Prognostic factors affecting survival in children and adolescents with HIV and Hodgkin lymphoma in South Africa

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ABSTRACT

South African children with Hodgkin lymphoma (HL) and human immunodeficiency virus (HIV) have low 5-year overall survival (OS) rates. In this retrospective multicenter study, 271 South African pediatric patients with HL were studied to determine OS and prognostic factors in those with HIV and HL. Univariate risk factor analysis was performed to analyze prognostic factors. The 29 HIV-infected patients were younger ($p = .021$), more likely to present with wasting (0.0573), stunting (0.0332), and Stage IV disease ($p = .000$) than HIV-uninfected patients. The 5- and 10-year OS of HIV-infected patients of 49% and 45% *versus* 84% and 79%, respectively for HIV-uninfected patients ($p = .0001$) appeared to be associated with hypoalbuminemia (<20 g/dL) and CD4 percentage of <15%. Causes of death in the HIV-infected group included disease progression (6/14), infection (4/14), unknown (3/14), and second malignancy (1/14). HIV-infected pediatric patients with HL experience increased mortality due to post-therapy opportunistic and nosocomial infections.

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Introduction

Hodgkin lymphoma (HL) and human immunodeficiency virus (HIV) are immune disorders which, when occurring in tandem in children with immature immune systems, can have devastating consequences. HL is associated with immune dysregulation [1] and HIV infection results in losses of both cellular and humoral immunity [2,3].

South Africa is home to the world's largest cohort of people living with HIV, with an estimated 7,700,000 people living with HIV in 2018, 260,000 of them children under 14 years [4]. The HIV epidemic has had a profound impact on childhood mortality and socio-economic conditions in Africa [5–7]. Steady improvements have been made in increasing access to antiretroviral therapy (ART) resulting in an increased lifespan of children with HIV [4,8,9]. While HL has

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been associated with HIV in adults, it is not considered an AIDS-defining cancer, and a similar trend has not been conclusively shown in children and adolescents [10–12].

Limited studies report an increased mortality risk for patients with both HIV and various cancers due to infections [13,14] but there is no published data on pediatric HIV and HL. A retrospective, multicenter study identified that HIV-infected children in South Africa who develop HL have a significantly lower 5-year overall survival (OS) rate than their HIV uninfected counterparts [14]. The aim of this study was to identify risk factors associated with inferior survival rates between these HIV-infected and -uninfected children and adolescents and to determine long-term OS.

Materials and methods

The setting

South Africa is an upper-middle-income country which had ten pediatric oncology units (POUs) at the time of the retrospective study. The majority of children and adolescents with both HL and HIV were treated in state hospitals where care was largely subsidized, with free care for all children less than 6 years. ART was available free-of-charge in state facilities.

Patient population

Data were drawn from the ten participating centers for the period 1 January 2000–31 December 2010 and included all treatment-naïve, histologically confirmed cases of HL in children and adolescents (less than 18 years). Exclusion criteria included patients who were treated at other centers after diagnosis, and those in whom the HIV status was undocumented. Patients from both the private and the public sectors were treated with the same treatment protocols.

Ethics

Permission to conduct retrospective analyses was obtained from the human research ethics committee of the University of the Witwatersrand (clearance certificate number M1711100).

Histopathology

Pathology specimens were processed at the National Health Laboratory Services at the participating centers and reviewed by a single pathologist.

Staging of HL

Staging procedures have previously been described and consisted mainly of computerized tomography scans and chest X-rays [14]. Early-stage disease was defined as Stages I and II, while late-stage disease was defined as Stages III and IV. Bulky disease was defined as lymph nodes or lymph node aggregates greater than 6 cm in the long axis, or mediastinal adenopathy $\geq$33% of the thoracic diameter [15].

Treatment

Patients were treated according to institutional preference with vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine (OPPA/OEPA-COPP), adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), or ABVD-chlorambucil, vinblastine, procarbazine, prednisolone (ABVD-ChlVVP). Patients receiving OPPA/OEPA-COPP received involved-field radiotherapy (median 25 Gy) as a matter of course, while those receiving other regimens received radiation for residual or bulky disease only according to treating physicians' preference.

Interim assessments were not routinely performed in all centers but were done if there was clinical suspicion of lack of response to chemotherapy. HIV-infected patients were treated with the same chemotherapy protocols as uninfected patients. Dose modifications and administration of granulocyte-colony stimulating factor (G-CSF) were used in selected patients regardless of HIV status at the discretion of the treating clinicians. According to national policy at the time, cotrimoxazole prophylaxis was given to all HIV-infected patients with AIDS-defining CD4 counts, while prophylactic fluconazole was given at the discretion of the treating clinician. Cotrimoxazole was not given routinely to HIV-uninfected patients as *Pneumocystis jirovecii* was not commonly seen in this population. HIV therapy was freely provided to all HIV-infected patients in the public sector from 2003 onwards: this consisted of azidothymidine (AZT), stavudine, and lopinavir + ritonavir/efavirenz. Patients were screened for tuberculosis if there was clinical suspicion and treated if infected.

HIV infection characteristics

HIV infection was diagnosed by ELISA in all patients, either before presentation with their oncological diagnosis, or concurrently in those whose HIV diagnosis was made when they presented with HL. HIV viral loads were measured by polymerase chain reaction.

Further documentation included whether patients were on ART at the time of diagnosis with HIV, and whether they had achieved viral suppression defined as an undetectable viral load. Immunological stage data of HIV disease was not available for any of the patients.

Nutritional parameters

Height, weight, body mass index (BMI), and albumin level were recorded. Nutritional parameters were defined according to WHO definitions: obese/overweight, adequate, or BMI <2 standard deviations (2SD) according to standardized tables for age and sex. Wasting was defined as weight-for-age <2SD and stunting was defined as height-for-age <2SD. Weight-for-height tables were not used as the WHO recommends these for the age group 2–5 years, and the majority of patients in this study fell out of this age range.

Statistical analysis

This study analyzes a subset of HIV-infected patients from a previously published report which found that HIV-infected children had a significantly lower survival rate, but did not elucidate the reasons for this finding.

Demographic data included age, sex, nutritional parameters as defined above, HIV status with CD4 percentage and HIV viral load for HIV-infected patients. Other variables included histological subtype, stage, autoimmune manifestations of HL (nephrotic syndrome, hemolytic anemia, and immune thrombocytopenic purpura), treatment regimen, treatment site, last follow-up date (date last seen alive or date of abandonment of treatment), survival status, and cause of death. Baseline characteristics were summarized using descriptive statistics. The characteristics and outcomes of HIV-infected patients were compared to the group of uninfected patients. Odds ratio with Pearson's chi-square test was applied to categorical data to determine if differences between groups were statistically significant. Statistical significance was defined as a p value <.05.

Primary refractory disease was diagnosed in those with progression during treatment or up to 3 months from end of treatment. Treatment abandonment was defined as failure to complete curative treatment, or failure to appear for scheduled therapy for more than 4 weeks, except when patients were managed palliatively and these patients were censored at the time of abandonment. Loss to follow-up was defined as failure to return for follow-up appointments for more than 1 year after successful completion of therapy. These patients were censored in the survival curves.

OS was defined from the date of diagnosis until death or date last seen alive and included patients not treated with curative intent. Five- and ten-year OS rates were calculated using Kaplan–Meier analysis with log-rank Cox regression modeling to assess survival differences between groups (parameters included age, sex, nutritional parameters, B symptoms, stage, bulky disease, histological subtype, CD4 percentage, treatment site, and chemotherapy regimen) with unadjusted hazard ratios for OS. Radiotherapy was not considered in this analysis as it was inconsistently administered. The cutoff for data analysis was 1 January 2020 to obtain data on 10-year survival rates.

Results

Between January 2000 and December 2010, 299 cases of pediatric HL patients were identified, of which 28 were excluded because they were treated elsewhere (8), had an unknown HIV status (14) or refused treatment upfront (6) (see Figure 1). Of the 271 eligible patients, 29 (10.7%) were HIV-infected (see Figure 1). The median age of HIV-infected patients was 7.2 years (range 3.3–16.3 years), in comparison with a median of 10 years (range 2.9–18.8 years) in the HIV-uninfected patients ($p = .021$), with a male predominance in both groups (3.4:1 in both). Although there were no specific policies precluding treatment of children with HIV, one POU reported no children with HIV in their dataset.

The majority (17/29, 76%) of HIV-infected children presented with late-stage disease, while 132/242 (55%) HIV-uninfected children presented with late-stage disease ($p = .015$) (see Table1). There were no significant differences in BMI between the two groups, but HIV-infected patients exhibited more wasting, stunting, and hypoalbuminemia. HIV-infected patients were more likely to present with autoimmune manifestations of HL but the trend was not significant ($p = .117$) (see Table 1).

Of the 29 HIV-infected patients, 23 had documented CD4 counts, ranging from 2.4% to 45% (median 18.3%) with absolute counts ranging from <1 to 1441 cells/mm^3 (median 353). Five patients (5/23, 22%) had absolute CD4 counts under 100 cells/mm^3 and one had a count between 101 and 200 cells/mm^3, while the remainder had counts more than 200 cells/mm^3. Only 14 patients had HIV viral load results available at the start of HL therapy, ranging from

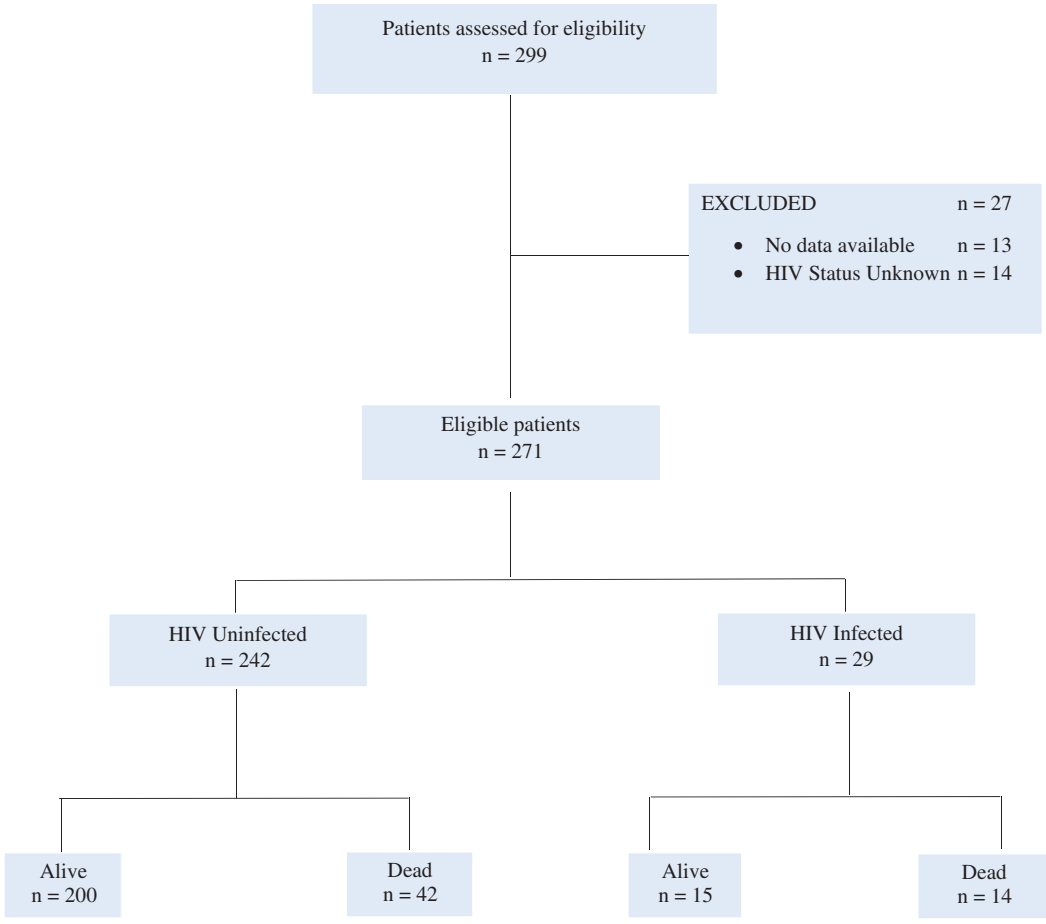

Figure 1. Consort diagram of enrollment, retention, and status at conclusion of follow-up.

undetectable to 656,000 copies/mL. The majority (27/29) presented after 2003 when the national ARV roll-out was firmly established. Eight patients (29%) were receiving ART at the time of diagnosis of HL, and four of these patients were virally suppressed. The length of time each patient was on ART prior to diagnosis was not documented. The remaining 21 patients were commenced on ART concurrently with chemotherapy, except for one patient who abandoned treatment early on.

Management protocols and causes of death

Most patients were treated with ABVD (see Table 1): two patients with HIV (6.6%) and four HIV-uninfected patients (1.7%) died before treatment, and one patient with Stage I nodular lymphocyte-predominant HL had surgical excision and did not require chemotherapy. Tuberculosis was diagnosed and treated in 4/29 (13.8%) HIV-infected patients at the start of treatment; information on tuberculosis was not captured in the HIV-uninfected patients. Both HIV-infected and -uninfected patients received the same chemotherapy protocols, according to institutional preference.

In the HIV-infected cohort, five patients abandoned therapy before completion and the remainder received a median of five cycles of chemotherapy (range 0–8 cycles). Similarly, the HIV-uninfected patients received a median of 5 cycles of chemotherapy.

Overall survival

The 5- and 10-year OS rates for HIV-infected patients were 49% (95% CI 29–65%) and 45% (95% CI 26–62%), respectively, in contrast with 84% (95% CI 78–88%) and 78% (95% CI 72–84%) for the HIV-uninfected group ($p = .0001$) (see Figure 2). The median follow-up was 3.2 years in the HIV-infected group and 6.7 years in the HIV-uninfected group. Causes of death in the 14 HIV-infected children who demised were infection (6), relapsed/progressive disease (1), untreated disease in patients who presented in extremis (2), undocumented (3), and second malignant neoplasm (1) (see Table 2). Based on this small sample, the odds ratio of death by infection in the HIV-infected group was 15 ($p = .004$), and HIV-uninfected patients were more likely to succumb to relapse than

Table 1. Baseline characteristics of children and adolescents with Hodgkin lymphoma.

Parameter	HIV pos $n = 29$	%	HIV neg $n = 242$	%	Chi-square p-value
Sex					
Male	22	75.8	184	76.3	.865
Female	7	24.2	57	23.7	.865
Nutritional parameters					
BMI obese/overweight	2	6.9	9	3.7	.413
BMI adequate	23	79.3	180	74.7	.704
BMI <- 2SD	3	10.3	36	14.9	.361
BMI undocumented	1	3.4	16	6.6	.488
Wasting (weight/age <2SD)	9/21[a]	42.9	26/113[a]	23.0	.0573
Stunting (height/age <2SD)	15/27[a]	55.6	79/228[a]	34.7	.0332
Hypoalbuminemia (<20g/dL)	7/24[a]	29.2[a]	22/205[a]	10.7[a]	.005
Age					
Median	7.2		10.0		.021
Range	3.3-16.3		2.9-18.8		
Stage					
I	1	3.4	17	7.1	.467
II	5	17.2	92	38.1	.025
III	5	17.2	74	30.7	.136
IV	17	58.6	58	24.1	.000
Unknown	1	3.4	0	0	.004
Histological subtype					
Nodular sclerosing	6	20.7	104	43.2	.019
Mixed cellularity	14	48.3	102	42.3	.530
Lymphocyte depleted	2	6.9	9	3.7	.414
HL NOS	6	17.2	20	8.3	.032
B symptoms					
Yes	20	69.0	144	59.8	.347
No	8	27.6	96	39.8	.208
Undocumented	1	3.4	1	0.4	.072
Bulky disease					
Yes	9	34.5	97	40.2	.347
No	20	65.5	144	59.8	.208
Autoimmune disease					
Yes	6	20.7	26	10.8	.118
No	23	79.3	215	89.2	.118
Treatment					
ABVD	17	56.7	130	53.9	.916
ABVD-ChlVVP	1	3.3	28	11.6	.583
OEPA/OPPA-COPP	9	30.0	79	32.8	.450
Died before treatment initiated	2	6.6	4	1.7	.070

[a]Denominators less than the total above reflect missing data.
SD: standard deviations; NOS: not otherwise specified; ABVD: adriamycin, vinblastine, bleomycin, dacarbazine; OPPA/OEPA-COPP: vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine; ABVD-ChlVPP: ABVD-chlorambucil, vinblastine, prednisone, procarbazine.

HIV-infected patients ($p = .044$) but no other significant trend was demonstrated.

Table 3 demonstrates that, although infection was an important cause of death in HIV-infected children, these infections occurred mainly after treatment, indicating that these patients tolerated chemotherapy but succumbed later. Infectious causes of death were culture-negative neutropenic sepsis (2), methicillin-resistant *Staphylococcus Aureus* (1), and *P. jirovecii* with immune reconstitution syndrome (1). One patient demised 3 years post completion of treatment from varicella and *Streptococcus pneumoniae* septicemia.

Poor prognostic features

Although late stage of disease predicted poor survival outcome in the entire cohort [14], the same trend was not confirmed with statistical significance in the smaller HIV-infected subset of patients (see Table 4). Among HIV-infected patients, an albumin level <20 g/dL ($p = .006$) and a CD4 percentage <15% ($p = .04$) were prognostic of poor survival (see Table 4). Factors that did not achieve statistical significance were: age, sex, race, Ann Arbor stage, B symptoms, bulky disease, histological subtype, treatment site, and nutrition.

Discussion

This report analyzes the largest documented cohort of pediatric HIV-infected patients with HL to date and presents both 5- and 10-year survival data. These patients presented mainly with late-stage disease and the majority was not on ART at the time of diagnosis with HL. The widespread state-sponsored rollout of

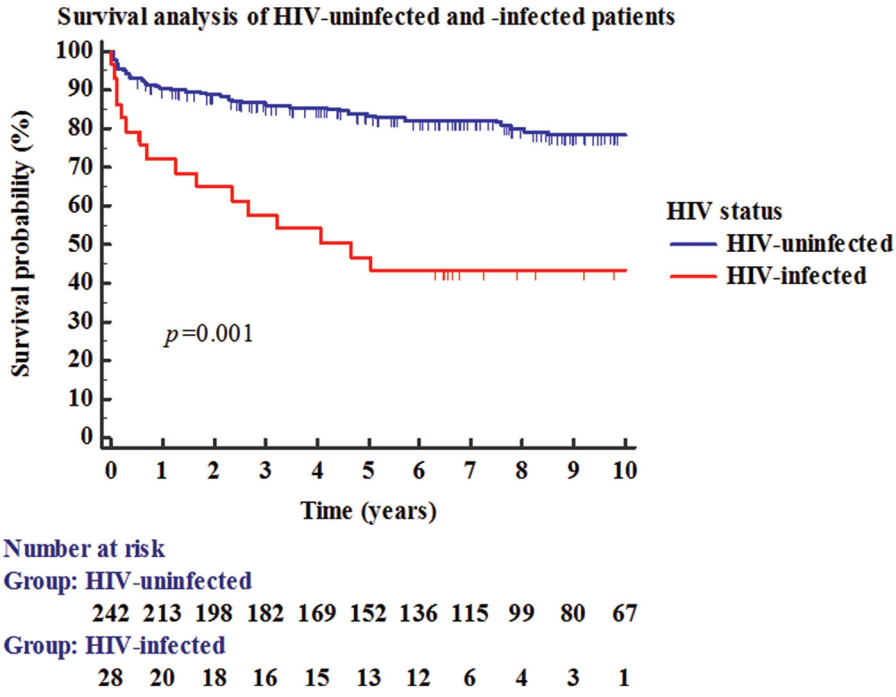

Figure 2. Kaplan–Meier survival analysis of HIV infected and infected pediatric patients.

Table 2. Causes of death in South African children and adolescents with Hodgkin lymphoma.

Causes of death	HIV-infected $n = 14$	%	HIV-uninfected $n = 42$	%	Odds ratio	p-value chi square
Infection	6	42.9	2	4.8	15	0.004
Undocumented	3	21.4	2	4.8	5.45	0.0582
Late presentation	2	14.3	4	9.5	1.58	0.6179
Refractory disease	1	7.1	10	23.8	0.246	0.1740
Second malignancy	1	7.1	0	0	N/A	0.0805
Abandoned therapy	1	7.1	12	28.6	0.0	0.0241
Relapse	0	0	10	23.8	0.0	0.0440
Tuberculosis	0	0	2	4.8	0.0	0.4057

LTFU: lost to follow up.

ART launched in 2003 but did not gain full traction in many parts of the country for some time. AZT is not recommended for use with chemotherapy in high-income settings, however, the ARV regimen containing this agent was the only one available to patients in South Africa at the time. The low 5-year survival rate of 49% may be associated with hypoalbuminemia and low CD4 percentages at diagnosis. The most prominent causes of death were infection in the HIV-infected patients and relapsed/refractory disease in HIV-uninfected patients; although these numbers are small and conclusions should be interpreted with reserve. It is important to note that most of the deaths in the HIV-infected children occurred in the period 18–50 months post completion of therapy, which implies that they were not related to the cancer or treatment thereof.

Adults with HL and HIV were reported to have similar 5-year OS rates to their HIV-uninfected counterparts [16]. In contrast, in this study, pediatric patients with HIV and HL had a significantly lower survival rate than both HIV-uninfected children with HL and HIV-infected children without HL. It was also markedly lower than that of patients with HL and HIV reported in a South African study [10] although only 12 patients from seven South African centers were reported. ART was made widely available in South Africa in 2003 [17] and good coverage was initially achieved, though this has not been sustained [18]. Although the early initiation of ART has been shown to improve outcomes of HIV-infected children with cancer [10,19], only 8/29 patients in this study were on ART at presentation; however, all patients who received chemotherapy were also initiated on ART.

Bohlius et al. [12] reported that children who were on ART were less likely to develop cancer than children who were not on ART. HL is not considered an AIDS-defining malignancy in either adults or children, despite an excess of HL being demonstrated in these

Table 3. Details of demised South African HIV-infected children and adolescents with Hodgkin lymphoma, diagnosed 2000–2010.

Age (years)	Nutritional status			Stage	On ART at diagnosis	CD4 (%)	HIV viral load	TB	Chemotherapy	Cause of death	Survival time (months)
	Wasting wt/age	Stunting ht/age	BMI/age								
8.5	severe	severe	severe	IV	N	29	2,45,465	N	OEPA-COPP	Progression of disease	8.2
8.4	severe	moderate	adequate	IV	Y	20.8	UDL	N	ABVD	Progression of disease	14.8
3.3	overweight	adequate	adequate	IV	Y	3.9	1,54,542	N	OEPA-COPP	Acinetobacter septicemia	48.9
6.5	moderate	adequate	adequate	IV	N	N/D	N/D	N	OEPA-COPP	Neutropaenic sepsis, culture negative	28.0
6.5	adequate	moderate	adequate	IV	N	N/D	2,57,078	N	OEPA-COPP	Second malignancy: primitive neuroectodermal tumor of the central nervous system	55
3.8	adequate	moderate	adequate	II	N	14	N/D	N	ABVD	*S. pneumoniae* and varicella septicemia	38.7
4.5	moderate	adequate	adequate	IV	N	45	N/D	N	ABVD	Abandoned therapy	1.1
13.3	N/A	adequate	adequate	II	N	10.7	N/D	N	ABVD	Not documented	60.5
13.4	N/A	adequate	obese	IV	N	16	1,97,000	N	ABVD	Abandoned therapy	2.3
7.8	adequate	severe	adequate	IV	Y	11	140	Y	ABVD	Neutropenic sepsis, methicillin resistant *Staphylococcus aureus*	0.7
6.2	moderate	severe	adequate	II	Y	N/D	N/D	N	ABVD	Not documented	19.7
5.8	adequate	adequate	adequate	III	N	N/D	N/D	Y	ABVD	*Pneumocystis jirovecii*/ immune reconstitution syndrome	17.9
7.2	adequate	adequate	adequate	N/D	N	12	N/D	Y	ABVD	Not documented	3.4
11.0	N/A	N/D	N/D	IV	N	N/D	N/D	N	Died before chemotherapy	Progression of disease (presented in extremis)	0.9
3.8	moderate	moderate	adequate	IV	Y	18.3	UDL	Y	Died before chemotherapy	Progression of disease (presented in extremis)	0.03

BMI: body mass index; UDL: under detectable limit; N/D: not documented/done; TB: tuberculosis; ABVD: adriamycin, vinblastine, bleomycin, dacarbazine; OPPA/OEPA-COPPA: vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine.

populations [20]. The prevalence of HIV infection (10.7%) in the entire HL cohort was higher than that in the South African pediatric population during the study [21] but the expected referral bias precludes accurate prevalence estimates. In an HIV-endemic region such as South Africa, conditions such as HIV lymphadenopathy, reactive lymphoid hyperplasia, and tuberculosis may mask the presentation of HL [22], which may have contributed to the increased proportion of patients with late presentation.

Although hypoalbuminemia is a recognized risk factor for poor prognosis in childhood HL [19], this must be used in conjunction with various other parameters in a locally specific manner, as albumin levels may be low in malnutrition, decreased as part of an acute-phase reaction, and may also reflect cachexia from advanced disease. We postulate that children with HIV are more likely to present with hypoalbuminemia (see Table 1), due to both malnutrition associated with HIV infection and late presentation, and that this may contribute to increased chemotherapy toxicity through various mechanisms.

Limitations of this study are the small numbers of HIV-infected patients reported and a possible sampling bias as all patient data was sourced from referral hospitals. It is also likely that many patients with HL were not diagnosed or referred to specialist centers as the rate of under-ascertainment of cases was high during this period [23]. Some records were incomplete, resulting in missing data, most notably CD4 counts and HIV viral loads, which would have been helpful in analyzing prognosis. The lack of prognostic impact of clinical signs of malnutrition (wasting, stunting, and low BMI) (Table 4) was unexpected but the most accurate measure of malnutrition in children with cancer, mid-upper arm circumference [24], was not recorded in these patients. It is possible that the use of three different chemotherapy protocols may have impacted on survival, especially as this was a finding in the larger study [14], but the sub-study was not powered to detect this difference. The numbers were also too small to determine whether being on ART at time of diagnosis of HL impacted positively on prognosis.

As HIV is a condition affecting large numbers of children in low and middle-income countries, and childhood cancer is receiving increasing attention, it is essential to initiate the process of creating guidelines for the management of these patients. The approach to treating children with HL and comorbid infection with HIV is underpinned with the awareness that HL in patients with AIDS is an aggressive disease with high mortality due to infection. The interplay of

Table 4. Univariate risk factor analysis of HIV positive pediatric patients with HL.

Variable	5 year OS (%)	Hazard ratio	95% CI, upper	95% CI, lower	*p*-value Cox regression
Sex					
Male	50.6	Ref			.9655
Female	42.9	1.026	0.3260	3.278	
Age					
<10 years	45.0	1.1063	0.3663	3.3407	.9806
>10 years	60.0	Ref			
Body mass index					
Moderate, severe decrease	66.7	0.5420	0.071	40145	.5053
Adequate, overweight	46.1	Ref			
Weight/age					
Moderate, severe decrease	44.4	1.2460	0.3780	4.111	.536
Adequate, overweight	50.0	Ref			
Height/age					
Moderate, severe decrease	50.3	Ref			
Adequate	50.0	1.007	0.3490	2.906	.9896
Ann Arbor stage					
Stage I and II	66.7	Ref			.5312
Stage III and IV	45.5	1.4396	0.4601	4.5041	
B symptoms					
Yes	42.1	1.7800	0.4950	6.395	.3051
No	72.9	Ref			
Bulky disease					
Yes	44.4	1.162	0.412	3.3276	.7758
No	50.8	Ref			
Autoimmune disorders					
Yes	16.7	2.226	0.754	6.569	.1472
No	55.3	Ref			
CD4 percentage					
<15%	37.5	1.7867	0.5862	5.4457	.0412
>15%	65.5	Ref			
On ART at diagnosis of HL					
No	37.5	0.7185	0.2315	2.2297	.5672
Yes	50.6	Ref			
Albumin level					
<20 g/dL	0.0	4.621	1.409	15.154	.0060
>20 g/dL	65.5	Ref			
Chemotherapy regimen					
ABVD	54.5	1.032	0.356	2.988	.9537
OPPA/OEPA-COPP	25.0	1.582	0.543	4.610	
ABVD-ChIVPP	100	Ref			

Ref: reference value; ART: antiretroviral therapy; ABVD: adriamycin, vinblastine, bleomycin, dacarbazine; OPPA/OEPA-COPP: vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine

environment, infections, nutrition, and the immune dysregulation of HL [25] with the immune compromize of HIV must also be taken into account. The progressive loss of both humoral and cellular immunity experienced by children with HIV on chemotherapy progressively increases the risk of infection, making these children more vulnerable to infection-associated treatment-related mortality. HIV-uninfected children, in contrast, recover their immunity between cycles of chemotherapy [3].

Although current guidelines recommend that all children with HIV initiate ART, regardless of the CD4 count, only 54% of children with HIV worldwide currently receive ART [26] and 31% (8/29) of our patients were on ART at time of diagnosis. Initiating children with HIV on ART also allows them to be more successfully treated with chemotherapy [10,19] although we were unable to test this hypothesis in this study due to small sample size.

If viral suppression has not been achieved in those patients already on ART, and adherence has been assured, it may be prudent to consider resistance testing if available and/or changing to a second-line ART regimen. ART should be initiated at diagnosis in those patients who have not yet commenced on ART. Instead of giving aggressive chemotherapy such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) [27] or doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, prednisone (AVBE-PC) [28] to high-risk patients, especially in settings where G-CSF and supportive care is not consistently available, the clinician could consider giving less toxic chemotherapy such as ABVD and consolidating with radiotherapy [29], if available. The use of GCSF is considered standard of care in many well-resourced settings, but it was not widely available in South Africa at the time of the study. It is essential to pay very close attention to the

prevention and treatment of opportunistic infections such as tuberculosis and *P. jirovecii*, as well as being aware of the devastating consequences of viral infections such as varicella, both during and after treatment of HL. A multidisciplinary team comprising oncologists, HIV clinicians, and infectious diseases specialists is desirable to ensure that both the expected infections associated with neutropenia and HIV-specific opportunistic infections are adequately managed.

In summary, the lower survival rate of South African pediatric patients with HIV who develop HL appears to be associated with a CD4 percentage <15% and hypoalbuminemia. Children with HIV in this cohort demonstrated increased mortality from infection, while those without HIV were more likely to demise from relapsed/progressive disease. For more definitive results, it would be necessary to enroll more patients prospectively in a multicenter, multinational study to accurately determine reasons for poor outcomes, and modern risk group assessment should be used to ensure results are comparable across studies. Standard treatment for HL in HIV-infected children has not yet been defined and it is hoped that the findings from this study will aid in the development of strategies to improve survival among those diagnosed with HL and HIV in similar settings.

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Disclosure statement

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