Published in final edited form as:

J Acquir Immune Defic Syndr. 2011 April ; 56(4): 312–319. doi:10.1097/QAI.0b013e31820c011a.

Predictors of Survival After a Diagnosis of Non-Hodgkin's Lymphoma in a Resource-Limited Setting: A Retrospective Study on the Impact of HIV Infection and Its Treatment

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Abstract

Objective—We examined factors associated with survival among patients with newly diagnosed non-Hodgkin's lymphoma (NHL) in Uganda.

Methods—Information was abstracted from medical records for all NHL patients >13 years of age at the Uganda Cancer Institute between January 2004 and August 2008. Cox proportional hazard models were used to identify predictors of NHL survival.

Results—160 patients with NHL were identified; 51 (31.9%) were known to be human immunodeficiency virus (HIV) positive. Overall, 154 patients had records sufficient for further analysis. The median person-time observed was 104 days (interquartile range (IQR) 26–222). Median survival after presentation among those whose mortality status was confirmed was 61 days (IQR 25–203). HIV-positive patients receiving antiretroviral therapy (ART) had survival rates approximating those of HIV-negative persons, but the adjusted hazard of death was significantly elevated among HIV-positive patients not receiving ART (aHR 8.99, $p < 0.001$) compared to HIV-negative patients. Both B-symptoms (HR 2.08, $p = 0.05$) and female gender (HR 1.72, $p = 0.05$) were associated with higher mortality.

Conclusions—In Uganda, overall survival of NHL patients is poor, and predictors of survival differed from those described in resource-rich regions. HIV is a common co-morbidity to NHL, and its lack of treatment was among the strongest predictors of mortality. Strategies are needed for optimal management of HIV-infected individuals with cancer in resource-limited settings.

Keywords

HIV; non-Hodgkin's lymphoma; antiretroviral therapy; Uganda

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Previous Presentations: These data were presented in part at the 5th International AIDS Society Conference on HIV Pathogenesis Treatment and Prevention, Cape Town, S. Africa (July 19–22, 2009) and at the 7th International Conference for the African Organisation for Research and Training in Cancer (AORTIC) Dar Es Salaam, Tanzania (November 11–14, 2009).

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INTRODUCTION

Infection with human immunodeficiency virus (HIV) has been associated with an increased incidence of non-Hodgkin's lymphoma (NHL) in both resource-rich countries^{1–3} and Africa.^{4,5} While the incidence of other HIV-related malignancies has declined markedly as access to antiretroviral therapy (ART) has expanded throughout Europe and North America, the incidence of NHL, still remains elevated.^{2,6} In Uganda the incidence of NHL and other HIV-related malignancies has risen dramatically since the onset of the HIV epidemic,⁷ but treatment outcomes for African NHL patients specifically those infected with HIV have not been conclusively determined.^{8–11}

A number of factors have been shown to impact survival among patients with NHL. In resource-rich settings, these have included the tumor stage, bulk and histopathologic type, age, serum lactate dehydrogenase (LDH) level, performance status, and the number of nodal and extra nodal sites involved.^{12–14} Receipt of both chemotherapy and supportive therapy (e.g., Granulocyte colony-stimulating factor, G-CSF) has also influenced treatment outcomes.^{15–17} In resource-poor settings, factors predictive of worse survival include older age, higher tumor stage, high LDH levels, and low hemoglobin concentration.^{12,18}

Additionally, HIV infection has been found to impact both the incidence and survival rates of patients with NHL.^{19–23} The survival rate of NHL patients infected with HIV in resource-rich countries has recently improved, perhaps attributable to improvements in both chemotherapeutic and antiretroviral regimens.^{24–27} However, scant data are available on the impact of HIV infection on survival after a diagnosis of NHL in resource-limited settings. We sought to describe the predictors of survival among HIV-infected and uninfected patients with NHL in Uganda.

METHODS

Study Setting and Participants

All patients older than 13 years of age with a diagnosis of NHL who were initially seen at the Uganda Cancer Institute (UCI) between January 2004 and August 2008 were eligible for inclusion in this study. Patients with Burkitt's lymphoma (BL) were excluded because most were <13 years and were therefore not eligible for enrollment on the basis of age, and also because the treatment response historically differs from that of other NHLs.^{28–30} Central nervous system lymphomas were excluded due to difficulties in ascertaining this diagnosis in the study setting.

The UCI is Uganda's national cancer referral center, where almost all patients diagnosed with NHL in Uganda receive care.³¹ Patients are referred to UCI from all over the country for further evaluation and treatment. There are no specific criteria for referral. During the study period, the protocol for initial evaluation of all patients with a recent diagnosis of histologically confirmed NHL included a detailed history, physical examination, complete blood count, blood chemistry, HIV antibody testing (since 2004),³² chest radiographs, abdominal ultrasound, bone marrow biopsy, and lumbar puncture. Computed tomography (CT) and magnetic resonance imaging (MRI) are not routinely available.

A variety of NHL classification systems are used by pathologists in Uganda, including the Working Formulation,³³ Rappaport, and REAL/WHO systems.³⁴ All cases were therefore assigned one of three categories, low, intermediate or high-grade lymphomas, a feature common to all three classification schemes and staged using the Ann Arbor system. Data on tumor subtypes, anatomical site, and CD-20 antigen status were not consistently available.

Patients infected with HIV were assigned an HIV clinical stage, based on the World Health Organization (WHO) criteria³⁵ and other current or past HIV-associated conditions (excluding NHL). Participants underwent CD4 testing but plasma HIV viral load testing was unavailable. HIV-infected patients were referred to the nearby Infectious Disease Institute and The AIDS Support Organization clinics for ART. Opportunistic infections, when present, were managed following the Ugandan national treatment guidelines and tuberculosis (TB) was managed at the nearby TB clinic. Patients without laboratory contraindications (hemoglobin >7gm/dL, platelet count >30,000 cells/μl; gamma-glutamyl transpeptidase (GGT) <5 times the upper limit of normal (ULN), aspartate aminotransferase (AST), or alanine aminotransaminase (ALT) < 2.5 times ULN, respectively) were started on a treatment regimen based on the body surface area for each patient. The standard regimen comprised cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and vincristine (1.4 mg/m²) given intravenously on day 1; and prednisone (60 mg/m²) given orally on days 1 through 5 (CHOP). The dose in subsequent courses was reduced if the patient lost significant weight or if HIV positive had a CD4 count below 200 (cells/microliter). In these instances cyclophosphamide, doxorubicin, and prednisone were given at 75%, 50%, and 60% of the standard dose, respectively.

CHOP was given approximately every 21 (±3) days for a minimum of 6 courses. Between cycles, patients were discharged if clinically stable. Clinical care, including cancer chemotherapy, was free at the UCI but patients or family members frequently had to purchase medicine if supplies were no longer available at the UCI pharmacy. Upon completion of the 6 courses of chemotherapy, patients were initially seen monthly for 3 months and then every 6 months thereafter for the next 3 years. G-CSF is not routinely used at UCI but may be prescribed for rare patients who become severely neutropenic and who can afford to purchase the drug. Rituximab is also not readily available in Uganda despite its proven benefits NHL patients.^{15–17,36} At UCI, it is rarely prescribed even for CD 20-positive lymphoma patients who could afford it.

Patients needing palliative care services were referred. Patients who died at home were reported to the UCI attending physician by family members in order to get a death certificate.

Ethical approval was obtained from the Makerere University Faculty of Medicine Research Ethics Committee and the University of Washington Human Subjects Division.

Variables and Data Sources

All data were obtained from review of the UCI patient records. We abstracted data from patient encounters noted between time of NHL diagnosis and death, or the date the patient was last seen in the clinic. We obtained baseline data including available demographic and clinical characteristics. The variables were chosen on the basis of known and potential influence on cancer survival. Treatment and outcome data included dates and doses of chemotherapy, date last seen in the clinic, or date of death. For patients infected with HIV CD4 count, WHO clinical stage, and ART use were abstracted.

Statistical Analysis

We hypothesized that HIV infection as well as receipt of ART among persons infected with HIV would affect the survival of patients with NHL.

We described demographic and clinical characteristics of the study subjects overall, by HIV status, and by ART status, if HIV infected. We used the Wilcoxon rank sum (or Mann-Whitney) and the Kruskal-Wallis equality of populations rank test for differences in median baseline demographic and laboratory values between two and three groups, respectively.

The primary outcome was death from any cause.³⁷ Survival curves were generated using the Kaplan-Meier method. Specifically, we compared the survival of patients in four subgroups defined by HIV serostatus and ART: HIV-negative, HIV serostatus unknown, HIV-positive and receiving ART during some or all of the observation period, and HIV-positive without ART. Other variables considered in the model included sex, age, tumor stage, hemoglobin, body mass index (BMI), presence of B-symptoms, LDH, and in the HIV-positive subgroup, CD4. Because of missing data for different variables, the numbers of subjects available for univariate and multivariate analysis (Tables 1 and 2) differed. The multivariate analysis of predictors of survival was performed using a Cox proportional hazard regression model and backward elimination that included factors that reached a statistical significance level of $P \leq 0.2$ in the univariate analysis or those that were considered clinically important (chemotherapy use). We hypothesized that chemotherapy would have a positive association with survival as other studies have shown²² but the number of doses each patient received would depend upon how long they remained alive (i.e., those who survived longer would receive more chemotherapy). Thus modeling the association between the total number of doses and survival would yield a biased estimate. To minimize this problem, we modeled the cumulative number of chemotherapy doses within the past 105 days as a time-varying covariate. One hundred five days was chosen based on previous work at UCI³⁸ and as the minimum approximate time needed to complete at least six 2–3 week cycles of chemotherapy, and treatment-free periods between them. This variable was kept in the multivariate model regardless of the significance level. All analyses were performed using Stata, versions 10.1 and 11.1 (StataCorp).

RESULTS

We identified 160 eligible patients in the UCI's admission register of whom 154 had sufficient information for further analysis. Demographic and baseline clinical characteristics of NHL patients shown in Table 1. The median age at diagnosis was 37 years (IQR = 24, 50); 54 (33.8%) were female. Of the 97 patients who had their lymphoma staged, only 9 (9.3%) had early disease stage (stages I & II). Fifty-one (31.9%) patients were HIV positive, 94 (58.8%) were HIV negative, and 15 (9.4%) did not have the HIV status noted. The prevalence of HIV was 35.2%. Among 145 patients for whom more complete histological grading and outcome data was available, the majority were high grade (67%), 13 (9%) were intermediate, 15 (10%) were low grade. Twenty (14%) were not classified.

Effect of HIV Serostatus on Patient Characteristics

Patients with unknown HIV status were younger (median age 29 years, vs. 36 and 37 for HIV negative ($P = 0.14$) and HIV positive ($P = 0.05$), respectively). They also had lower median hemoglobin (8.1g/dL) compared to those who were either HIV positive (11g/dL, $P = 0.013$) or HIV negative (10.5g/dL, $P = 0.066$). In the subset of patients infected with HIV, the median CD4 count was 142 cells/microliter (IQR = 90, 264; range = 11, 526). Forty (78.4%) patients of those with HIV had pre-existing HIV WHO-staging illnesses before NHL diagnosis. Nine (5.6%) of all patients had active TB at the time of NHL diagnosis. TB occurred mostly among those who were HIV positive ($P = 0.001$). Among those with data on histologic subtype category and HIV status (125), the odds of being HIV-infected was not significantly different between those with high vs. low and intermediate classifications (OR 0.62, 95% CI 0.25–1.55).

Chemotherapy

One hundred eighteen (73.8%) patients received chemotherapy. Among those with more complete data on treatment, those who received chemotherapy got a median of 5 courses (IQR 2–6), with 27.4% receiving only 1 or 2 courses; and 44.4% ($n = 52$) receiving at least 6

courses of chemotherapy. There were no significant differences between those who received and those who did not receive chemotherapy in terms of sex ($P = 0.41$), presence of B-symptoms ($P = 0.35$), or HIV status ($P = 0.19$).

Of all courses of chemotherapy, 47% (219/465) were received outside the “ideal treatment window” that we defined to extend from 3 days before to 3 days after the planned date of a subsequent infusion. For doses that were given outside the 6-day window, the median number of days between the scheduled time and the actual time that the dose was received was 30 (IQR 26–50). The majority of doses given outside the window (83%) were given later rather than earlier than the appointment date (median; 34 days (IQR 27–56) and 9.5 days (IQR 3–14) respectively.

Antiretroviral Therapy Use

Thirty-four of 45 HIV-positive subjects (75.6%) received ART. Of those, 13 (38.2%) started ART before chemotherapy, 5 (14.7 %) started chemotherapy and ART at approximately the same time, while for 16 (47.1%) the timing of ART initiation in relation to chemotherapy was unclear. There were no significant differences between ART recipients and non-recipients in terms of sex, age, hemoglobin, BMI, presence of B-symptoms, or serum LDH.

Follow-Up Times and Survival

Of the 154 subjects with adequate follow-up data, 35 (22.7%), 46 (30%), and 58 (37.7) were known to have died in the first 3, 6, and 12 months of follow-up, respectively. Only 20 were known to be alive ≥ 1 year after diagnosis. The remaining patients were censored at the time of the last recorded follow-up visit. The median person-time observed was 104 days (IQR 26–222). The median survival time for those known to have died before 1 year was 2 months or 61 days (IQR 25–203). Figure 1 shows Kaplan-Meier estimation of survival stratified by HIV status.

Predictors of Survival among Patients with Non-Hodgkin's Lymphoma

No clear relationship was seen between lymphoma classification and survival after stratification by HIV status. The one-year cumulative incidence of death among patients with low-grade NHL was 66.7% for HIV-positive patients and 75% for HIV-negative patients. For those with intermediate-grade tumors, 100% of HIV-positive patients were dead by one year and 25% of HIV-negative patients had died by the same time. In patients with high-grade lymphomas, 57% of HIV-positive and 51.4% of HIV-negative patients had died by one year. Because of the lack of obvious association between classification and mortality, as well as the large number of patients who were missing data on HIV infection status, lymphoma classification and mortality, classification was not included in further analyses of the predictors of mortality.

In univariate analysis, patients who were HIV positive and not receiving ART had the highest probability of death compared to those who were HIV negative (HR 5.37, $P = 0.001$) (Table 2). Additionally, higher hemoglobin at the time of admission was associated with better survival, with the risk of death decreasing with each additional gram of hemoglobin (HR 0.89 per 1 g/dL increase, 95% CI 0.82–0.97, $P = 0.005$). However, the survival rates did not differ significantly in association with tumor stage, BMI, serum LDH, cumulative doses of chemotherapy, or presence of B-symptoms. For patients infected with HIV, the survival rate was not significantly associated with CD4 count nor with pre-existing WHO HIV staging conditions prior to NHL diagnosis.

After adjusting for chemotherapy use, gender, and hemoglobin concentration, patients who were HIV positive and not receiving ART, as well as those having B-symptoms were

observed to have low survival rates (Table 2). Patients who were HIV positive and not receiving ART had the lowest survival rates compared to those who were HIV negative (adjusted HR 8.99, 95% CI 3.62–22.34, $P < 0.001$). Similarly, patients who had B-symptoms at the time of admission had lower survival rates compared to those who did not (adjusted HR 2.08, 95% CI 1.00–4.31, $P = 0.050$). In addition, higher hemoglobin at admission was significantly associated with better survival (adjusted HR 0.88 per 1 g/dL increase, 95% CI 0.80–0.97, $P = 0.008$).

The non-significant association between cumulative number of chemotherapy doses and mortality seen on univariate analysis did not change substantially when other variables were included in the model (unadjusted HR 0.94, $P = 0.49$ vs. adjusted HR 0.96, $P = 0.72$). Similarly, the inverse association between female sex and survival became stronger in multivariate analysis (HR 1.72, 95% CI 1.00–2.94, $P = 0.05$) but did not reach statistical significance.

DISCUSSION

In our review of outcomes of adult and adolescent NHL cases in Uganda, we found that NHL is a morbid condition with discrete predictors of survival in this resource-limited setting. Specifically, HIV infection in the absence of ART, female gender, anemia, and constitutional (“B”) symptoms at presentation were all independent predictors of mortality.

In general, we observed a low one-year survival among patients in our population with NHL. We found that several of the previously described prognostic factors for NHL in resource-rich settings were not predictive of survival in our cohort.^{39–41} Factors such as tumor histopathology, international prognostic index, presence of extra nodal disease, immunohistochemistry, or cytokine analyses were not routinely or reliably assessed in our cohort or other resource-limited settings,⁹ and this could explain why they were not found to be predictive of survival. Additionally, the amount of missing data in our cohort may have precluded finding significant associations between these factors and survival. Finally, the diagnostic and supportive care, as well as treatment regimens, available to patients in Uganda differs substantially from what is available in the United States. The unavailability of rituximab, G-CSF, and extended spectrum antimicrobials may result in different factors being more important to patient survival in Uganda. Alternatively, it is possible that the pathogenesis of NHL in Uganda differs to some extent from the disease in the United States, a hypothesis which is currently being investigated in translational studies of NHL tumors in Uganda. Differences in prognostic factor measurements are unlikely to completely explain the observed differences, as risk factors which are simple to measure, such as LDH and age, were not predictive in this cohort.

Future prospective studies are needed to assess the factors predictive of NHL survival in resource-limited settings more definitively, and examine others such as late presentation, nutritional status, access to supportive care, and socioeconomic status.

Our cohort had limited access to chemotherapy, ART, and other supportive therapies and had poor survival. The median survival was only 2 months (61 days) (IQR 25–203) in those determined to have died. This is significantly lower than for HIV-infected cohorts in the pre-ART era in resource-rich settings era^{39,41} and even lower compared to more recent cohorts in Europe.²⁵

We also found that the receipt of chemotherapy, which has been shown to be associated with a survival advantage in both HIV-positive and HIV-negative patients in resource-rich settings, was not significantly associated with survival among patients in Uganda. However, these data should be interpreted with caution in this retrospective study. In such a design,

patients needed to survive and remain in care for more than 4 months in order to receive all courses of chemotherapy. Patients with advanced NHL, or NHL and HIV, may have been too ill at presentation to receive, or tolerate, chemotherapy. To this point, we found that more than a quarter of patients did not receive chemotherapy. And even among those who received some, less than three quarters (72.6%) received more than 2 courses.

We acknowledge that our chosen method of treating chemotherapy as a time-varying covariate may have minimized but did not fully eliminate the bias of assuming constant hazards and using the Cox regression. Patients who received more courses of chemotherapy may have been healthier at the time of initiating chemotherapy than patients who received less, who were likely to die prior to scheduled treatment. Additional studies are needed to determine the optimal treatment strategy for patients presenting with advanced NHL in resource-limited settings.

HIV was a common co-morbidity to NHL in this cohort, with a prevalence of 31.9% among study subjects with known HIV serostatus. This prevalence is much higher than the national prevalence of HIV in Uganda (7%)^{42,43} reflecting observations elsewhere³⁷ and in Uganda and other places.⁸ Given the high prevalence of HIV among patients with NHL in Uganda, our study made important observations about the role of HIV and its treatment in the prognosis of NHL. We found that HIV infection alone may not be associated with a poorer outcome in Ugandans with NHL. More to the point, we found that patients with HIV infection who were receiving ART had survival rates which approximated those of HIV-negative persons. These results have important ramifications for the management of HIV-associated malignancies in resource-limited settings, showing that the appropriate co-management of HIV and cancer can result in improved outcomes. These results, however, require additional evaluation, as a number of factors could have potentially confounded the observed beneficial effects of HIV therapy. For example, it is possible that persons who received ART were in better health at baseline, were better able to start and tolerate chemotherapy, or differed from HIV-infected patients who failed to receive ART based on their socioeconomic status. Also, as noted earlier, we cannot assume that the association between ART and survival was the same for patients who remained in care and patients who were lost to follow-up.

This study has other limitations, in addition to missing baseline data and loss to follow-up. Construction of cause-specific mortality estimates was not possible based on available data, and we cannot assume that all deaths among cancer patients were entirely due to cancer. That assumption would be particularly faulty in patients infected with HIV, because they are also at risk of death from opportunistic infection or ART side effects. Diagnostic challenges precluded identification of some opportunistic infections in HIV-infected patients and in many study subjects, the characterization of NHL into types and subtypes. Similarly, missing data precluded description of reasons for causes of treatment delays, information which is probably of prognostic significance. Also, information on adherence to ART, ART interruption during chemotherapy administration, and the incidence or severity of chemotherapy- or ART-related side effects was not consistently collected or graded.

Despite these limitations, our data, although retrospectively collected from a single institution, describe a cohort of patients from an area that has one of the best cancer registries in sub-Saharan Africa, and represents the first attempt to study HIV and survival rates of patients with NHL in this setting.

The study findings have several implications both for research and for practice. Future studies should prospectively describe factors associated with late presentation for AIDS and NHL treatment, failure to initiate chemotherapy or to complete chemotherapy once initiated,

and loss to follow-up. Such studies would additionally determine optimal treatment strategies for AIDS-NHL in the era of increasing but still limited access to ART, and identify prognostic factors that are unique to these resource-limited settings.

Clinical practice should be improved through the design and implementation of comprehensive cancer plans, including plans for the management of concurrent cancer and HIV/AIDS. Such plans would allow for the more effective use of extremely limited funds for cancer control and treatment. Better strategies to improve the awareness, early diagnosis, referral and treatment of cancer in resource-limited settings will make meaningful impacts on the health of the overall population.

Acknowledgments

We wish to acknowledge the staff of Ugandan Cancer Institute for allowing us to access patient records as well as the Washington Global Health Alliance for funding the study.

Sources of Financial Support: This study was supported by a Global Partnerships Travel Grant from the Washington Global Health Alliance and NIH grants K24 AI-071113, P30 AI 027757-22 and D43-TW000007 and K24 AI 071113.

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Figure 1.
Kaplan-Meier estimation of survival stratified by HIV status.

TABLE 1

Demographic and Clinical Characteristics of NHL Patients upon Presentation to the Uganda Cancer Institute (January 2004–August 2008)

Characteristic	HIV Positive	HIV Negative	Status Unknown
Number, n (%) N = 160	51 (31.9)	94 (58.8)	15(9.4)
Gender, n (%)			
Female	15 (29.4)	36 (38.3)	3 (20.0)
Male	36 (70.6)	58 (61.7)	12 (80.0)
Age (years), Median (IQR), N = 160	37 (35, 45)	36 (18,55)	29 (14, 47)
Age Groups, n (%) N = 160			
≤35	11 (21.6)	46 (48.9)	8 (53.3)
35–44	30 (58.8)	12 (12.8)	3 (20.0)
≥45	10 (19.6)	36 (38.3)	4 (26.7)
Tumor Stage n (%), N = 97			
I & II	3 (8.8)	5 (9.3)	1 (11.1)
III & IV	31 (91.2)	49 (90.7)	8 (88.9)
Hemoglobin g/dl Median (IQR), N= 152	11 (9.2, 12.6)	10.5 (7.5, 12.6)	8.1 (6.2, 9.2)
BMI Median (IQR), ^a N=107	19.8 (17.7, 22.4)	19.9 (16.7, 22.9)	17.8 (14.7, 18.5)
BMI, ^a n (%) N=107			
<18.5	10 (28.6)	27 (40.9)	5 (83.3)
>18.5	25 (71.4)	39 (59.1)	1 (16.7)
B-Symptoms, n (%) N=160			
Yes	42 (82.4)	67 (71.3)	12 (80.0)
No	9 (17.6)	27 (28.7)	3 (20.0)
Outcome occurred, n (%) N = 160			
Death	22 (43.1)	34 (36.2)	7 (46.7)
Censored	29 (56.9)	60 (63.8)	8 (53.3)

NHL, non-Hodgkin's lymphoma; HIV, human immunodeficiency virus; IQR, interquartile range; BMI, body mass index.

^a Only for those ≥18 years.

* Statistically significant.

TABLE 2
Univariate and Multivariate Associations with Early (One Year) Mortality by Cox Proportional Hazards Model

	Univariate Models ^a			Adjusted Models ^b		
	HR	(95% CI)	P	HR	(95% CI)	P
Cumulative doses of chemotherapy w/in 105 days, n = 160	0.94	(0.77, 1.13)	0.49	0.96	(0.79, 1.18)	0.72
Age (year)	0.99	(0.98, 1.00)	0.18			
Gender, n = 160:						
Female						
Male	0.67	(0.41, 1.12)	0.12	0.58	(0.34, 1.01)	0.053
BMI (among those 18 years or older), n = 107						
<18.5						
>18.5	0.70	(0.36, 1.36)	0.29			
Tumor Stage, n = 160:						
I						
II	1.32	(0.18, 9.45)	0.78			
III	1.25	(0.28, 5.55)	0.77			
IV	1.55	(0.36, 6.64)	0.55			
Unknown	2.17	(0.50, 9.41)	0.30			
Tumor Stage, n = 160:						
I & II						
III & IV	1.25	(0.44, 3.52)	0.67			
Unknown	1.91	(0.65, 5.62)	0.24			
Preexisting HIV WHO staging illness* (among HIV+ participants), n = 40:						
I & II						
III & IV	0.29	(0.10, 0.88)	0.029			
Unknown	0.77	(0.23, 2.55)	0.67			
HIV Category, n = 154						
Negative						
Positive, no ARV treatment	5.37	(2.30, 12.53)	<0.001	8.99	(3.62, 22.34)	<0.001
Positive, any ARV	1.04	(0.56, 1.96)	0.89	1.14	(0.57, 2.30)	0.71
Unknown	2.25	(0.98, 5.13)	0.055	2.04	(0.82, 5.04)	0.12

	Univariate Models ^a			Adjusted Models ^b		
	HR	(95% CI)	P	HR	(95% CI)	P
Hemoglobin (g/dl) n = 152	0.89	(0.82, 0.97)	0.005	0.88	(0.80, 0.97)	0.008
LDH, n = 100						
<300		Reference				
≥300	0.95	(0.47, 1.91)	0.88			
CD4 Count (cells/uL) (among HIV+ participants), n = 37						
≤200		Reference				
>200	0.62	(0.21, 1.87)	0.40			
B-Symptoms, n = 160	1.99	(0.98, 4.05)	0.056	2.08	(1.00, 4.31)	0.050

BMI, body mass index categorized according to WHO^{44,45}; WHO, World Health Organization; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; ARV, Antiretroviral.

* had or had had another WHO stage-defining illness NHL diagnosis

^a = Number of observations in each the bivariate model are indicated by the different numbers, n

^b (146) = No. of observations used in the multivariate model.