Impact of HIV Infection on the Clinical Presentation and Survival of Non-Hodgkin Lymphoma: A Prospective Observational Study From Botswana

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Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

Date: 1 February 2018

Student Name: Michael Milligan

Scholarly Report Title: Impact of HIV infection on the clinical presentation and survival of non-Hodgkin lymphoma: a prospective observational study from Botswana

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Bruce A. Chabner, MD, Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana
Abstract

**Purpose:** Botswana has a high prevalence of human immunodeficiency virus (HIV) infection. Currently, there is little data regarding the sociodemographic factors, clinical characteristics, and outcomes of non-Hodgkin lymphoma (NHL)—an acquired immune deficiency syndrome (AIDS)-defining cancer—in the country.

**Patients and Methods:** This study utilized a prospective cancer registry to identify patients with a new diagnosis of NHL, reporting for specialty cancer care at 3 hospitals in Botswana between October, 2010 and August, 2016. Treatment patterns and clinical outcomes were analyzed.

**Results:** One hundred four patients with a new diagnosis of NHL were enrolled into this study, 72% of whom had HIV infection. Compared to HIV-uninfected patients, HIV-infected patients were younger (median age: 53.9 vs. 39.1 years, p = 0.001) and more likely to present with an aggressive subtype of NHL (65.5% vs. 84.0%, p = 0.008). All HIV-infected patients received combined antiretroviral therapy (ART) throughout the course of the study, and similar chemotherapeutic regimens were recommended for all patients, regardless of subtype or HIV-status (6 to 8 cycles of CHOP or R-CHOP). There was no difference in 1-year mortality among HIV-uninfected and HIV-infected patients (unadjusted analysis: 52.9% vs. 37.1%, HR: 0.73, p = 0.33; adjusted analysis: HR: 0.57, p = 0.14). However, when compared to a cohort of patients in the United States matched by subtype, stage, age, sex, and race, patients in Botswana fared worse (1-year mortality: 22.8% vs. 46.3%, HR: 1.89, p = 0.001).

**Conclusion:** Among patients with NHL reporting for specialty cancer care in Botswana, there is no association between HIV status and 1-year survival.
Submitted and accepted manuscript:

Student Contribution:

**General:** I spent roughly 2 months living in Gaborone, Botswana and working as a research assistant in the Botswana Harvard Partnership (BHP). As a part of my duties, I was able to meet with many patients undergoing cancer care at the nation’s main public hospital, Princess Marina Hospital. I also assisted in several patient outreach trips, in which BHP team members traveled to patient homes to gather important patient follow-up information. Other responsibilities included data entry, database programing, and the development of procedures to streamline future information gathering efforts.

**Design:** I aided my advisor, Dr. Dryden-Peterson in the design of my specific research project. Dr. Dryden-Peterson had previously instituted a prospective database of cancer patients receiving treatment in 3 hospitals in Botswana, and had collected roughly 4 years of follow-up data by the time of my project. I developed an analysis to compare the demographics, treatment patterns, adverse effects, clinical outcomes, and mortality of patients diagnosed with Non-Hodgkin’s Lymphoma based on their coinfection status with the Human Immunodeficiency Virus (HIV).

**Execution:** I primarily executed all portions of this study with input from my coauthors and other research assistants at the Botswana Harvard Partnership.

**Analysis:** With the help of Dr. Dryden-Peterson, I wrote codes in SAS to assemble patient data from the cancer database, analyze the information, and print out results. I was able to compare demographic factors, treatment patterns, and adverse events among HIV-infected and HIV-uninfected patients using X-squared analysis, and compared survival between the two cohorts utilizing a cox proportional hazards model. Furthermore, I again utilized SAS to compare the mortality of patients in Botswana to American patients included in the SEER database.

**Writing:** I wrote the entirety of the first draft of the manuscript, and made edits as recommended by my coauthors and reviewers.
Introduction:

A “second epidemic” of cancer has emerged in the setting of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS)\(^1,2\). Worldwide, patients with HIV are more likely to develop cancer than those without HIV\(^3\), and face higher rates of mortality\(^4\). HIV infection predisposes to many cancers, including the AIDS-defining cancers (ADCs)—Kaposi sarcoma, cervical cancer, and non-Hodgkin lymphoma (NHL)\(^5\).

Non-Hodgkin lymphoma, specifically, represents a major source of cancer-related mortality among HIV-infected patients\(^6\). Since the introduction of combined antiretroviral therapy (ART) in the developed world, survival among HIV-infected patients has dramatically improved. However, the effect of ART on the incidence and mortality of AIDS-related NHL has been debated\(^7,8,9\).

Recently, many resource-limited nations in southern Africa have adopted nationwide ART programs. Botswana, a middle-income nation with an adult HIV prevalence of 22\(^%\)\(^10\), implemented a comprehensive HIV treatment program in 2003. The program has provided ART to more than 87\% of HIV-infected individuals nationwide\(^11\), and in the years since its introduction overall HIV-associated mortality has fallen. However, Botswana’s persistently high burden of HIV has been associated with an increased incidence of lymphoma\(^12\), and little is currently known about the epidemiology, treatment patterns, or outcomes of NHL in the country.

There are only limited published reports regarding the incidence and outcomes of HIV-associated NHL in similar, resource-limited African settings\(^13,14,15,16,17\). Thus, the primary objective of this study was to characterize the current burden of NHL in Botswana. We sought to determine the impact of HIV-infection on patients with NHL, describe the specific subtypes of lymphoma observed, catalogue clinical presentations, evaluate responses to treatment, and analyze associated outcomes. We expect that the findings from this study will aid in the development of strategies to further improve the survival among those diagnosed with NHL in Botswana and across Africa.

Patients and Methods:

Study Participants
Patients aged 18 years or older with a new diagnosis of NHL presenting for specialized oncology care in Botswana were considered for enrollment into this study. All diagnoses of NHL were histologically confirmed at the Botswana National Health Laboratory prior to enrollment. The study was rolled out progressively with enrollment at Princess Marina Hospital occurring from October, 2010 to August, 2016, Gaborone Private Hospital from November, 2012 to August, 2016, and Nyangabgwe Referral Hospital from January, 2015 to August, 2016. Patients were excluded if they were unable or refused to provide consent, if they were not citizens of Botswana, or if they had been previously treated for another cancer. Upon enrollment, all patients provided written documentation of their informed consent.

Patient demographics, clinical presentation, prior workup, lymphoma subtype, comorbidities, and HIV-status were abstracted from patient records and interviews. All patients not already known to be HIV-infected underwent HIV testing. For patients accessing care at public hospitals, immunohistochemistry and molecular testing were rarely available, and most cases could only be classified by histological appearance as large cell lymphoma, small lymphocytic lymphoma, or low-grade follicular lymphoma. A limited number of patients treated in the private sector, or by special request, had their pathology reviewed in South Africa (Lancet Laboratories, Johannesburg) with the benefit of immunohistochemistry. Cancers were staged by clinical exam, chest radiographs, and ultrasound imaging. Computed tomography, positron emission tomography, bone marrow biopsy, and cerebrospinal fluid analysis were not routinely performed due to limited resource availability.

After enrollment, patients were contacted quarterly during clinic visits, or when unable to present to clinic, by telephone. In the event of a patient’s death, the official cause was recorded from the death certificate, with additional context provided by family members and healthcare workers.

Treatment

Standard treatment regimens were equivalent at each study site. In general, patients treated with curative intent were prescribed six to eight cycles of CHOP—cyclophosphamide, doxorubicin, vincristine, and prednisone—in 3-week intervals. Starting in 2014, treatment regimens were updated for all patients, adding rituximab to each cycle of CHOP (R-CHOP). Treatment centers in Botswana do not retain chemotherapy administration records, and thus the types of treatment, dosages, timing, and any information on toxicity or clinical response were
collected from individual medical records provided by patients. A majority of the treatment records were analyzed during intensive case reviews of living patients, via patient interviews and medical record interrogation, conducted between May and August of 2014 and June and August of 2016.

HIV therapy was provided to all seropositive patients without cost by the government of Botswana. In 2012, the threshold for ART increased from 250 to 350 CD4 T cells/μL. Regardless of CD4 T-cell count, NHL is a WHO stage 4 condition and represents an absolute indication for ART in Botswana\textsuperscript{19}. Standard first-line ART consisted of co-formulated tenofovir, emtricitabine, and efavirenz.

Data and Analysis

Lymphoma subtypes were grouped into indolent, aggressive, or unspecified categories\textsuperscript{20}. Survival of patients with large cell NHL, NOS and DLBCL were similar, and these diagnoses were grouped together as aggressive.

The primary analytic objective was to evaluate the association between HIV status and survival from the time of cancer diagnosis. Fisher’s exact test for categorical variables and student’s T-test for continuous variables were used to assess the significance of differences in baseline and treatment characteristics. Plots of the Kaplan-Meier estimator and log rank tests were used to compare unadjusted survival by HIV status, and adjusted models were built utilizing Cox proportional hazards and propensity score models, stratified by NHL behavior\textsuperscript{21}. Dichotomized variables known to be associated with HIV infection\textsuperscript{22} or survival\textsuperscript{23} were utilized to calculate the propensity score and included age, sex, performance status, cancer stage, education, and employment.

We compared survival in this cohort with cases included in the Surveillance, Epidemiology, and End Results (SEER) Program of 20 cancer registries in the United States between 2006 and 2011. Each patient in Botswana was matched with 5 randomly selected patients in the SEER database on the basis of race, age, sex, NHL subtype, and stage at presentation.

Analyses were performed using SAS version 9.4 (SAS; Cary, North Carolina) and p-values less than 0.05 were considered significant.
Results:

Enrollment and Demographics

Between October, 2010 and August, 2016, 104 patients with a new diagnosis of NHL were enrolled. Seventy-five (72.2%) patients were HIV-infected. Compared to their HIV-uninfected counterparts, HIV-infected patients were younger (median age: 53.9 vs. 39.1 years, p = 0.001) and more likely to present with an aggressive subtype of NHL (65.5% vs. 84.0%, p = 0.008). There was no relationship between HIV status and cancer stage or functional status at the time of diagnosis. Additional demographic and clinical characteristics are presented in Table 1.

Among HIV-infected patients, median CD4 T-cell count at the time of lymphoma diagnosis was 198 cells/µL (IQR: 112 – 291 cells/µL). The majority (64.4%) of HIV-infected patients had been on ART prior to cancer diagnosis, with median treatment duration of 9.8 months (IQR 1.3 – 28.8 months). Figure 1 presents a histogram of ART initiation relative to time of lymphoma diagnosis.

There was a long duration between the initial development of symptoms and the eventual diagnosis of NHL, amounting to 280 days on average. There was no association between the time to NHL diagnosis and HIV status (p = 0.42).

Subtypes of Non-Hodgkin Lymphoma

Table 2 presents the subtypes of NHL most frequently diagnosed in this cohort. Among all cases, 82 (78.9%) consisted of large cells on histology. Sixty-five of these large cell cases underwent further analysis with immunohistochemical staining and 61 (58.7% of the entire cohort), were consistent with DLBCL. Of the other large cell lymphomas, 1 was diagnosed as Burkitt lymphoma and 3 were of T-cell lineage. Indolent subtypes of NHL included small lymphocytic lymphoma (4.8%) and low-grade follicular lymphoma (2.9%) and constituted a larger proportion NHL among HIV-uninfected patients as compared to HIV-infected patients (20.7% vs. 2.7%, p = 0.008).

Treatment and Toxicities

Treatment records were analyzed for 46 patients (44.2%), including 34 HIV-infected patients and 12 HIV-uninfected patients. All patients were initiated on CHOP (67.4%) or R-CHOP
(32.6%), and received 6 cycles of treatment on average. Surgical tumor excision was performed prior to chemotherapy in a single patient (medial maxillectomy). Seven patients with limited stage DLBCL received radiation after completing 6-8 cycles of R-CHOP.

Treatment modifications were common, with a total of 22 modifications among 20 patients. Two modifications were due to insufficient vincristine supply—vinblastine was given in its place. The remaining modifications were due to toxicities. There was one instance of treatment-related cardiac toxicity. Otherwise, 19 individual cycles of chemotherapy were delayed or cancelled due to neutropenia. There was no association between a patient’s HIV-status and the likelihood of treatment toxicity (p = 0.41).

**Survival**

Among the total cohort, 46 patients (44.2%) died over a median follow-up of 11.9 months (IQR: 3.9 – 29.6 months), including 30 HIV-infected (40.0% of HIV-infected cohort) and 16 HIV-uninfected (55.2% of HIV-uninfected cohort) patients. The cause of death was reportedly due to cancer in 41 instances (89.1% of all deaths) and complications of treatment in 5 (10.9%). All treatment-related deaths occurred in patients with aggressive lymphomas treated solely with CHOP or R-CHOP. There was no association between the likelihood of treatment related death and HIV-status, cancer stage at diagnosis, or performance status.

In an unadjusted model, HIV-status was not associated with mortality, with HIV-uninfected and HIV-infected patients having 1-year mortality rates of 52.9% (95% CI: 28.2 – 77.6%) and 37.1% (95% CI: 30.1 – 44.1%), respectively (HIV-infected HR: 0.73, p = 0.33). In a model adjusted for age, sex, cancer stage, performance status, and indolent vs. aggressive disease, HIV-status remained unassociated with mortality (HIV-infected HR: 0.57, p = 0.14). The propensity score model also confirmed that HIV-infected patients have similar outcomes to their uninfected counterparts (HR: 0.73, p = 0.39).

Regardless of HIV-status, patients in Botswana with DLBCL fared worse than the matched cohort of patients in the USA. Respective 1-year mortality rates were 21.8% (95% CI: 20.5 – 23.1%) in the USA and 47.2% (95% CI: 35.6 – 58.8%) in Botswana, (Botswana HR: 1.89, p = 0.001).
Discussion:

Patient Outcomes

Among patients with a new diagnosis of non-Hodgkin lymphoma presenting for specialized cancer care in Botswana, HIV-infection is not associated with increased mortality. This prospective study is one of the first of its kind to assess the demographics and outcomes of patients with NHL, based on HIV status, in a resource-limited setting in Africa. Based on our review of the literature, only 2 prior studies have explored this relationship in similar settings, in Malawi\textsuperscript{17} and Uganda\textsuperscript{25}.

The prevalence of HIV infection in this cohort was markedly higher than in the general adult population of Botswana—72.1% vs. 22.8\%\textsuperscript{10}. This is consistent with the known link between HIV-associated immunosuppression and the development of NHL\textsuperscript{24}. HIV-infected patients were younger and more likely to be diagnosed with an aggressive subtype of NHL, similar to data presented elsewhere\textsuperscript{25,26}. Many HIV-infected patients had severe levels of immunosuppression at the time of their cancer diagnosis, which should portend worse outcomes. However, along with being younger, HIV-infected patients tended to have markers of higher socioeconomic status, and younger, wealthier, HIV-infected patients may have more readily accessed cancer care, better tolerated treatment, or suffered from fewer comorbidities than their HIV-uninfected counterparts. These key differences among HIV-infected and HIV-uninfected patients may have contributed to the similar outcomes observed in this study.

Extensive evidence has linked HIV infection to a poorer prognosis of NHL in much of the developed world\textsuperscript{25,26,27,28}. This relationship has been reported in other resource limited settings as well. In Uganda, HIV-infected lymphoma patients are twice as likely to die in the first year after NHL diagnosis as those without HIV\textsuperscript{29}. HIV-infected patients on ART had similar outcomes to those of without HIV, but those not on ART had a nearly 9-fold increased risk of death\textsuperscript{30}. A prospective study evaluating the use of CHOP among patients with NHL in Malawi, revealed a population with similar characteristics to the one described in this study\textsuperscript{17}. There was a high prevalence of HIV-infection with majority of infected patients receiving ART. Their study found a similar 1-year mortality rate to that in Botswana (41\% among those on CHOP). Though HIV-infected patients tended to experience greater treatment toxicities, they did not find a significant survival difference based on HIV status.
Based on these reports, the comparable survival among HIV-infected and HIV-uninfected patients in Botswana appears encouraging, if not unexpected. However, regardless of HIV status, patients in Botswana fared significantly worse than similar patients in the United States. This discrepancy likely arises from many factors. HIV-infection is much more prevalent in Botswana than the United States. We did not match patients in the 2 countries based on HIV status, and though we report no HIV-related survival difference in Botswana, HIV-infected patients with NHL in the United States have a nearly twofold risk of death over a 2-year period than their uninfected counterparts\textsuperscript{31}. Furthermore, the United States has a resource-intensive healthcare system with rapid diagnosis and the delivery of optimal, evidence-based treatments. In Botswana, however, patients tended to present to clinic later in the course of their disease, underwent limited diagnostic workups, and had poor access to modern treatment regimens Error! Bookmark not defined.. Thus, interventions aimed at improving the diagnosis and treatment of NHL in Botswana may lead to better outcomes in the future.

Current challenges in the care of non-Hodgkin lymphoma in Botswana

There are many challenges inherent in the diagnosis and treatment of lymphoma in Botswana. The country is sparsely populated with the greatest prevalence of HIV—and presumably HIV-associated illnesses—concentrated in the isolated northeastern region\textsuperscript{22}. When presenting for care, patients with NHL typically reported vague symptoms, complicating the diagnostic workup in an HIV endemic region Error! Bookmark not defined.. Lymphomas may show atypical morphology and behavior in the setting of HIV\textsuperscript{32}, and many conditions like reactive lymphoid hyperplasia, HIV lymphadenopathy, and \textit{M. tuberculosis}\textsuperscript{33} infection can mimic the presentation of NHL.

Once patients were diagnosed with NHL, many of their tumors remained incompletely characterized\textsuperscript{20}. The cases of NHL identified in this cohort represented a large proportion of subtypes known to be associated with HIV infection, like DLBCL\textsuperscript{34}. Indeed, a similar extent of subtypes has been reported in South Africa\textsuperscript{35,36} and among HIV-infected patients in the United States\textsuperscript{28}.

Even after a diagnosis is made, the treatment options for patients in Botswana are limited. All patients received similar care, and it reasons that those with indolent subtypes may have been exposed to undue treatment toxicity while those with higher grade malignancies might have
been better served by more aggressive treatments. Data has shown that treating all HIV-related cases of NHL alike leads to sub-optimal outcomes\textsuperscript{37}. Additionally, while a majority of the HIV-infected patients had been receiving ART prior to enrollment in this study, with 100% taking ART after NHL diagnosis, the early initiation of ART has been shown to improve the outcomes of NHL\textsuperscript{12,28,36,38,39,40}, and the broad administration of ART to patients with HIV infection remains key for reducing the risk and mortality of NHL.

\textit{Strengths and Limitations}

It is important to consider the results of this study in the context of its design and analysis. This study is one of the first to describe the demographics, treatments, and outcomes of patients with NHL in a resource-limited setting with a heavy burden of HIV infection. It was able to collect prospective data on a relatively large number of patients and followed them over time with minimal loss to follow-up. However, patients were enrolled into the study only after presenting for specialized cancer care. In Botswana, recent estimates have placed the incidence of NHL at roughly 5.5 cases per 100,000 person-years\textsuperscript{12}, substantially higher than the number of patients assessed for enrollment each year. It is likely that we were unable to characterize many patients who either never obtained a definitive diagnosis of NHL, received care in alternative settings, refused or were too ill to participate, or died prior to enrollment. The estimated ascertainment rate of cases was low, potentially adding bias into the study, and future studies should seek to characterize these unrepresented patients.

Additionally, there were instances of missing clinical data. The ability to diagnosis specific subtypes of NHL is crucial for treatment\textsuperscript{41}. In Botswana, limited diagnostic capacity decreases the precision of subtype classification, and advanced imaging modalities like CT and PET scanning are not routinely used for staging. The prevalence of other viral infections, like EBV and CMV, was not assessed, though they are highly prevalent across Africa\textsuperscript{42} and known to play a role in the pathogenesis of NHL\textsuperscript{34}. Specific treatment records were unavailable for a majority of patients, and information about treatment response or relapse was not collected. Put together, this incomplete information limited the resolution of our analysis.

Finally, the power to detect differences in survival was somewhat limited. Despite the poor survival outcomes, only 46 deaths occurred during follow-up, with 1-year mortality rates of 52.9% and 37.1% among HIV-uninfected and HIV-infected patients, respectively. Thus, the
study only had limited power to detect a difference in the mortality between HIV-infected and HIV-uninfected patients.

Conclusion:

This study enrolled HIV-infected and HIV-uninfected patients from Botswana with a new NHL diagnosis, and follow them prospectively to assess their treatment and survival over time. The prevalence of HIV infection was higher among patients with NHL than in the general population. Patients infected with HIV tended to be younger and have more aggressive subtypes of lymphoma than their uninfected counterparts. At the time of NHL diagnosis, HIV-infected patients were likely to have severely depressed CD4 T-cell counts, independent of ART status, suggesting that HIV-associated immune dysfunction played a role in the development of NHL. Overall, 44.2% of patients died during the follow-up period with a 1-year overall mortality rate of 41.5%. While HIV-status was not significantly associated with mortality, outcomes in Botswana lagged far behind the outcomes in more developed nations. Although many factors are likely contributing, the heavy burden of HIV, greater prevalence of aggressive subtypes, and limitations in the diagnosis and treatment of NHL likely explain much of this discrepancy. Therefore, efforts to increase the clinical awareness of lymphoma, expand the in-country diagnostic capacity, and improve the quality of treatment may lead to improvements in survival.
Tables and Figures:

Consort Diagram. * Enrollment, retention, and vital status at the conclusion of follow-up.

*Note: Enrollment registries of the Botswana Prospective Cancer Cohort include all cancers and do not differentiate by site. The number of eligible patients excluded was estimated from observed percentages of the full cohort.
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**Table 1.** Descriptive baseline characteristics of patients with non-Hodgkin lymphoma stratified by HIV-status.
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**Table 2.** Subtypes of non-Hodgkin lymphoma (NHL) in this cohort. Large cell NHL, NOS are those cases found to consist of large cells on histological analysis, but for which further classification by immunohistochemistry (IHC) was not performed. They are grouped as aggressive based on overall similar rates of mortality with diffuse large B-cell lymphoma (DLBCL). All cases of peripheral T-cell lymphoma consisted of large cells and were non-cutaneous, suggesting an aggressive subtype. Unspecified NHL cases were described as such on pathological reports, and any further defining features or advanced analyses were not reported. There was no significant different in the proportion of unspecified NHL cases between the two groups.
Figure 1. Timing of ART initiation in relation to diagnosis of non-Hodgkin lymphoma in HIV-infected patients. The largest portion (32.0%) of patients started ART after the diagnosis of NHL, an absolute indication for therapy. Other indications for initiating ART are the development of other WHO stage 4 diseases or CD4 counts falling below threshold. Among 75 HIV-infected patients, 28.0%, 17.3%, and 22.7% were started on ART less than 6 months before their diagnosis of NHL, between 6 months and 2 years before diagnosis, or more than 2 years before diagnosis, respectively.
Figure 2. Kaplan-Meier estimated survival by HIV-status. Shaded areas indicate 95% confidence intervals. In unadjusted analysis, survival is not significantly different by HIV-status ($p = 0.33$).
Figure 3. Kaplan-Meier estimated survival comparing the patients with DLBCL in Botswana to a cohort in the United States with DLBCL matched by race, age, sex, and stage at presentation. Patients in Botswana had a significantly lower rate of 1-year survival ($p = 0.001$).
References:


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