

Research article

Epidemiological impact of HIV on Non-Hodgkin's lymphoma in Zimbabwe (2004-2007)

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Abstract

Background: Zimbabwe is one of the countries hardest hit by the HIV epidemic and the incidence of HIV-related non-Hodgkin's lymphoma (NHL) has been increasing. **Objectives:** This study was done to assess patient characteristics, disease characteristics and the effect of HIV on the epidemiology. **Patients and methods:** A retrospective study was done at the Radiotherapy Centre at the Parirenyatwa Group of Hospitals. The study population was of all the adult patients with a histological diagnosis of NHL between January 2004 and December 2007.

Results: Of 127 patients eligible for the study 90/127 were between 21 and 50years. HIV results were known in only 67/127 (52.8%) and of these 67 patients, 55 were positive and 25 were already on Antiretroviral treatment. High-grade histology was found in 93/127 patients, it was significantly associated with HIV positive serology status ($p < 0.001$). Stage III was the most common stage with 37/127 (29%) patients. Extra-nodal disease was in 29/127 (23%) patients and all these were HIV positive. None of the HIV negative patients had axillary symptomatic disease as compared to 7/11 (64%) patients who were HIV positive and 4/7 (36%) patients whose HIV status was not known.

Conclusion: A significant number of NHL patients in Zimbabwe are HIV positive. HIV serology status affects patient and disease characteristics. **Copyright © WJMMS, all rights reserved.**

Keywords: Non Hodgkin's Lymphoma (NHL), Human Immune deficiency Virus (HIV)

Introduction

Non-Hodgkin's lymphoma (NHL) comprises of a biologically diverse group of hematologic malignancies, with clinical courses ranging from indolent to highly aggressive.

The incidence of non-Hodgkin lymphoma (NHL) has increased about 100-fold in individuals infected with HIV [1]. Zimbabwe is one of the countries hardest hit by the HIV pandemic, with about 20% of its population infected with the HIV [2]. One would therefore expect a high incidence rate of NHL as noted in an analysis made by Chokunonga et al. [3].

Materials and Method

This study was carried out at the Radiotherapy Centre (RTC) situated at the Parirenyatwa Group of Hospitals in Harare Zimbabwe. It is one of the public cancer units during the period under review.

The subjects of this study were patients who presented at the Radiotherapy Centre at the Parirenyatwa Group of Hospital with a histological diagnosis of non-Hodgkin's lymphoma (NHL) between January 2004 and December 2007.

All the data was obtained from patient's case file records kept at RTC record stores. The files included referral letters, histology reports, the history and physical examinations records, staging investigations treatment protocols; radiotherapy treatment charts and follow up records.

The histological classification of the NHL was based on the Working Formulation classification system, as high grade, intermediate grade, and low grade or unspecified.

Patients were staged according to the Ann Arbor classification. The staging investigations included, clinical finding and the radiological investigations, which were limited only to an ultrasound scan and chest X-ray. CT scans and bone marrow analysis were not offered to all these patients during this period.

The laboratory investigations were limited to an FBC, U&E and LFT's. HIV testing was offered to all consenting patients when the test was available in the hospital laboratories or the patients were encouraged to go the voluntary counseling and testing centers.

The following information was recorded into a data sheet: Age, sex, histological subtypes, stage, type of treatment, hematological profiles at presentation, and CD4 counts.

HIV serology data was for confidentiality kept in a different file away from the rest of the other data acquired for the study.

The Joint Parirenyatwa Hospital and College of Health Sciences Research Ethics Committee approved the study.

Data Analysis

The data was entered using Excel and Epi-Info Version 3.3.2 2005 software package was used for data analysis. Descriptive statistics were documented and T-test was used for comparison between two groups; Chi-squared test was used to test for association between variables. The cut off point for statistical significance was when $p < 0.05$.

Results

Between January 2004 and December 2007 at total of 156 patients with a diagnosis of NHL were seen at the Radiotherapy Centre at the Parirenyatwa Group of Hospitals. Twenty five patients were excluded from the study because they were only referred for radiotherapy and had the rest of their treatment offered either in the private sector or at other hospitals. Four patients were also excluded because they were being managed by the pediatric oncologist and were only referred for radiotherapy.

Thus this study is based on 127 adult cases of NHL.

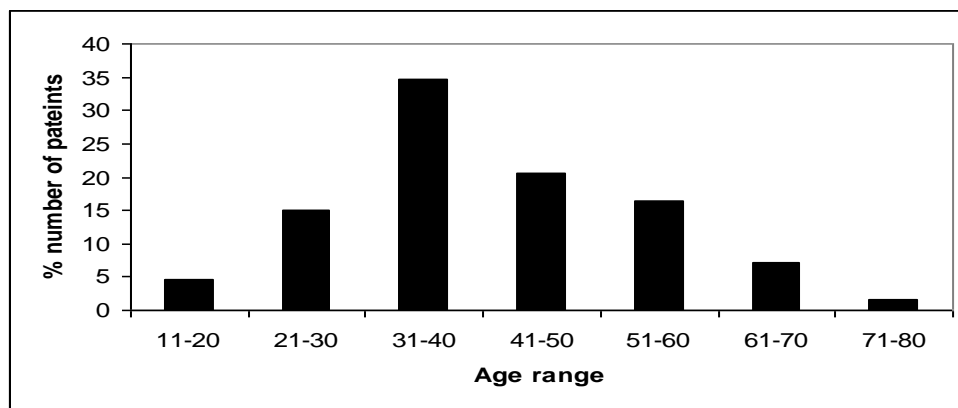
Patients Characteristic

The age range was from 13 to 74. The median age was 41 and 75% of the patients were below the age of 51.

Distribution of NHL with age

There was a general increase in the frequency of NHL with age from the second decade of life with a peak number of 44 patients in the fourth decade and a general decrease there after. About 70% (89/127) of the patients were between the age of 21 and 50 as shown in Fig1

Figure 1: The distribution of NHL with age



Sex The male to female ratio was 1 to 0.9

Disease Characteristics

Of the 127 patients, 126 patients had a known primary tissue involved. Nodal origin of NHL was in 97/126 (77%) of those patients with known primary tissue, and 29/126 (23 %) had Extra-nodal disease origin.

All 127 patients except for only one had the stage recorded as determined from the records. The most frequent stage was stage III with a total of 37/126 (29.4%) patients and stage I was the least frequent stage with 7/12 (5.6%) patients as shown in Table 1

Table 1: Distribution of clinical stage

Stage	I	IE	II	IIIE	III	IV	Total
No. of patients (n%)	7	15	28	14	37	25	126

	(5.6)	(11.9)	(22.2)	(11.1)	(29.4)	(19.8)	
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Histological Grade

Of all the patients, 93/127 (73.2%) patients had high grade NHL and 23/127 (18.1%) patients did not have a specified histological grade as shown in Table 2

Table 2: Distribution of NHL Histology grades

Histology Grade	Number of patients	(%)
High grade	93	(73.2)
Intermediate grade	1	(0.8)
Low grade	10	(7.9)
Grade not specified	23	(18.1)
Total	127	(100.0)

Of those patients 104/127 who had known specified histological grade, high grade NHL was the commonest grade found in 93/104 (89.42%) of the patients as show in table 2.

HIV serology status after staging investigation, (before starting treatment)

HIV serology status was known in 67/127 (52.8%) of the patients after completion of staging investigation. Of these patients with known HIV status 55/67(82%) were HIV positive and 12/67 (18%) were HIV negative. This included patients who came in with a known HIV status and those who were tested as part of the staging investigations, as shown in Table 3

Table 3: The distribution of HIV serology status and sex

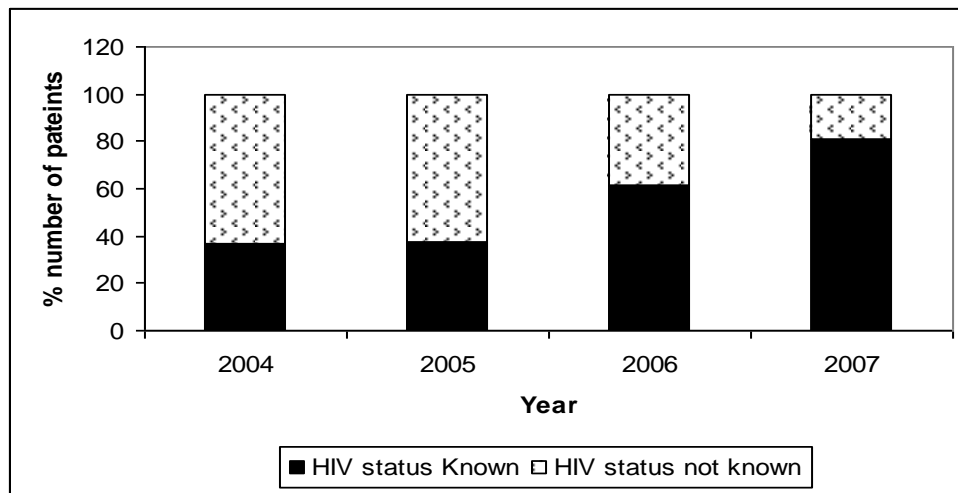
Sex	HIV positive n (%)	HIV Negative n (%)	HIV status unknown n (%)	TOTAL n
Male	28 (41.8)	8 (11.9)	31(46.3)	67
Female	27(45.0)	4 (6.7)	29 (48.3)	60
TOTAL	55(43.3)	12 (9.4)	60 (47.2)	127

Of the 55 HIV positive patients 28/55 (50.9%) were male and 27/55(49.1%) were female. More males tested HIV negative as compared to females (11.9% versus 6.7%), however this difference was not statistically significant.

Distribution of the knowledge of HIV serology before starting treatment

There was a steady increase in the number of patients who had a known HIV serology result before starting any treatment from 2004 to 2007. There was more than a 100% increase in patients who had known HIV serology from the 37.5% in 2005 to 80.8% in 2007 as shown in Fig 2.

Figure 2: Knowledge of HIV serology before starting treatment



ARV treatment in HIV positive patients

Of the 55 patients who were known to be sero-positive 25/55 (45.5 %) were already taking ARV's.

There was a marked increase in the number of patients who presented for NHL treatment on ARV with a peak in 2006 where 12/19 (63.2%) of the patients who were HIV positive presented for treatment already on ARV's as shown in Table 4

Table 4: The distribution of ARV treatment with year of presentation

Year	On ARV's n (%)	Not On ARV's n(%)	Total
2004	1(14.3)	6 (85.7)	7
2005	4 (33.3)	8 (66.7%)	12
2006	12 (63.2)	7 (36.8)	19
2007	8 (47.1)	9 (52.9)	17

Total	25 (45.5)	30 (54.5)	55

HIV and Histology grade

High-grade histology was the commonest grade in both groups of patients that either had a positive HIV status or whose status was not known. High-grade histology occurred in 46/55 (83.6%) who were HIV positive as compared to 42/60 (70%) of those whose HIV status was not known.

For those patients whose HIV status was known and had specified histology, HIV positive status was highly associated with high grade histology as compared to HIV negative status 46/47 (97.9%) versus (5/11) 45.5% ($p < 0.001$).

Table 5: The distribution of Histological grade with HIV serology

Histology Grade	HIV positive n (%)	HIV negative n (%)	HIV Not known n (%)	TOTAL n
High grade	46 (49.5)	5 (5.4)	42 (45.2)	93
Intermediate grade	0 (0.0)	1 (100.0)	0 (0.0)	1
Low grade	1 (10.0)	5 (50.0)	4 (40.0)	10
Not specified	8 (34.8)	1 (4.3)	14 (60.9)	23
TOTAL	55 (43.3)	12 (9.5)	60 (47.2)	127

HIV and stage

There was an association between stage and the HIV serology status of the patients. There was no extra-nodal disease in the HIV negative patients as compared to patients who were HIV positive or whose status was not known ($P<0.001$).

All 12 of the patients who were HIV negative were equally distributed in stages II, III, and IV as shown in

Table 6: The distribution of stage with HIV serology

Stage	HIV positive n (%)	HIV negative n (%)	HIV not known n (%)	TOTAL n
I	5 (71.4)	0 (0.0)	2 (28.6)	7
IE	8 (53.3)	0 (0.0)	7 (46.7)	15
II	7 (25.0)	4 (14.3)	17 (60.7)	28
IIIE	6 (42.9)	0 (0.0)	8 (57.1)	14
III	21 (56.8)	3 (8.1)	13 (35.1)	37
IV	8 (32.0)	4 (16.0)	13 (52.0)	25
TOTAL	55 (43.7)	11 (8.7)	60 (47.6)	126

HIV positive serology: CD4 count

The CD4 counts were only known in 19/55 (30.9%) of the patients who were HIV positive during the course of NHL treatment. Of patients these known CD4 counts 10/19(53.6) had a count less than or equal to 200 and 9/19 (47.4%) had a count of more than 200.

Symptomatic site

The overall most common symptomatic sites were the neck nodes found in 38/127 (29.9%) of all the patients followed by the aero-digestive tract (nasopharynx, oropharynx, oral cavity and hypopharynx.) with 14/127 (11%) patients. The axillary and the inguinofemoral region had the same frequency of 8.9% (11/127) each, however axillary, as a symptomatic site was not found in HIV negative patients. Inguinofemoral symptomatic disease was found in only 1/11 (9%) of the HIV negative patients as compared to 7/11(63.6%) of the HIV positive.

Only one of the HIV negative patients had symptomatic extra-nodal site as stage IV disease involving the skin.

Discussion

NHL is a one of the HIV-related malignances that presents a great challenge for management in resource constrained countries like ours facing an HIV epidemic. With the high number of patients seen at our center, our experience could have an impact in the management of lymphoma world wide if resources were permitting. A research done in Canada in 2007, showed that of 115 lymphoma treating physicians 99/115 (86%) had not seen more than 6 new cases of HIV related lymphoma [4] in the last 5 years, where as this study shows that of the 127 NHL patients seen, 55 patients had HIV related NHL over a period of 4 years. This number could be much more if all the patients had being HIV tested.

NHL constituted about 6,4% of all the cancers in Zimbabwe according to the National Cancer Registry [5]. In a resource constrained Zimbabwe, the HAART program is only just starting to gather momentum and it is going to take some time before we can start making our own comments about the effects of this program on NHL incidence. However there have being some conflicting information about the effect of ARV's on the incidents rate of NHL. Following the introduction of HAART the incidence of both Kaposi's sarcoma and primary cerebral lymphoma has fallen significantly in both registry linkage and cohort studies [6], this is thought to be secondary to the immune reconstitution that occurs with HAART [7]. In contrast, the effects of HAART on systemic NHL are less clear [8, 9] although some cohort studies suggest a modest non-significant decline in the incidence.

Age

In this study it was shown that NHL is more common between the ages of 21 and 50. This age group constituted about 70% of all the patients with NHL in this study. This age group is composed of the most sexually (20 to 40years) active and the most productive (20-50) age groups. This has an economic bearing since these patients seeking medical treatment lose a lot of working hours. This age distribution is also reported by other authors [10].

Sex

A slight male predominance was seen in this study and this was consistent with our cancer registry and virtually across all cancer registries [11].

Stage

The staging was performed using the Ann-Arbor classification, but none of the patients were adequately staged due to lack of resources and expertise. The missing investigations included the computerized tomography of the thorax, abdomen and pelvis. This facility, though present within the hospital, was not functional at most times and the charges were prohibitive for most of our patients. Private CT scans were even more expensive. Bone marrow biopsies were not offered to any of the patients during the period of this study as there was no government hematologist.

This issue of inadequate staging was not a problem unique to our setting, though in other systems other staging investigations were omitted at the discretion of the treating clinician. In a study of 270 patients in Manchester UK only 25% of the patients were completely staged [12].

Our showed that 37/127 patients were stage III whilst 25/127 patients were stage IV. There is a great chance that some of these stage III patients or even the earlier stages could be up-staged if all staging investigations including a bone marrow analysis were done.

Histology Grade

High-grade histology was the most common histology grade in this study, accounting for about 73% of all histology grades. Other studies have also shown an increase in high grade NHL, but it accounted for only about 20% of the newly diagnosed. The majority of the newly diagnosed NHL's were of intermediate grade followed by low grade [13]. The high rates of high grade NHL in this study were probably due to the HIV epidemic facing Zimbabwe. When histology was stratified according to HIV serology, it was shown in this study that 83.6% of the patients with high grade NHL were HIV positive. This high proportion of high-grade histology in HIV patients was also reported by many authors, including Frantz et al in a France study where this proportion is about 88% [14]

Symptomatic site

In this study extra-nodal symptomatic sites were shown to be highly associated with an HIV positive status or unknown HIV status. This tendency was also reported by Huy Tan [15]. Of interest was that HIV infection could determine the region of symptomatic nodes, as none of the patients with symptomatic axillary nodes was HIV negative.

None of the patients in this study had primary cerebral lymphoma; however the incidence of this entity has greatly increased in HIV patients in developed countries where CT scan and MRI scan facilities are available. There is a higher chance that most of the possible patients with this diagnosis are being managed by the internal medicine physician as CVA, tuberculomas or cerebral toxoplasmosis due to the unavailability of these imaging techniques. The body cavity lymphomas whose incidence is reported to be high in immune compromised patients were also not recorded in this study.

HIV testing and ARV's access

This study showed a marked increase in HIV testing from 2004 to 2007 in NHL patients. This marked increase of testing, particularly in NHL patients, was probably due to the increasing physician's appreciation of NHL as an HIV related malignancy during this period. The increase could also have been due to the increase in HIV testing of the general population due to HIV awareness programs and the increase in the number of Voluntary Counseling and Testing services (VCT's).

There was also an increased access to ARV's to those patients who were HIV positive in the study from 14%, 33%, 63% and 48% in 2004, 2005, 2006, and 2007 respectively. This seems to be consistent with the report from the Ministry of Health that the percentage of adults and children with advanced HIV infection receiving antiretroviral therapy increased from 8.0% to 17.7% and 38% in 2005, 2006, 2007 respectively [16].

Conclusion

This study shows that 82% (55/67) of the patients that were tested for HIV, were positive. There was a marked difference between the disease and patient's characteristics of HIV positive patients as compared to those of an HIV negative status. Given the limited access to antiretroviral drugs in our resource constrained country, we should be prepared to face an increased number of patients in need of co-treatment of both HIV and NHL, increasing the burden of the already constrained health care system in our country.

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References

- [1] Cote TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. *Int J Cancer*, 1997;73: 645-650
- [2] UNAIDS, 2006 Report on the Global AIDS Epidemic update, Sub-Sahara Africa
- [3] Chokunonga E, Levy LM, Bassett MT, et al AIDS and Cancer in Africa: the evolving epidemic in Zimbabwe. *AIDS* 1999 13:2583-2588
- [4] Matthew C. Cheung & Kevin R. Imrie & Physician perceptions and preferences in the treatment of acquired immunodeficiency syndrome (AIDS)-related lymphoma *Ann Hematol* (2007) 86:631–638
- [5] Chokunonga E, Borok M Z, Chirenje ZM, Nyakabau AM, Zimbabwe National Cancer Registry 2007 Annual report
- [6] Ledergerber B, Telenti A, Egger M. Risk of HIV related Kaposi's sarcoma and Non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study. *Br Med J* 1999;319:23–4.
- [7] Lederman M. Immune restoration and CD4+ T-cell function with antiretroviral therapies, *AIDS* 2001;15(Suppl. 2):S11–5.
- [8] Appleby P, Beral V, Newton R, Reeves G; International Collaboration on HIV and Cancer Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults, *J Natl Cancer Inst* 2000;92:1823–30.
- [9] Rabkin CS. AIDS and cancer in the era of highly active antiretroviral therapy (HAART) *Eur J Cancer* 2001; 37:1316–9
- [10] Non-Hodgkin lymphoma among young adults with and without AIDS in Italy, *Int J Cancer* 2001 Aug 1;93(3):430-5
- [11] Weisenburger DD (1994) Epidemiology of non-Hodgkin's lymphoma: recent findings regarding an emerging epidemic. *Ann Oncol* 5:19–2
- [12] James P. Wylie, Richard A. Cowan, David P. Deakin. The role of radiotherapy in the treatment of localized intermediate and high-grade non-Hodgkin's lymphoma in elderly patients. *Radiotherapy and Oncology* 49 (1998) 9–14
- [13] Palackdharry CS (1994) The epidemiology of non-Hodgkin's lymphoma: why the increased incidence? *Oncology* 8:67–73
- [14] Frantz Thiessard, Philippe Morlat, Catherine Marimoutou, Eric Labouyrie, Prognostic Factors after Non-Hodgkin Lymphoma in Patients Infected with the Human Immunodeficiency Virus. *Cancer* 2000; 88:1696–702
- [15] Tran H; Nourse J; Hall S; Green M; Griffiths L; Gandhi, Immunodeficiency-associated lymphomas, *Blood Reviews* (2008; 22(5):261-81
- [16] Zimbabwe's UNITED NATIONS GENERAL ASSEMBLY (UNGASS) REPORT on HIV AND AIDS 2008