Short Communication: CD4 Count and HIV RNA Trends for HIV-Associated Lymphoproliferative Disorders in Malawi

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Abstract

Given scarce data from sub-Saharan Africa (SSA), we sought to describe CD4 count and HIV RNA trends over time among patients with HIV-positive lymphoproliferative disorders in Malawi. We prospectively enrolled HIV-positive individuals with pathologically confirmed lymphoproliferative disorders between 2013 and 2016. Chemotherapy was standardized with concurrent antiretroviral therapy (ART). We assessed CD4 count and HIV RNA at baseline and every 6 months for up to 2 years. Of 72 HIV-positive patients, 59 had non-Hodgkin lymphoma (NHL), 5 classical Hodgkin lymphoma (CHL), and 8 multicentric Castleman disease (MCD). Median age was 43 years (range 23–64). Fifty-five patients (76%) were on ART at enrollment for a median 47 months (range 1–387), with median CD4 count of 138 cells/ μ l (range 2–2,235) and median HIV RNA of 2.2 log₁₀copies/ml (range 0.3–7.3). MCD patients had longer median ART durations, higher median CD4 counts, and lower median HIV RNA at baseline than NHL or CHL patients. CD4 count and HIV RNA steadily improved during follow-up, with different patterns in different histological groups. Twelve-month overall survival (OS) was 55% [95% confidence interval (CI) 42%–66%]. There were trends toward baseline CD4 count <100 cells/ μ l and HIV RNA >2.0 log₁₀copies/ml being associated with worse OS. However, CD4 count and HIV RNA improvements during follow-up were independent of possible effects on OS. Distribution of HIV-positive lymphoproliferative disorders may change with continued ART scale-up in SSA. Chemotherapy and concurrent ART can lead to good immunological and virological outcomes.

Keywords: non-Hodgkin lymphoma, Hodgkin lymphoma, multicentric Castleman disease, sub-Saharan Africa

INCIDENCE OF LYMPHOPROLIFERATIVE disorders is increasing in sub-Saharan Africa (SSA), and HIV is a major contributor.¹ Despite progress in scaling up antiretroviral therapy (ART), declines in incidence for HIV-associated lymphoproliferative disorders have not been clearly observed in SSA.^{2,3} HIV prevalence in this population is high in SSA, ranging from 60% to 90% for aggressive non-Hodgkin lymphoma (NHL) and 20% to 60% for classical Hodgkin lymphoma (CHL).^{3–5}

In resource-rich settings, the relative frequency of various HIV-associated lymphoproliferative disorders has changed with earlier ART application. Declines in incidence for CHL and Burkitt lymphoma (BL) have not been clearly observed, unlike diffuse large B cell lymphoma (DLBCL) and primary central nervous system lymphoma.^{6,7} In addition, despite concerns about administering chemotherapy to HIV-infected

patients with lymphoproliferative disorders, studies have demonstrated that patients can be treated comparably to HIV-negative individuals with similar outcomes, as well as CD4 count recovery and HIV RNA suppression.^{8,9}

Such data are lacking from SSA, where most HIV-associated lymphoproliferative disorders occur worldwide. We therefore sought to describe CD4 count and HIV RNA trends for patients in the Kamuzu Central Hospital (KCH) Lymphoma Study.

The KCH Lymphoma Study has been described in detail.⁴ It is a prospective cohort study of patients with newly diagnosed lymphoproliferative disorders at a national teaching hospital in Lilongwe, the capital of Malawi. All diagnoses are pathologically confirmed and supported by immunohistochemistry and weekly real-time telepathology consultation involving United States and Malawian pathologists. We

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included all HIV-infected adults ≥ 16 years of age enrolled between June 1, 2013 and October 31, 2016.

All patients received standardized chemotherapy: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for aggressive NHL, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for CHL, and etoposide for multicentric Castleman disease (MCD). All HIV-infected patients received ART concurrently with chemotherapy, typically with tenofovir–lamivudine–efavirenz as per national guidelines. Patients on ART with virological failure received adherence counseling and consideration of second-line ART with a boosted protease inhibitor (atazanavir/ritonavir). CD4 count and HIV RNA were measured at baseline and every 6 months.

Cohort characteristics were summarized using simple descriptive statistics. Differences between lymphoproliferative disorder categories were assessed using Fisher's exact and Kruskal–Wallis tests. Follow-up was calculated from enrollment until death, loss to follow-up, or administrative censoring on December 31, 2016. Kaplan–Meier methods were used to estimate overall survival (OS). Cox models were used to estimate unadjusted hazard ratios (HRs) for mortality. Analyses were conducted using Stata version 12.1 (College Station, Texas).

Between June 1, 2013, and October 31, 2016, 72 of 189 adults (38%) with newly diagnosed, indolent, or aggressive lymphoproliferative disorders at KCH were HIV positive. Of these 72 HIV-positive patients, 59 (82%) had NHL, 8 (11%) MCD, and 5 (7%) CHL. Baseline characteristics at initial lymphoproliferative disorder diagnosis are shown in Table 1. Median age for the cohort was 43 years (range 23–64). Fifty-five patients (76%) were on ART at enrollment for a median 47 months (range 1–387), with median CD4 count of 138 cells/ μ l (range 2–2,235) and median HIV RNA of 2.2 log₁₀copies/ml (range 0.3–7.3). Patients with MCD had longer median ART durations, higher median CD4 counts, and lower median HIV RNA at baseline than patients with NHL or CHL ($p < .05$ for all comparisons). Statistically significant differences were otherwise not observed between groups. Among patients with NHL, DLBCL was most common ($n = 44$, 75%), followed by BL ($n = 6$, 10%), plasmablastic lymphoma ($n = 4$, 7%), low-grade B cell lymphoma ($n = 2$, 3%), and NHL not otherwise specified ($n = 3$, 5%). Although limited by small numbers especially in non-DLBCL groups, CD4 count and HIV RNA did not clearly differ between NHL subtypes.

CD4 count steadily increased to a median of 263 cells/ μ l (range 81–570) and HIV RNA declined to a median of

0.3 log₁₀copies/ml (range 0.3–5.0) at 2 years (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/aid), with trends being similar for NHL. MCD was characterized by high CD4 counts and HIV RNA suppression throughout the follow-up period. CHL patients exhibited more marked CD4 count increases than other groups, with largely suppressed HIV RNA throughout the follow-up period, likely reflecting CHL-associated lymphopenia responding to chemotherapy,[18] in addition to HIV-associated lymphopenia responding to ART.

As of December 31, 2016, vital status was known for all patients, after median follow-up of 18.7 months (range 5.0–42.2) among patients still alive. For the cohort overall, 12-month OS was 55% [95% confidence interval (CI) 42%–66%] and 24-month OS was 44% (95% CI 31%–56%). For patients with NHL, 12-month OS was 48% and 24-month OS was 38%. For patients with MCD, 12-month OS was 75%, and for patients with CHL, 12-month OS and 24-month OS were 100%. In unadjusted analyses, there was a trend toward baseline CD4 count < 100 cells/ μ l being associated with increased mortality (HR 1.7, 95% CI 0.9–3.2, $p = .12$), along with HIV RNA > 2.0 log₁₀copies/ml (HR 1.6, 95% CI 0.8–3.0, $p = .16$). However, CD4 count and HIV RNA trends appeared independent of possible effects on survival, and remained consistent even in sensitivity analyses restricted to patients surviving for at least 12 or 24 months (Supplementary Fig. S2).

This is the first description of CD4 count and HIV RNA trends among patients treated for HIV-associated lymphoproliferative disorders in SSA, which are common complications of HIV in the region.^{1–3} As in resource-rich settings, we found CD4 count and HIV RNA heterogeneity among diverse lymphoproliferative disorders, associations between CD4 count and HIV RNA with survival, and CD4 count recovery and HIV RNA suppression among patients receiving chemotherapy with concurrent ART.^{6–9}

Heterogeneity in the immunological and virological contexts for various lymphoproliferative disorders suggests that their relative distribution may shift with continued ART scale-up. These shifts may partially resemble resource-rich settings, but unique trends might also emerge, for instance increasing MCD in a region that is endemic for the causative agent, Kaposi sarcoma-associated herpesvirus. Although MCD incidence trends are not entirely clear in resource-rich settings, increasing incidence in the ART era has been suggested.¹⁰ In our cohort, MCD was the second most frequent HIV-associated lymphoproliferative disorder, and was largely observed in individuals on long-term ART with

TABLE 1. BASELINE CHARACTERISTICS OF HIV-INFECTED PATIENTS WITH NEWLY DIAGNOSED LYMPHOPROLIFERATIVE DISORDERS IN LILONGWE, MALAWI

	All (n = 72)	NHL (n = 59)	MCD (n = 8)	CHL (n = 5)
Age, years, median (range)	43 (22–63)	45 (22–63)	36 (28–57)	33 (30–52)
CD4 count, cells/ μ l, median (range)	138 (2–2235)	122 (24–2235)	316 (2–1146)	138 (23–329)
HIV RNA, log ₁₀ copies/ml, median (range)	2.1 (0.3–7.3)	2.9 (0.3–7.3)	0.3 (0.3–5)	0.3 (0.3–3.7)
On ART ^a , n (%)	55 (76)	43 (73)	7 (88)	5 (100)
ART duration, months, median (range)	47 (1–387)	37 (1–387)	225 (2–278)	38 (5–347)

^aOn ART defined as ≥ 1 month of ART exposure before enrollment.

ART, antiretroviral therapy; CHL, classical Hodgkin lymphoma; MCD, multicentric Castleman disease; NHL = non-Hodgkin lymphoma.

relatively preserved CD4 counts and HIV RNA suppression, suggesting that MCD may become more important as ART scale-up continues.

We also observed significant immunosuppression at diagnosis of HIV-associated lymphoproliferative disorders overall, with lower CD4 counts and higher HIV RNA being possibly associated with worse survival, and positive trends in CD4 count and HIV RNA over time in patients receiving standardized chemotherapy with concurrent ART. These findings highlight ongoing HIV treatment gaps despite tremendous progress in ART scale-up in Malawi. However, salutatory trends in CD4 count and HIV RNA during follow-up also suggest that curative chemotherapy with concurrent ART is possible in SSA. This is important to disseminate in countries where stigma for both HIV and cancer can lead to unjustified therapeutic nihilism and even outright denial of potentially curative treatment for lymphoproliferative disorders.

In conclusion, we found CD4 count and HIV RNA heterogeneity among Malawian patients with diverse HIV-associated lymphoproliferative disorders, trends toward lower baseline CD4 count and higher HIV RNA being associated with worse survival, and long-term CD4 count recovery and HIV RNA suppression in patients receiving chemotherapy with concurrent ART. These results highlight the changing distribution of lymphoproliferative disorders that may occur with continued ART scale-up and provide reassurance that chemotherapy and concurrent ART can be administered with good immunological and virological outcomes.

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Author Disclosure Statement

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