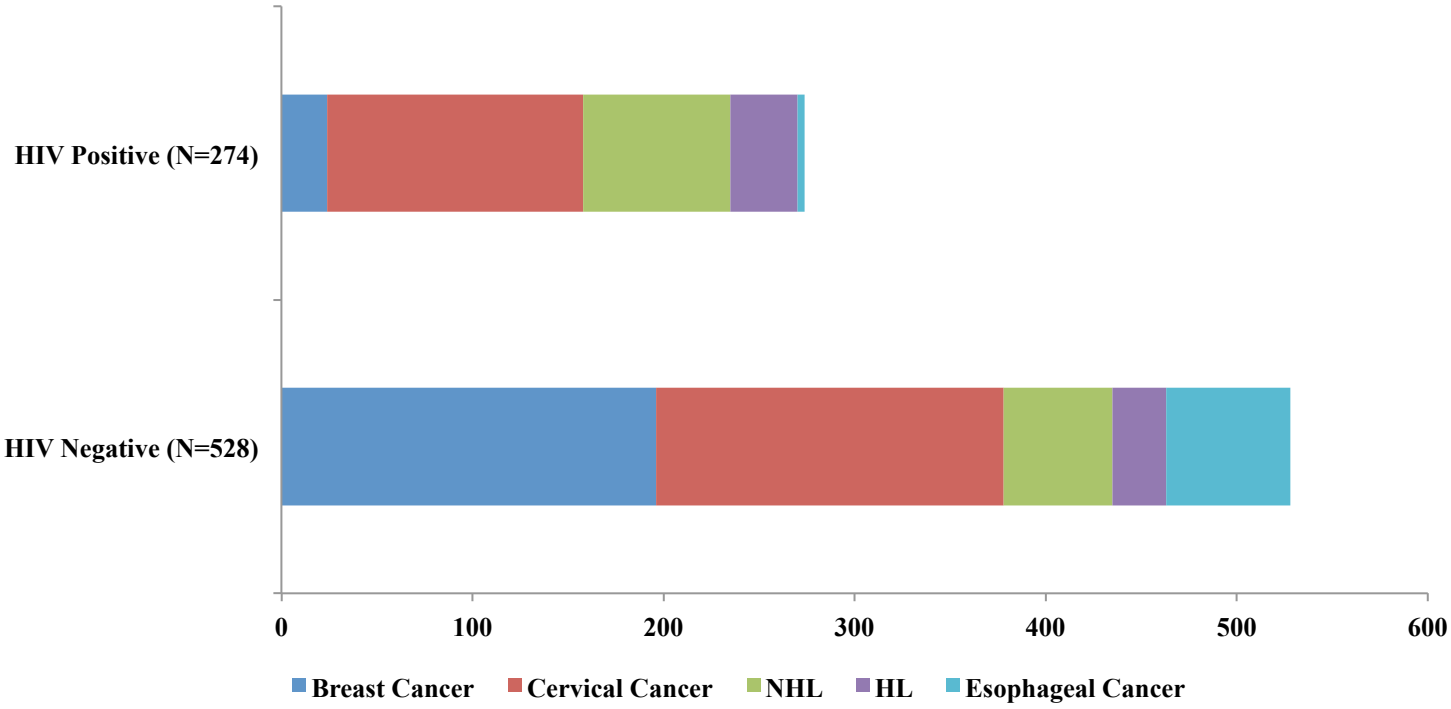


Figure 2. 1-year Survival, according to HIV Status

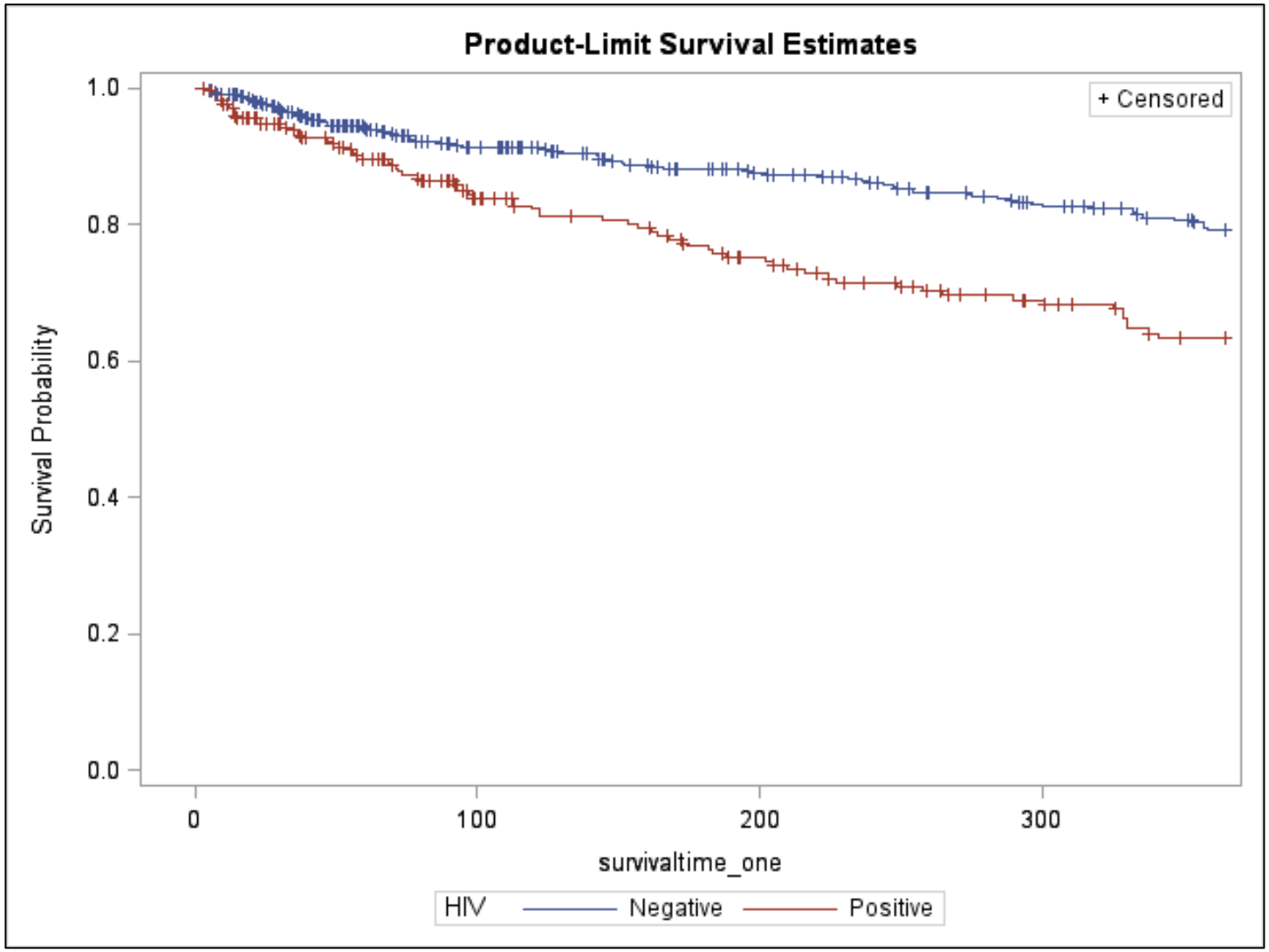
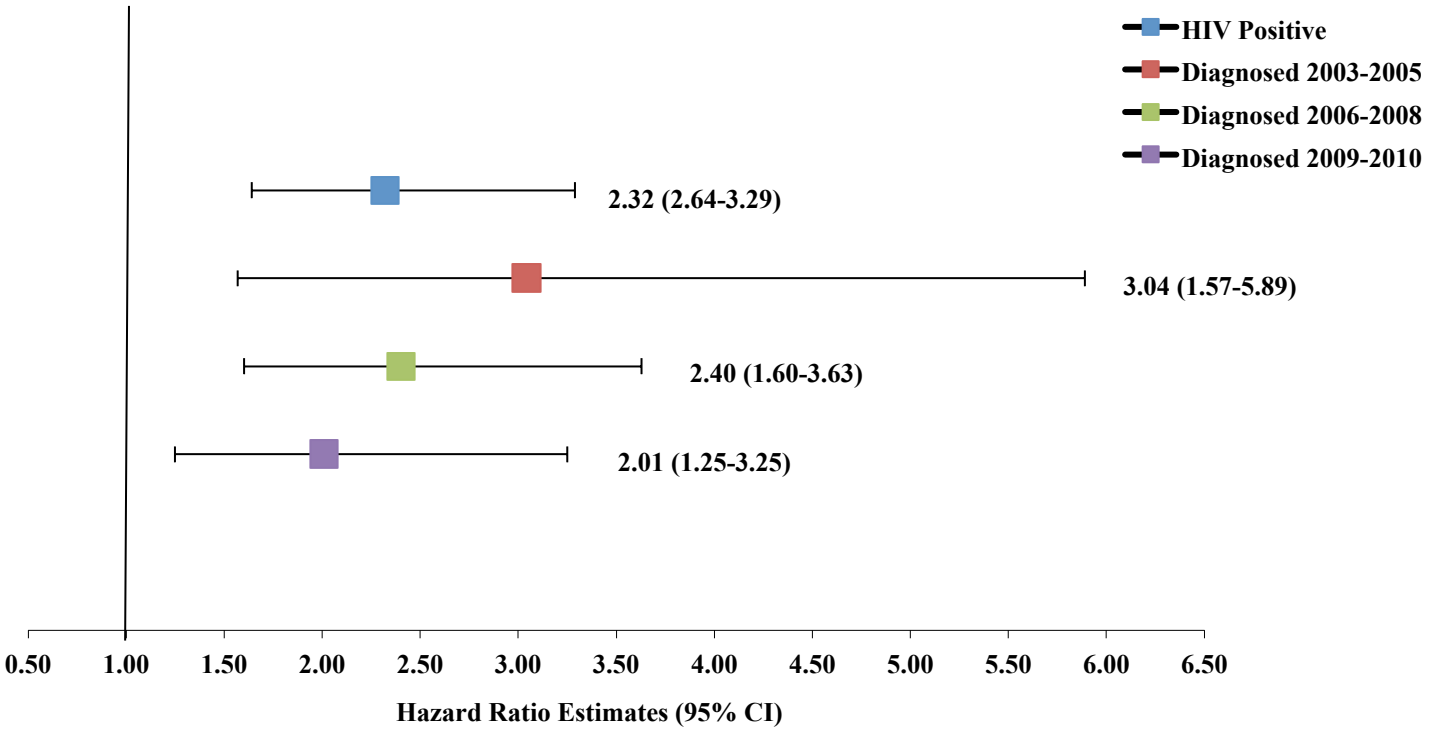


Figure 3.HIV and 1-Year Cancer Survival, according to ART Availability [a]



[a] Estimated ART availability in Uganda: 2003-2005:5-25%; 2006-2008:30-45%; 2009-2010: assumed to have increased above 50%

VITA

Anna Elizabeth Coghill grew up in Charleston, South Carolina. She has lived in many places and has called Seattle home for the past four years. At Duke University she earned a Bachelor of Science degree in Cell and Molecular Biology and a Master of Public Health from Emory University. In 2012 she earned a Doctor of Philosophy at the University of Washington in Epidemiology and recently moved to Washington, DC to begin a postdoctoral fellowship at the Infections and Immunoepidemiology Branch of the National Cancer Institute.

Abstraction Date: ☐☐ ☐☐☐ ☐☐

Case ID: ☐☐ ☐☐ ☐☐☐☐

UPCID_803

Form A: Medical Record Intake Form

FORM A: MEDICAL RECORD INTAKE FORM

Abstraction Information	1. Location of Primary Abstracted Medical Record: Uganda Cancer Institute **1** ☐ Mulago Hospital **2** ☐
Sex of Case	2. Male **1** ☐ Female **2** ☐
Age of Case	3. Age In Years At First Presentation (listed on **Face Sheet**): ☐☐ 4. Date of Birth: ☐☐ ☐☐☐ ☐☐ D D M M M Y Y
Referral Clinic and Contact Information	5. Name of Referral Clinic: _____ 6. Location of Referral Clinic: _____
Cancer Diagnosis Information	7. Date Of First Cancer Suspicion (listed on **Referral Letter**): ☐☐ ☐☐☐ ☐☐ D D M M M Y Y 8. Date Of First Cancer Presentation (listed on **Face Sheet**): ☐☐ ☐☐☐ ☐☐ D D M M M Y Y 9. Type of Cancer Diagnosis: Breast Cancer **1** ☐ Non-Hodgkin Lymphoma **2** ☐ Cervical Cancer **3** ☐ Hodgkin Lymphoma **4** ☐ Oesophageal Cancer **5** ☐ 10. Was a **Histological** Cancer Diagnosis Made? Yes **1** ☐ No **2** ☐ **If Yes**, complete questions 11-13 below: 11. Histological Type (**Write and fill in code.**): _____ ☐☐

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First Entry: _____ __ __/__ __ __/__ __ Second Entry: _____ __ __/__ __ __/__ __

Initials dd mmm yy Initials dd mmm yy

	12. Date Tissue Taken for Biopsy: ☐☐ (D D) ☐☐☐ (M M M) ☐☐ (Y Y) 13. Date Biopsy Results Reported: ☐☐ (D D) ☐☐☐ (M M M) ☐☐ (Y Y) 14. Subtype Clinically Suspected (**if no Histology done**): _____
Presenting Symptoms	15. Patient Began Reporting Symptoms How Many Months Before Presentation: ☐☐ 16. Major Symptoms Present (check all that apply) at First Presentation: Detection of Mass/Swelling **1** ☐ — Bleeding **7** ☐ Difficulty Swallowing **2** ☐ — Extreme Fatigueability **8** ☐ Bone Pain **3** ☐ — Ascites **9** ☐ Edema **4** ☐ — Wasting **10** ☐ Fever **5** ☐ — Anemia **11** ☐ Enlarged Liver/Liver Disease **6** ☐ — Fluid in Lungs **12** ☐
Extent of Disease at First Cancer Suspicion	17. Lymph Node Involvement: Yes **1** ☐ No **2** ☐ 18. Indication of Spread to Distant Organs: Yes **1** ☐ No **2** ☐
HIV Status at Time of First Presentation	19. **HIV Positive:** **Yes** 1 ☐ **No** 2 ☐ **IF HIV POSITIVE, PLACE STICKER ON FILE AND COMPLETE FORM C**
Anthropometry at First Presentation	20. Body Weight (kg): ☐☐ ☐☐ 21. Height (cm): ☐☐☐ ☐☐
Family History	22. Is there Family History of the Presenting Cancer? Yes **1** ☐ No **2** ☐ 23. Is there Family History of any other Cancer? Yes **1** ☐ No **2** ☐

Ever Smoked	24. Did the Patient Report Ever Smoking Prior to First Presentation? Yes 1 ☐ No 2 ☐
Ever Had a Child (for Females only)	25. Did the Patient Report Having Given Birth Prior to First Presentation? Yes 1 ☐ No 2 ☐ **If yes,** complete questions 26-27. 26. How Many Children: ☐☐ 27. Age at First Birth: ☐☐
Menarche and Menopausal History	28. Age at Menarche: ☐☐ 29. Menopausal Status: Pre-Menopausal 1 ☐ Post-Menopausal 2 ☐ 30. **If Post-Menopausal**, Age at Onset of Menopause: ☐☐
Contraceptive History	31. Ever Used Birth Control: Yes 1 ☐ No 2 ☐ **If yes,** complete questions 32-33. 32. Used for How Many Years: ☐☐ 33. Used What Type (check all that apply): Injections 1 ☐ Patches 2 ☐ Pills 3 ☐ IUD 4 ☐
Existence of Prior Medical Conditions	34. Diabetes: Yes 1 ☐ No 2 ☐ 35. Tuberculosis: Yes 1 ☐ No 2 ☐ 36. Lung Disease: Yes 1 ☐ No 2 ☐ 37. Liver Disease: Yes 1 ☐ No 2 ☐ 38. Cardiovascular Disease: Yes 1 ☐ No 2 ☐ 39. Meningitis: Yes 1 ☐ No 2 ☐
Lab Measures at First Presentation	40. Hemoglobin (**Hb**): ☐☐☐ ☐☐ 41. Platelet Count (**PLT**): ☐☐☐ ☐☐ 42. White Blood Cell Count (**WBC**): ☐☐☐ ☐☐

Abstraction Date: ☐☐ ☐☐☐ ☐☐ UPCID_803

Case ID: ☐☐ ☐☐ ☐☐☐☐ Form A: Medical Record Intake Form

	43. Liver Enzymes (**ALB**): ☐☐☐ ☐☐ 44. Liver Enzymes (**AST**): ☐☐☐ ☐☐ 45. Liver Enzymes (**ALT**): ☐☐☐ ☐☐ 46. Serum Creatinine (**CREA**): ☐☐☐ ☐☐ 47. LDH: ☐☐☐ ☐☐
Tumor Size and Location At First Presentation	48. Mass Size of Primary Tumor : ☐☐ **X** ☐☐ **CM** 49. Tumor Location: _____
Lymph Node Involvement At First Presentation	50. Lymph Node Involvement: Yes **1** ☐ No **2** ☐ **If Yes**, complete questions 51-52 below: 51. Is lymph node involvement local or distant? Local **1** ☐ Distant **2** ☐ 52. Size of Largest Node : ☐☐ **X** ☐☐ **CM**
Spread of Disease at First Presentation	**Has the tumor mass spread** to any of the following organs (check all that apply)? 53. Spread to Lungs: Yes **1** ☐ No **2** ☐ 54. Spread to Liver: Yes **1** ☐ No **2** ☐ 55. Spread to Spleen/Kidney Yes **1** ☐ No **2** ☐ 56. Spread to Skeletal System: Yes **1** ☐ No **2** ☐ 57. Spread to Bone Marrow: Yes **1** ☐ No **2** ☐
Tumor Stage	58. Tumor Stage Suspected at Diagnosis (listed in **Referral Letter**): _____ 59. Tumor Stage as Determined at **First Presentation**: _____
Treatment Recommended	60. Patient Recommended Treatment for Primary Cancer Diagnosis: Yes **1** ☐ No **2** ☐ **If Yes, COMPLETE FORM B**

Abstraction Date: ☐☐ ☐☐☐ ☐☐

Case ID: ☐☐ ☐☐ ☐☐☐☐

UPCID_803

Form B: Treatment Form

FORM B: TREATMENT FORM

Treatment Number

1. Is this the Case's First Recommended Treatment? Yes **1** ☐ No **2** ☐

If No, complete questions 2-3 below:

2. How Many Previous Courses of Treatment has this Case Completed? ☐

3. Why is the Case Being Recommended for More Treatment?

- Cancer Has Progressed or Remained Stable During Prior Treatment **1** ☐
- Patient was Lost to Follow up after Prior Treatment and has Returned with symptoms **2** ☐
- Patient was prescribed a Maintenance Dose **3** ☐

Surgery Information

4. Surgery Recommended : Yes **1** ☐ No **2** ☐

5. Surgery Received: : Yes **1** ☐ No **2** ☐

If Yes, complete questions 6-7 below:

6. What was the purpose of the Surgery? _____

7. Date of Surgery: ☐☐ ☐☐☐ ☐☐
   D D M M M Y Y

Radiation Information

8. Radiation Recommended : Yes **1** ☐ No **2** ☐

9. Radiation Received: : Yes **1** ☐ No **2** ☐

If Yes, complete questions 10-14 below:

10. Number of Grays of Radiation Recommended: ☐☐☐

11. Number of Grays of Radiation Given: ☐☐☐

12. Date Radiation Treatment Recommended to Begin: ☐☐ ☐☐☐ ☐☐
    D D M M M Y Y

13. Date Radiation Treatment Actually Began: ☐☐ ☐☐☐ ☐☐
    D D M M M Y Y

14. Date Radiation Treatment Ended: ☐☐ ☐☐☐ ☐☐
    D D M M M Y Y

********** For Data Management Purposes Only **********

First Entry: _____ __ __/__ __ __/__ __ Second Entry: _____ __ __/__ __ __/__ __

Initials dd mmm yy Initials dd mmm yy

Abstraction Date: ☐☐ ☐☐☐ ☐☐

Case ID: ☐☐ ☐☐ ☐☐☐☐

UPCID_803

Form B: Treatment Form

Chemotherapy Information	15. Chemotherapy Recommended : Yes **1** ☐ No **2** ☐ 16. Chemotherapy Received: : Yes **1** ☐ No **2** ☐ **If Yes**, complete questions 17-22 below: 17. Type of Chemotherapy Given (Write the number corresponding to each drug in the combination in a separate box.) ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ 18. Number of Cycles of Chemotherapy Recommended: ☐ 19. Number of Cycles of Chemotherapy Given: ☐ 20. Date Chemotherapy Recommended to Begin: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y) 21. Date Chemotherapy Actually Began: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y) 22. Date Chemotherapy Ended: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y)
Total Palliation	23. Only Palliative Care Recommended : Yes **1** ☐ No **2** ☐
Missed Treatment	24. Did the Case Receive the Full First Course of Recommended Treatment: Yes **1** ☐ No **2** ☐ 25. **If No,** Reason for Failure to Complete Treatment: Case Did Not Return for Treatment and was Lost to Follow Up **1** ☐ Case Died Prior to Treatment Completion **2** ☐ Case Could Not Afford Treatment **3** ☐ Reason Not Listed in the Clinical Notes **4** ☐

IF CASE COMPLETED A COURSE OF RECOMMENDED TREATMENT, FILL OUT RESTAGING FORM (FORM D)

Completed By (Initials): _____

Abstraction Date: ☐☐ ☐☐☐ ☐☐

Case ID: ☐☐ ☐☐ ☐☐☐☐

UPCID_803

Form D: Restaging Form

FORM D: RESTAGING FORM

Reason for Restaging

1. Did the Case Complete Restaging? Yes **1** ☐ No **2** ☐
2. Is this the Case's First Restaging? Yes **1** ☐ No **2** ☐
3. **If No**, how many times previously has this Case Completed Restaging? ☐
4. Why is the Case Being Restaged?
   - Case is Being Assessed After Completing a Course of Treatment **1** ☐
   - The Case has been Transferred to a New Clinic for Care **2** ☐
   - Patient was Lost to Follow up and has Returned with Symptoms **3** ☐
   - Case is Being Assessed During Routine Surveillance **4** ☐
5. Date Restaging of Case Began : ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y)

Major Symptoms

6. Major Symptoms Present (check all that apply) at Restaging:

Detection of Mass/Swelling	**1** ☐	Bleeding	**7** ☐
Difficulty Swallowing	**2** ☐	Extreme Fatigueability	**8** ☐
Bone Pain	**3** ☐	Ascites	**9** ☐
Edema	**4** ☐	Wasting	**10** ☐
Fever	**5** ☐	Anemia	**11** ☐
Enlarged Liver/Liver Disease	**6** ☐	Fluid in Lungs	**12** ☐

Not Applicable/Patient Reported No Complaints: _____

Lab Measures At Restaging

7. Hemoglobin (**Hb**): ☐☐☐ ☐☐
8. Platelet Count (**PLT**): ☐☐☐ ☐☐
9. White Blood Cell Count (**WBC**): ☐☐☐ ☐☐
10. Liver Enzymes (**ALB**): ☐☐☐ ☐☐

********** For Data Management Purposes Only **********

First Entry: _____ __ __/__ __ __/__ __ (Initials dd mmm yy)

Second Entry: _____ __ __/__ __ __/__ __ (Initials dd mmm yy)

Completed By (Initials): _____

Abstraction Date: ☐☐ ☐☐☐ ☐☐

Case ID: ☐☐ ☐☐ ☐☐☐☐

UPCID_803

Form D: Restaging Form

	11. Liver Enzymes (**AST**): ☐☐☐ ☐☐ 12. Liver Enzymes (**ALT**): ☐☐☐ ☐☐ 13. Serum Creatinine (**CREA**): ☐☐☐ ☐☐ 14. LDH: ☐☐☐ ☐☐
Tumor Size and Location	15. Mass Size: ☐☐ **X** ☐☐ **CM** 16. Tumor Location: _____ Not Applicable/No Mass Exists: _____
Lymph Node Involvement	17. Lymph Node Involvement: Yes **1** ☐ No **2** ☐ **If Yes**, complete questions 18-19 below: 18. Is lymph node involvement local, regional, or distant? Local **1** ☐ Distant **2** ☐ 19. Size of Largest Node : ☐☐ **X** ☐☐ **CM**
Spread of Disease	**Has the tumor mass spread** to any of the following organs (check all that apply)? 20. Spread to Lungs: Yes **1** ☐ No **2** ☐ 21. Spread to Liver: Yes **1** ☐ No **2** ☐ 22. Spread to Spleen/Kidney Yes **1** ☐ No **2** ☐ 23. Spread to Skeletal System: Yes **1** ☐ No **2** ☐ 24. Spread to Bone Marrow: Yes **1** ☐ No **2** ☐
Tumor Stage	25. Was a new tumor stage assigned? : Yes **1** ☐ No **2** ☐ 26. Tumor Stage Assigned after Restaging: _____

Completed By (Initials): _____

Tumor Response to Treatment	27. **How was Tumor Response Classified?** Complete Response **1** ☐ No Response/Stable **3** ☐ Partial Response **2** ☐ Progressive Disease **4** ☐
IF CASE RECOMMENDED TREATMENT AFTER RESTAGING, FILL OUT TREATMENT FORM (FORM B)	

FORM E: VITAL STATUS FORM

Date Information	1. Date of First Presentation: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y) 2. Date One Year Following First Presentation: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y)
Source of Information	3. **Source** of Vital Status Information: Uganda Cancer Institute/Mulago **1** ☐ HIV Clinic **2** ☐ National Hospice **3** ☐
Vital Status Information	4. Vital Status at One Year Following First Presentation: Alive **1** ☐ Dead **2** ☐ Unknown **3** ☐ **5. If Alive**, Date of Last Medical Record: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y) **6. If Dead**, Date of Death: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y) **7. If Unknown**, Date of Last known Follow-up: ☐☐ ☐☐☐ ☐☐ (D D M M M Y Y)
Cause of Death Information	**If Dead** , complete questions 8-10 below: 8. Cause of Death Listed: Yes **1** ☐ No **2** ☐ 9. **If Yes,** Listed Probable Cause of Death: _____ 10. **Setting** in which Patient Died: Home **1** ☐ Hospital or Clinic **3** ☐ Hospice Care **2** ☐ Unknown **4** ☐

********** For Data Management Purposes Only **********

First Entry: _____ __ __/__ __ __/__ __ (Initials dd mmm yy)

Second Entry: _____ __ __/__ __ __/__ __ (Initials dd mmm yy)

Completed By (Initials): _____