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## Hodgkin lymphoma, HIV, and Epstein–Barr virus in Malawi: Longitudinal results from the Kamuzu Central Hospital Lymphoma study

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### Abstract

**Background**—Contemporary descriptions of classical Hodgkin lymphoma (cHL) are lacking from sub-Saharan Africa where human immunodeficiency virus (HIV) and Epstein–Barr virus (EBV) are prevalent.

**Methods**—We describe a prospective cHL cohort in Malawi enrolled from 2013 to 2015. Patients received standardized treatment and evaluation, including HIV status and EBV testing of tumors and plasma.

**Results**—Among 31 patients with confirmed cHL, the median age was 19 years (range, 2–51 years) and 22 (71%) were male. Sixteen patients (52%) had stage III/IV, 25 (81%) B symptoms, and 16 (52%) performance status impairment. Twenty-three patients (74%) had symptoms >6

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#### CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

#### SUPPORTING INFORMATION

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months, and 11 of 29 (38%) had received empiric antituberculosis treatment. Anemia was common with median hemoglobin 8.2 g/dL (range, 3.1–17.1 g/dL), which improved during treatment. No children and 5 of 15 adults (33%) were HIV+. All HIV+ patients were on antiretroviral therapy for a median 15 months (range, 2–137 months), with median CD4 count 138 cells/ $\mu$ L (range, 23–329 cells/ $\mu$ L) and four (80%) having undetectable HIV. EBV was present in 18 of 24 (75%) tumor specimens, including 14 of 20 (70%) HIV– and 4 of 4 (100%) HIV+. Baseline plasma EBV DNA was detected in 25 of 28 (89%) patients, with median viral load 4.7 (range, 2.0–6.7) log<sub>10</sub>copies/mL, and subsequently declined in most patients. At 12 months, overall survival was 75% (95% confidence interval [CI], 55%–88%) and progression-free survival 65% (95% CI, 42%–81%). Baseline plasma EBV DNA and persistent viremia during treatment were associated with poorer outcomes.

**Conclusion**—cHL in Malawi is characterized by delayed diagnosis and advanced disease. Most cases were EBV associated and one-third of adults were HIV+. Despite resource limitations, 12-month outcomes were good.

### Keywords

Epstein–Barr virus; Hodgkin lymphoma; Malawi; pediatric cancer; sub-Saharan Africa

## 1 | INTRODUCTION

In sub-Saharan Africa (SSA), classical Hodgkin lymphoma (cHL) is a common malignancy among children and young adults, accounting for 4%–9% of pediatric cancers.<sup>1–3</sup> Given limited pathology infrastructure, cHL is also likely underreported since gradually progressive lymphadenopathy may be empirically treated as tuberculosis, leading to delayed or missed cHL diagnosis.<sup>3–5</sup> In resource-rich countries, 75% of newly diagnosed patients present with early stage I/II cHL,<sup>6,7</sup> while in resource-limited countries, more than half of patients present with advanced stage III/IV disease.<sup>2</sup> In resource-rich settings, cHL is highly curable with greater than 90% long-term survival for stage I/II and 80% for stage III/IV.<sup>8</sup> Although data are scarce, reported survival rates for cHL in SSA are lower ranging from 60% to 70%.<sup>3,9</sup>

In resource-rich settings, cHL is one of the commonest non-AIDS defining cancers among individuals infected with human immunodeficiency virus (HIV).<sup>10</sup> Despite reductions in other HIV-associated lymphoma subtypes, the incidence of cHL appears stable or increasing in the current antiretroviral therapy (ART) era.<sup>9,11–17</sup> Moreover, the risk of HIV-associated cHL may be increased in the first months after ART initiation due to immune reconstitution.<sup>12,17,18</sup> Studies in the United States have shown that cHL incidence is 5–20 times higher among HIV+ patients, with 3%–4% of newly diagnosed cHL cases occurring in HIV-infected individuals.<sup>11–13,19</sup> HIV-infected individuals with cHL are more likely to present with advanced stage, B symptoms, and extranodal involvement.<sup>10,11,19</sup> However, when treated appropriately, cHL patients with HIV can receive similar regimens and experience comparable outcomes to those without HIV.<sup>12,20,21</sup>

cHL is also often associated with Epstein–Barr virus (EBV),<sup>22</sup> an oncogenic herpesvirus that infects more than 80% of children in SSA typically before 5 years of age.<sup>23</sup> The frequency

of EBV-positive cHL differs geographically, being more common in resource-limited regions of the world including SSA where 70%–90% of cHL cases are EBV-positive.<sup>3,22,24</sup> EBV-positive cHL is also more common in children, males, and HIV-infected individuals.<sup>10,12,22,24</sup>

Although cHL is a common cancer frequently associated with HIV and EBV, both of which are highly prevalent in SSA, to our knowledge there are no prospective clinical studies of cHL from SSA from the contemporary era of widespread ART availability. Herein we describe clinical characteristics, treatment course, HIV and EBV associations, and survival for a longitudinal cHL cohort at Kamuzu Central Hospital (KCH), a national teaching hospital in the Malawian capital, Lilongwe. It serves approximately 8–9 million people in a country with an HIV prevalence of 10%, ART coverage of 67%,<sup>25</sup> annual gross domestic product per capita of 314 US dollars,<sup>26</sup> and Human Development Index rank of 173 of 188 countries.<sup>27</sup>

## 2 | METHODS

The KCH Lymphoma Study is a prospective cohort initiated in June 2013. Patients with pathologically confirmed lymphoproliferative disorders are eligible to participate after informed consent. We focused on patients with newly diagnosed cHL between June 1, 2013, and December 31, 2015. The study was conducted in accordance with the Helsinki Declaration, after approval by the University of North Carolina Institutional Review Board and Malawi National Health Sciences Research and Ethics Committee.

All cases were diagnosed through weekly telepathology consultation involving two to four pathologists in Malawi and the United States who rendered a consensus opinion after reviewing hematoxylin and eosin stained tissue sections.<sup>28,29</sup> Immunohistochemistry (IHC) was performed locally at the interpreting pathologists' discretion, including CD3, CD20, CD30, CD45, CD138, Ki-67, and terminal deoxynucleotidyl transferase. In rare pediatric cases, a cytologic diagnosis of cHL was made when clinical findings were consistent and binucleated Reed–Sternberg cells were clearly identified, only when tissue biopsy was not possible due to anatomic location and limited pediatric surgery capacity. All specimens were then shipped to the United States for secondary hematopathologist review, where diagnoses were confirmed by a larger panel of automated IHC stains, including CD3, CD15, CD20, CD30, and PAX5. For cHL subtyping, two US hematopathologists (Y.F. and N.D.M.) assigned a consensus subtype. EBV was assessed in tumors by EBV-encoded RNA (EBER) *in situ* hybridization (Leica Biosystems, Wetzlar, Germany) and in plasma using a proprietary real-time quantitative polymerase chain reaction (qPCR) assay performed at the University of North Carolina Vironomics Core with a linear detection range of 2.0–8.0 log<sub>10</sub>copies/mL.<sup>30</sup> Plasma EBV qPCR was assessed at baseline, mid-treatment (cycle 3, day 21), treatment completion, and whenever possible at clinical relapse.

At cHL diagnosis, a comprehensive baseline evaluation was performed including chest radiography, abdominal ultrasound, performance status, and Ann Arbor stage. Unilateral bone marrow examination was performed routinely in adults but not children due to lack of pediatric sedation capabilities. Response was assessed using standardized criteria

incorporating physical examination, chest radiography, and abdominal ultrasound. There are no formal cancer treatment guidelines or radiotherapy in Malawi. However, efforts to standardize care have been ongoing. Adult patients received ABVD (doxorubicin 25 mg/m<sup>2</sup>, bleomycin 10,000 IU/m<sup>2</sup>, vinblastine 6 mg/m<sup>2</sup>, dacarbazine 375 mg/m<sup>2</sup> on days 1 and 15) every 4 weeks for a total of six cycles. Adults could receive up to eight cycles if they achieved a partial response after six cycles without severe adverse events related to therapy. Children received modified ABVE-PC without etoposide (doxorubicin 40 mg/m<sup>2</sup>, vincristine 2 mg/m<sup>2</sup>, bleomycin 10 units/m<sup>2</sup>, cyclophosphamide 800 mg/m<sup>2</sup> on day 1, prednisolone 1.5 mg/kg/day on days 1–5) every 3 weeks for a total of eight cycles. Patients were not routinely screened at baseline for malaria or parasitic infections unless clinically indicated.

Laboratory studies were performed before each chemotherapy dose. If blood counts prohibited chemotherapy, they were repeated 1 week later and treatment proceeded if blood counts allowed, with standardized algorithms for cytotoxic dose adjustment. Hematopoietic growth factors were not available, and supportive care was standardized. Antiemetics included ondansetron, promethazine, and/or dexamethasone. Transfusions were provided for hemoglobin less than 7 g/dL and platelets less than 20×10<sup>3</sup>/μL. Febrile neutropenia was treated empirically with a third-generation cephalosporin until a source was identified. Nutritional supplementation for malnourished children included ready-to-use therapeutic feeding packets three times per day, and high-protein diet counseling for adults. HIV-infected patients received ART concurrently with chemotherapy, typically with tenofovir–lamivudine–efavirenz regimen as per Malawi guidelines.

Interval complications were recorded prior to each cycle. Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.<sup>31</sup> Transportation reimbursement was provided to promote retention throughout care. Medicines were freely provided by the Ministry of Health, supplemented by external funding for back-up chemotherapy to mitigate treatment interruptions.

Baseline characteristics were summarized using descriptive statistics. Follow-up time was calculated from enrollment until progression or death, loss to follow-up, or administrative censoring on May 15, 2016. Overall survival and progression-free survival were estimated using Kaplan–Meier methods, and the log-rank test was used to assess survival differences between groups. Cox proportional hazards were used to estimate unadjusted hazard ratios for overall survival and progression-free survival. The cause of death was adjudicated by consensus review involving two study investigators (K.D.W. and S.G.). All analyses were performed using STATA SE version 12.1 (College Station, TX).

## 3 | RESULTS

### 3.1 | Baseline characteristics

Between June 1, 2013, and December 31, 2015, 31 patients (11%) with cHL were enrolled of 274 total patients with pathologically confirmed lymphoproliferative disorders in the cohort overall. During the study period, we were aware of three cases, all children, diagnosed with Hodgkin lymphoma who were not enrolled in the study for the following

reasons: one child died before the pathologic diagnosis was confirmed, one child's family elected not to participate, and one child was diagnosed during a brief enrollment pause resulting from minor administrative delay in obtaining annual Malawi regulatory renewal for the study.

Baseline characteristics for patients with cHL are shown in Table 1. The median age was 19 years (range, 2–51 years) and 22 (71%) were male. A total of 16 patients (52%) had stage III/IV disease, 25 (81%) B symptoms, and 16 (52%) significant performance status impairment. Of 26 patients with primary sites that could be accurately measured, 11 (42%) had bulky disease.<sup>32,33</sup> Twenty-three of 31 patients (74%) had symptom durations greater than 6 months at cHL diagnosis, and 11 of 29 (38%) had received empiric antituberculosis treatment for lymphadenopathy. Eleven of 31 patients (35%) were significantly underweight. Anemia was common with median hemoglobin 8.2 g/dL (range, 3.1–17.1 g/dL) and bone marrow involvement in 6 of 12 (50%) adults assessed. Of three adults who did not undergo bone marrow evaluation, two declined and one was felt to be too sick to tolerate the procedure safely in clinic. Elevated lactate dehydrogenase (LDH) was also common with a median baseline LDH of 359 IU/L (range, 161–894 IU/L, laboratory upper limit of normal 250 IU/L). No children and five (33%) adults were HIV-infected, all of whom were on ART at cHL diagnosis for a median 15 months (range, 2–137 months), with a median CD4 count of 138 cells/ $\mu$ L (range, 23–329 cells/ $\mu$ L) and four of five patients (80%) having undetectable HIV RNA.

Table 2 depicts histologic subtypes and tumor EBV status. Of 24 cases further classified according to cHL subtype, 8 were mixed cellularity, 7 lymphocyte depleted, 6 nodular sclerosing, and 3 lymphocyte rich. Of these, 18 (75%) were EBER-positive by *in situ* hybridization, including 14 of 20 (70%) HIV-negative patients and 4 of 4 (100%) HIV-positive patients.

### 3.2 | Treatment course and toxicities

As of May 15, 2016, the median number of cycles completed for all 31 patients was 7 (range, 1–8). Twenty-one (68%) patients completed all prescribed chemotherapy, nine (29%) died before treatment completion, and one (3%) was still completing front-line treatment. Figure 1 depicts peripheral blood counts during treatment. Median ANC generally remained above  $1.0 \times 10^3/\mu$ L throughout treatment for both children and adults, with subsequent recovery after chemotherapy completion. In both children and adults, anemia at baseline improved over the course of treatment.

Of 81 grade 3/4 neutropenia events, 56 (69%) were grade 3 and 25 (31%) grade 4. Eleven of 15 (73%) adults and nine of 16 (56%) children experienced at least one grade 3/4 neutropenia event during treatment. Fifteen grade 3/4 anemia events occurred, with four adults and three children experiencing at least one grade 3/4 anemia event during treatment. In the entire cohort, there was only one grade 3 thrombocytopenia event, and no grade 3/4 non-hematologic toxicity recorded. Of 16 patients with at least one chemotherapy cycle delayed by more than 7 days, all delays were due to neutropenia.

Of three HIV-infected patients who had follow-up CD4 and HIV RNA measurements 6 months after enrollment, after they had completed chemotherapy, median CD4 count increased to 483 cells/ $\mu\text{L}$  (range, 349–517 cells/ $\mu\text{L}$ ) from a median of 138 cells/ $\mu\text{L}$  (range, 102–298 cells/ $\mu\text{L}$ ) at baseline, with all three patients having undetectable HIV RNA at baseline and 6-month follow-up. One HIV-infected patient was still completing first-line chemotherapy as of May 15, 2016, and one patient was known to be well at home through regular telephone contact, but had not returned to clinic for repeat blood draws.

### 3.3 | Outcomes and associations with plasma EBV DNA

As of May 15, 2016, disease status and vital status were known for all patients after a median follow-up of 12.3 months (range, 5.9–26.8 months) among 22 patients still alive. Overall survival estimates with 95% confidence intervals (CIs) are shown in Table 3. Overall survival was 75% (95% CI 55%–88%) 12 months after enrollment, and 61% (95% CI 35%–79%) 24 months after enrollment, without significant differences between adults and children. Progression-free survival was 71% (95% CI 42%–81%) 12 months after enrollment, and 56% (95% CI 14%–68%) 24 months after enrollment. All five HIV-infected patients were alive as of the censoring date after a median follow-up of 14.5 months (range, 6.0–26.0 months). Of the patients still alive, 18 were in complete remission, 2 in partial remission, and 2 had progressed or relapsed cHL. Central adjudication of nine deaths during the study period was undertaken to attribute cause of death (Supplemental Table S1). Six deaths were attributed to progressive cHL and three to treatment-related complications.

Of 28 patients with baseline plasma tested for EBV DNA, 25 (89%) had detectable viremia with a median viral load of 4.7  $\log_{10}$ copies/mL (range, 2.0–6.7  $\log_{10}$ copies/mL), which resolved in most patients by the mid-point of chemotherapy treatment (Fig. 2). While very high plasma EBV DNA was clearly demonstrated in two patients at the time of clinical relapse as shown, a total of six patients including those two cases had increasing plasma EBVDNA at either the chemotherapy mid-point or chemotherapy completion. Of these, five experienced relapse or death during follow-up, with only one patient alive and in remission four months after enrollment. In addition, for patients in whom both baseline plasma EBV DNA and tumor EBER were assessed, results were strongly correlated, with plasma EBV DNA being detected in 17 of 17 EBER-positive patients versus 4 of 7 EBER-negative patients ( $P=0.017$ ).

Our small cohort did not allow robust multivariate assessment of risk factors associated with outcomes. However, in exploratory unadjusted analyses, only increased LDH was associated with increased risk of progression or death in the cohort overall (unadjusted hazard ratio [HR] 1.37 per 100 IU/L increase, 95% CI 1.02–1.84,  $P=0.038$ ), while baseline plasma EBV DNA was not (unadjusted HR 1.09, 95% CI 0.73–1.63,  $P=0.66$ ). Similarly, stage and performance status were not significantly associated with outcomes. However, when restricted only to patients with detectable baseline plasma EBV DNA, both LDH (unadjusted HR 1.47, 95% CI 1.06–2.04,  $P=0.022$ ) and plasma EBV DNA (unadjusted HR 2.53, 95% CI 1.17–5.45,  $P=0.018$ ) were associated with increased risk of progression or death. In addition, among patients with plasma EBV DNA measurement at the mid-point of

chemotherapy, there was a significant association between detectable virus at this time point and worse progression-free survival subsequently (Fig. 3).

## 4 | DISCUSSION

To our knowledge, this is the first prospective clinical description of cHL from SSA reflecting the current ART era for HIV. Our cohort was characterized by advanced stage, poor performance status, long symptom durations prior to cHL diagnosis, frequent empiric treatment for tuberculosis lymphadenitis, and significant anemia. However, both children and adults had reasonably good overall and progression-free survival with standardized treatment in a severely resource-limited environment, irrespective of HIV status.

Marked anemia was a notable feature of our cohort, much more so than our previous Malawi reports of adult and pediatric non-Hodgkin lymphoma.<sup>34,35</sup> Although comprehensive evaluation to identify various causes of anemia was not routinely done unless clinically indicated, hemoglobin improved during treatment, and half of adults had demonstrated bone marrow involvement. Anemia is also commonly reported in cHL in resource-rich countries, typically in advanced disease even without bone marrow involvement, and is much less severe in published descriptions than we observed in our Malawi cHL population.<sup>36</sup> This suggests that anemia should not be viewed as a major barrier to pursuing curative-intent treatment for cHL in SSA with appropriate cumulative dose and dose intensity, despite difficulties with reliable transfusion support in the region.

Among adults with cHL, one-third were HIV-infected. All HIV-infected adults were on ART at cHL diagnosis for a median of more than a year, and most had undetectable HIV RNA. cHL may therefore emerge as a more frequent lymphoma subtype in Malawi among HIV-infected individuals, as earlier and more widespread application of ART continues, just as in resource-rich countries.<sup>11</sup> In high-income countries, HIV is present in 3%–4% of cHL cases with higher proportions among lymphocyte-depleted and mixed cellularity subtypes,<sup>13</sup> and it remains unclear whether cHL incidence has changed significantly among HIV-infected individuals in the ART era.<sup>14–17</sup> In cross-sectional studies from SSA, HIV prevalence has typically been reported as 20%–50% among adults with cHL,<sup>37–39</sup> and <10% among children,<sup>40,41</sup> with cHL incidence appearing to be stable thus far despite ART scale-up.<sup>42</sup>

We also found strong associations between cHL and EBV as expected, with 75% of cases being EBER-positive and 89% having elevated baseline plasma EBV viral load, similar to other reports from SSA.<sup>3,22,24</sup> In resource-rich settings, quantitative plasma EBV DNA has been demonstrated to have potential utility in cHL for diagnosis, prognosis, and monitoring.<sup>43–46</sup> Although our small cohort allowed only limited assessment of plasma EBV DNA for cHL prognosis and response assessment, to our knowledge, this is the first study from SSA to specifically examine serial EBV viral loads during cHL treatment. We observed markedly elevated levels at baseline, which declined in the majority of patients during chemotherapy. We also found significant associations between plasma EBVDNA levels at baseline and persistence of plasma EBV DNA at the mid-point of chemotherapy with subsequent progression-free survival. These results deserve further investigation in larger cohorts from the region. If confirmed, EBV viral load could represent an important,

clinically implementable biomarker in SSA, a region where capacity for plasma HIV RNA measurement is already well established.<sup>47</sup> Existing HIV RNA instruments in many settings could likely be readily adapted to also measure plasma EBV DNA. In addition, EBV DNA measurement in plasma has greater utility as a clinical biomarker than measurement in peripheral blood mononuclear cells for EBV-associated lymphoproliferative disorders, an approach that is far more implementable at the point of care in low-resource settings.<sup>48</sup>

Despite adverse baseline characteristics and a severely resource-constrained environment, overall survival was 75% at 12 months and 61% at 24 months for the cohort, with generally good outcomes for children and adults irrespective of HIV status. This compares favorably with other reports from SSA settings,<sup>3,9</sup> and demonstrates that outcomes can be good even in Malawi if patients receive appropriate treatment with standard regimens and careful monitoring.

The strengths of our study include a detailed, prospective cohort with high-quality pathologic diagnoses, protocol-guided treatment, and longitudinal follow-up with standardized assessments. In addition, we had complete retention and outcome ascertainment. Patient retention in clinical cancer studies in SSA is a major challenge, and survival can be significantly overestimated when patients are lost to follow-up, since death is a major cause of loss to follow-up in this environment. Finally, all patients received standardized treatment according to institutional guidelines during the study period. The limitations include referral bias at a national teaching hospital, small sample size, lack of systematic evaluation for various causes of anemia, and assigning cause of death based on inference after centralized review. In addition, our cohort was likely understaged relative to cohorts in resource-rich settings due to absent bone marrow evaluation particularly in children and lack of advanced imaging for all patients.

To conclude, cHL occurred primarily among adolescents and young adults in Malawi, typically associated with EBV and often HIV. Despite advanced disease and impaired performance status, children and adults were successfully treated with good short-term outcomes irrespective of HIV status. Survival can likely be further improved through continued efforts to achieve earlier diagnosis and define optimal treatment approaches for cHL in this environment. Such efforts may benefit from further evaluation of plasma EBV DNA as a clinically important and implementable biomarker in Malawi and comparable settings to facilitate better risk-adapted and response-guided therapeutic strategies.

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## Abbreviations

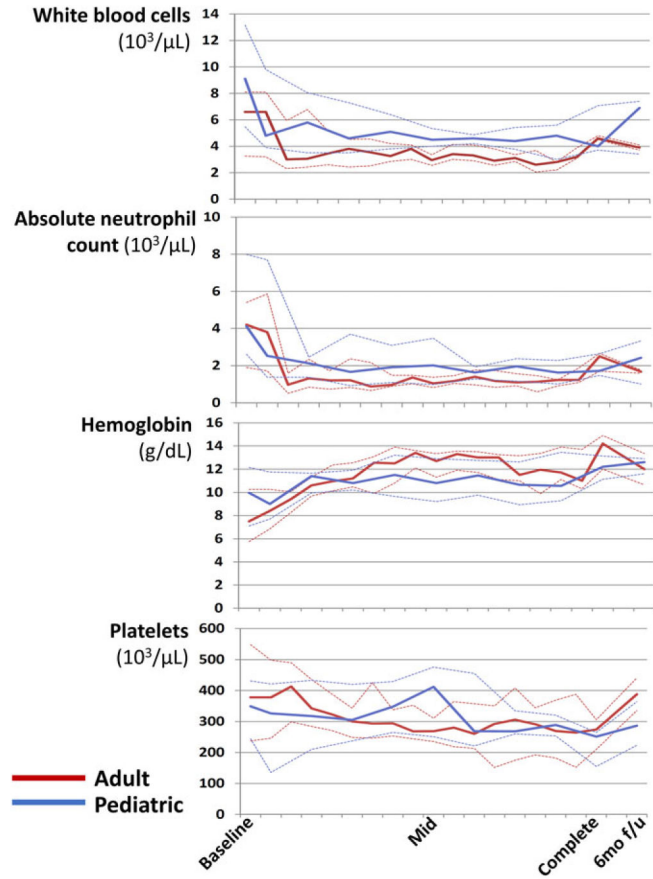
<b>ABVD</b>	doxorubicin, bleomycin, vincristine, dacarbazine
<b>ABVE-PC</b>	doxorubicin, bleomycin, vincristine, etoposide, prednisolone, cyclophosphamide
<b>ART</b>	antiretroviral therapy
<b>cHL</b>	classical Hodgkin lymphoma
<b>CI</b>	confidence interval
<b>EBER</b>	Epstein–Barr virus-encoded RNA
<b>EBV</b>	Epstein–Barr virus
<b>HIV</b>	human immunodeficiency virus
<b>HR</b>	hazard ratio
<b>IHC</b>	immunohistochemistry
<b>KCH</b>	Kamuzu Central Hospital
<b>LDH</b>	lactate dehydrogenase
<b>qPCR</b>	quantitative polymerase chain reaction
<b>SSA</b>	sub-Saharan Africa

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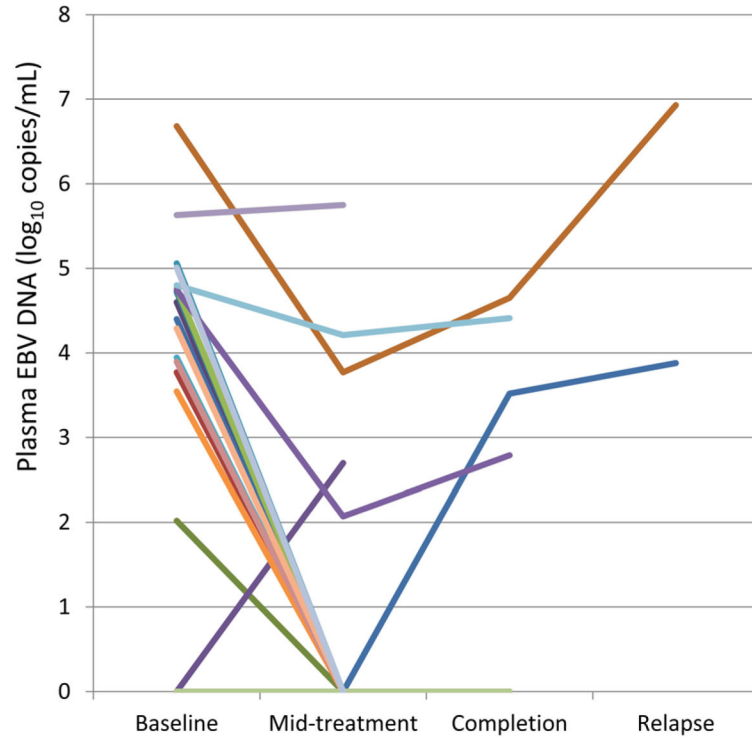
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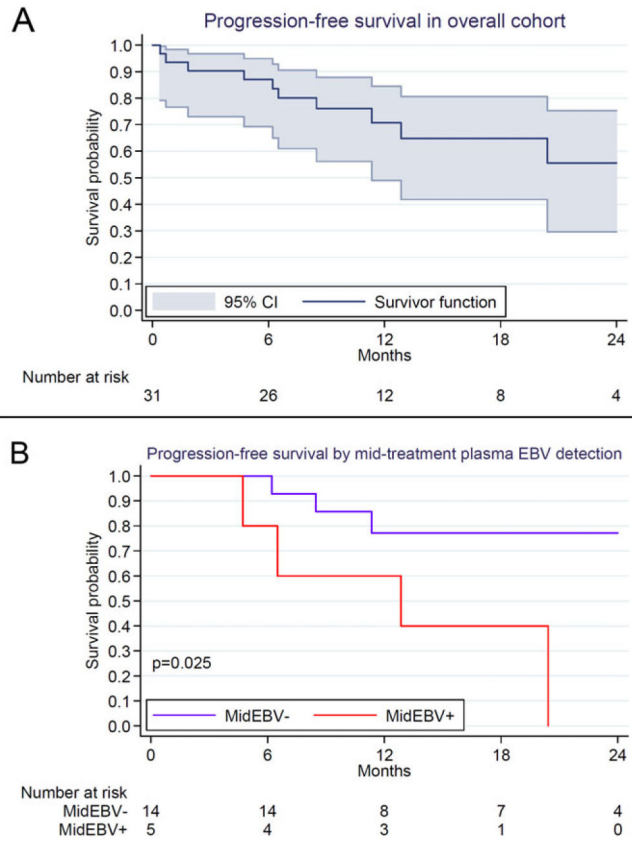
**FIGURE 1.** Median peripheral blood counts with interquartile ranges during chemotherapy for classical Hodgkin lymphoma in Malawi. Mid= mid-treatment; Complete=Treatment completion; 6mo f/u=6-month follow-up



Plasma EBV DNA		Baseline	Mid-treatment	Completion	Relapse
<b>Detected</b>	All	25/28 (89%)	5/19 (26%)	4/12 (33%)	2/2 (100%)
	EBER+	17/17 (100%)			
	EBER-	4/7 (57%)			
<b>Median log<sub>10</sub>copies per mL (range)</b>	All	4.8 (2.0-6.7)	3.8 (2.1-5.6)	4.0 (2.8-4.7)	5.4 (3.8-7.0)
	EBER+	4.8 (2.0-6.7)			
	EBER-	4.0 (3.5-6.7)			

**FIGURE 2.**

Quantitative Epstein–Barr virus plasma DNA during classical Hodgkin lymphoma treatment in Malawi. EBV = Epstein–Barr virus; EBER = Epstein–Barr virus encoded RNA in situ hybridization



**FIGURE 3.** Kaplan–Meier progression-free survival for classical Hodgkin lymphoma patients in Malawi. (A) Overall cohort with 95% confidence intervals. (B) Stratified by mid-treatment plasma Epstein–Barr virus DNA detection. EBV = Epstein–Barr virus

TABLE 1

Baseline characteristics of classical Hodgkin lymphoma patients in Malawi, June 2013–December 2015

Total, n	Entire cohort 31	HIV positive 5
Demographics		
Male, n (%)	22 (71)	4 (80)
Pediatrics, <18 years, n (%)	16 (51)	0
Age, years, median (range)	19 (2–51)	33 (30–51)
Diagnostic specimen, n (%)		
Cytology	3 (10)	0
Histology	28 (90)	5 (100)
Clinical stage, n (%)		
Stage I/II	15 (48)	0
Stage III/IV	16 (52)	5 (100)
Clinical presentation		
Underweight <sup>a</sup> , n (%)	11 (35)	1 (20)
B symptoms, n (%)	25 (81)	4 (80)
Symptoms >6 months, n (%)	23 (74)	4 (80)
Cervical lymph node involvement, n (%)	22 (71)	3 (60)
Bulky disease <sup>b</sup> , n (%)	11/26 (42)	0
Received prior empiric anti-tuberculosis treatment for lymphadenopathy <sup>c</sup> , n (%)	11/29 (38)	3 (60)
Impaired performance status <sup>d</sup> , n (%)	16 (52)	2 (40)
Laboratory data		
White blood cells, 10 <sup>3</sup> /μL, median (range)	7.6 (1.5–46.0)	4.1 (1.5–7.8)
Absolute neutrophil count, 10 <sup>3</sup> /μL, median (range)	4.2 (0.5–35.0)	2.4 (0.8–5.6)
Hemoglobin, g/dL, median (range)	8.2 (3.1–17.1)	9.8 (5.7–10.7)
Platelets, 10 <sup>3</sup> /μL, median (range)	351 (27–839)	381 (182–764)
Lactate dehydrogenase <sup>e</sup> , IU/L, median (range)	359 (161–894)	359 (161–492)
Albumin, g/dL, median (range)	2.7 (1.7–5.2)	3.4 (2.0–3.7)
HIV specific		
On ART at cHL diagnosis, n (%)	–	5 (100)
Duration of ART prior to diagnosis, months, median (range)	–	15 (2–137)
CD4 count, cells/μL, median (range)	–	138 (23–329)
HIV RNA <400 copies/mL, n (%)	–	4 (80)

ART = antiretroviral therapy.

<sup>a</sup>Underweight defined as weight-for-age z-score < -2 if <5 years, bodymass index (BMI) z-score < -2 if ≥ 5 years, or BMI < 16.5 kg/m<sup>2</sup> for adults.<sup>b</sup>26 of 31 total cases had primary sites that could be accurately measured, with bulky disease defined as >10 cm in adults and >6 cm in children.<sup>c</sup>29 of 31 total cases had known tuberculosis treatment history.

<sup>d</sup> Impaired performance status defined as Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$  in adults or Lansky performance status  $<70$  in children.

<sup>e</sup> Laboratory upper limit of normal is 250 IU/L.

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Subtypes and tumor Epstein-Barr virus association for classical Hodgkin lymphoma in Malawi

TABLE 2

	N	EBER+	Mixed cellularity	Lymphocyte depleted	Nodular sclerosing	Lymphocyte rich
All	24	18 (75%)	8	7	6	3
HIV+ adults	4	4 (100%)	1	0	2	1
HIV- adults	10	7 (70%)	2	5	2	1
Children	10	7 (70%)	5	2	2	1

EBER = Epstein-Barr virus encoded RNA *in situ* hybridization.

Kaplan–Meier overall survival and progression-free survival for classical Hodgkin lymphoma patients in Malawi, stratified by age and stage

**TABLE 3**

	n	12-month			24-month			24-month		
		OS %	95% CI	PFS %	95% CI	OS %	95% CI	PFS %	95% CI	
Overall	31	75	55–88	71	49–85	61	36–79	56	30–75	
Pediatric	16	74	45–89	74	45–89	59	24–83	56	18–82	
Adult	15	78	46–92	69	36–87	62	24–85	57	24–81	
Stage I/II	15	72	42–89	72	42–89	72	42–89	72	42–89	
Stage III/IV	16	78	46–92	70	36–88	54	19–79	45	13–73	

CI = confidence interval; OS = overall survival; PFS = progression-free survival.