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Review

Non-Hodgkin Lymphoma in Adults Living with HIV in Botswana: Morphology and Immunophenotypes

Gaone Abigail Moalosi[1,2,#,*], Lynnette Tumwine Kyokunda[2,3,#], Moses Rugemalila[2], Blessing Zambuko[4], Pier Paolo Piccaluga[2,5]

[1]Department of Molecular Medicine and Hematology, University of Witwatersrand Medical School and National Health Laboratory Service, Johannesburg Gauteng, South Africa

[2]Department of Pathology, Faculty of Medicine, University of Botswana, Gaborone, Botswana

[3]Department of Pathology, School of Medicine, Kabale University, Kabale, Southwestern Uganda, Uganda

[4]Department of Pathology, Faculty of Medicine, National University of Science and Technology, Bulawayo, Zimbabwe

[5]Biobank of Research, IRCCS Azienda Ospedaliera-Universitaria di Bologna Policlinico di S. Orsola, Bologna, Italy

[*]Corresponding author: Gaone Abigail Moalosi, abigailgm@yahoo.com

[#]These authors contributed equally to this work.

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Abstract

Background and Objective: The onset of the Human Immunodeficiency Virus/Acquired Immunodeficiency syndrome (HIV/AIDS) pandemic was marked by a rapid increase in aggressive non-Hodgkin lymphomas (NHLs). Botswana has made tremendous efforts in HIV control having surpassed the UNAIDS 90:90:90 target. In addition, commendable efforts have been made towards the elimination of mother-to-child transmission of HIV (eMTCT). There is limited data on immunophenotypes of non-Hodgkin lymphoma (NHL) in Botswana, it is therefore against this background that we sought to bridge that knowledge gap in Botswana. To determine the clinical, morphological and immunophenotypes of non-Hodgkin lymphoma in adults living with HIV (ALWH) in Botswana.

Methods: Archived pathology slides and reports of 131 ALWH who had a diagnosis of non-Hodgkin lymphoma were retrieved from the repository. Descriptive statistics were used to summarize the clinicopathological data: age, sex, HIV status, anatomical site of disease, histopathology and immunophenotype results. SPSS version 27.0 software package was used for data analysis. Fisher's exact test with a p-value of 0.05 was used to determine the significance of the findings.

Results: The majority of ALWH were male 78 (59.5%) while females were 53 (40.5%). The maximum incidence of NHL in both sexes was in the 41-60 years age group at 75/131 patients (57.3%). Most NHLs were of B-cell origin and accounted for 121 (92.4%), of which diffuse large B-cell lymphoma (DLBCL) was the most common subtype at 76 (58.0%) followed by Plasmablastic lymphoma (PBL) 32 (24.4%). T-cell lymphoma accounted for 10 (7.6%) in total with peripheral T-cell lymphoma not otherwise specified (PTCL/NOS) the most common. There was no statistically significant association between gender and NHL subtypes which were identified in the study including DLBCL and PBL (two-tailed, p=0.158).

Conclusion: DLBCL and PBL were the most common subtypes of NHL in ALWH in Botswana. Notably, the subtype distribution of NHL has not changed despite widespread anti-retroviral therapy (ART) use. This data further strengthens the existing knowledge on the distribution of NHL subtypes in ALWH in Botswana.

1. Introduction

1.1 Global Burden of NHL in HIV

HIV infection is associated with aggressive NHL. The global incidence of lymphoma increased by 3-4% annually and in developing countries, it is largely driven by the HIV/AIDS pandemic [1]. According to the GLOBOCAN 2020 estimates, NHL accounted for 544,000 new cases and 260,000 deaths globally in 2020 [2].

1.2 Regional and Botswana-Specific Data

Recent review on different lymphoma subtypes have shown that Burkitt lymphoma (BL) is the most common

childhood lymphoma accounting for 82%, while DLBCL was the most common lymphoma in adults accounting for 55% of cases [3,4]. Overall, in Southern Africa, there is a higher proportion of aggressive B-NHL compared to indolent ones [5,6]. A study on NHL in Southern Africa showed a significantly higher number of aggressive B-NHL cases at 51.1% and lower proportion of indolent B-NHL cases at 34.3% [5]. This contrasts with Western Europe (36.4% and 54.5% respectively) and North America (34.3% and 56.1% respectively) [5,6].

In Botswana, NHL closely follows Kaposi sarcoma (KS) and cervical cancer as AIDS defining malignancies [7]. NHL contributes to increased cancer-related morbidity and mortality in patients with HIV/AIDS in countries where it is highly prevalent [7-9]. The evolution of anti-retroviral drugs (ARV) [10] has significantly reduced the incidence of some AIDS-defining cancers and overall mortality from these conditions [7-9]. However, the mortality risk in ALWH when compared to HIV negative individuals remains poorer as shown in a study from British Columbia, Canada [11].

Although the prevalence of HIV in Botswana is still high, a notable decline has been registered since the introduction of dedicated nationwide ART comprehensive care was instituted in 2002. The prevalence of HIV is reducing and is now at 16.4% with 4,300 new infections and about 3,800 deaths. A total of 320 000 (93%) ALWH on ART [2]. According to The Fifth Botswna AIDS Impact Survey (BAIS V) report nationally, 95 percent of ALWH aged 15 to 64 years in Botswana reported knowing their status, 98 percent of people who knew their status were receiving ART, and 98 percent of adults receiving ART achieved viral load suppression by July 2022.

1.3 ART Rollout and Cancer Trends

According to the Global Cancer Observatory statistics (2020), NHL is amongst the top 10 cancers in Botswana with an incidence of 3.8 per 100,000, prevalence of 9.95 per 100,000 and mortality of 2.4 per 100,000 greater amongst males than females [12]. Clearly, the incidence of NHL increased since the beginning of the HIV/AIDS pandemic and reported incidences of 2- to 3-fold in some countries but reaching 13-fold in others from which 467 histological specimens were reviewed with 132 cases from Lacor in Uganda, 86 cases from Kenyatta National Hospital, 79 cases from Aga Khan University Hospital in Kenya, 92 cases from Muhimbili National Hospital in Tanzania, 44 cases from Obafemi Awolowo University in Nigeria and lastly 34 cases from University College, Ibadan in Nigeria [3]. Information on proportions of AIDS associated with NHL is scarce, but it is estimated that it could be as high as 50%, which is significant and markedly varies depending on the geographical region and different age groups [3].

1.4 Existing Gaps and Research Justification

Notably, there has been a decline in age-adjusted cancer incidence amongst ALWH mostly due to a decline in the KS cases between the years 2003 and 2008, but HIV-associated malignancy statistics remain unchanged in the aging HIV-infected population causing a strain on the health system [7]. Regarding HIV associated malignancy, much more attention has been geared towards addressing the increase in cervical cancer with much less attention towards NHL in Botswana [4]. While substantial attention has been given to cervical cancer among ALWH in Botswana, limited data exists on clinicopathological features of NHL in this population. In this study, we therefore sought to determine the clinicopathological characteristics of NHL, which will help bridge the knowledge gap that pre-exist.

2. Materials and Methods

2.1 Study Site

The study was conducted at the National Health Laboratory, Gaborone, Botswana. The laboratory conducts pathological investigation such as histopathology for Botswana's tiered health care system serving all primary, district and tertiary referral hospitals.

2.2 Study Population and Eligibility Criteria

All ALWH who were newly diagnosed with NHL by tissue biopsy during the period 2017-2021 were considered for this study. To ensure data quality and representative sampling, predefined inclusion and exclusion criteria were applied. Hence, eligible participants were all adult patients (aged ≥18 years) with a new diagnosis of NHL by tissue biopsy confirmed by a qualified histopathologist. Whereas cases were excluded if they had insufficient information, inconclusive histopathological or immunophenotypic findings, or if they represented relapsed or previously treated (follow up) patients.

2.3 Study Design

This study used a combination of a cross-sectional descriptive design with a retrospective element. The cross-sectional descriptive design was used to describe the clinical, morphological and immunophenotypes of NHL in ALWH diagnosed during the period 2017-2021. While retrospective patient data was used to identify characteristics of the population within the study period.

2.4 Data Collection and Management

Retrospective patient data retrieval from Integrated patient management system (IPMS) was used to identify patients previously evaluated for NHL from January 2017 to December 2021. IPMS is a comprehensive software solution used in all Botswana healthcare centres. It records and integrates patient demographics clinical information including results of all laboratory investigations done in order to provide a holistic view of a patient's records. IPMS was accessed from the National Health Laboratory, Gaborone, Botswana, which is the central laboratory in the country.

Of the 249 cases retrieved, 131 archived slides and reports of ALWH who had a diagnosis of NHL were included in the study according to the eligibility criteria. The sociodemographic and pathology data was recorded

which included: age, sex, HIV status, biopsy anatomical site of specimen, histopathology, and immunohistochemistry report findings. The principal investigator (GAM) extracted and selected reports which met the eligibility criteria, which were verified by the co-investigators. At least two experienced pathologists (LTK & PPP) revised the diagnoses according to the WHO 2022 [13]. The histopathological characteristics (assessed at H&E), and the immunophenotypic patterns (assessed by IHC) were used to identify the specific NHL subtypes. Immunophenotypic markers included CD3, CD5, CD10, CD20, CD23, CD30, CD38, CD79a, CD138, BCL1/CCND1, BCL2, BCL6, IRF4, TdT, ALK1 and Ki67/MIB1 (general proliferation index). The patient cancer data registries at Princess Marina Hospital, Gaborone, Botswana and Nyangabwe Referral Hospital Oncology Units, Francistown, Botswana were also searched to obtain missing demographic data for all HIV-infected patients diagnosed with NHL and this data included age, sex, and HIV status.

Confidentiality was maintained so that participants are not identifiable to persons not involved in the research. All patient identifiers removed from the final data analysis including the laboratory number. The data was anonymised with each patient given a study number different from the identifiable laboratory number. Only the researchers had access to the raw data.

2.5 Data Analysis

Descriptive statistics were used to summarize the sociodemographic data and match with anatomical site of disease, histopathology and immunophenotype results. Data were recorded in a Microsoft Excel spreadsheet (Version 16.78) and analysed using SPSS version 27.0 software. Normally distributed continuous data were presented as mean ± standard deviation (SD) and variables with non-Gaussian distribution as median [interquartile range (IQR)]. Categorical data were presented as frequencies and percentages Fisher's exact test was used when necessary for categorical variables which include NHL subtypes and a $p \leq 0.05$ was considered significant.

2.6 Ethical Considerations

This study was approved by the University of Botswana Institutional Review Board and permission to conduct the study was obtained from the Ministry of Health & Wellness Research and Development Committee (HPDME: 13/18/1).

3. Results

3.1 Sociodemographic and Anatomical Site Distribution

A total of 131 ALWH who had a diagnosis of NHL was studied, 78 (59.5%) were male, while 53 (40.5%) were female. The median age was 45 years (range 19-78 years). The age group 40-50 years was the most affected at 69/131(52.7%), while the least affected age group was <20 years (3% of the total) (Figure 1).

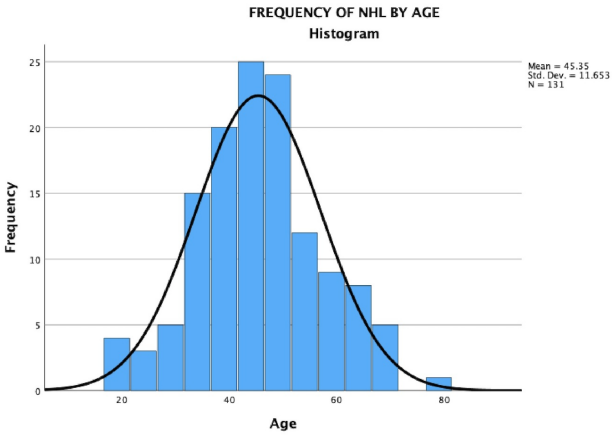

Figure 1. Distribution of 131 Non-Hodgkin Lymphoma cases in ALWH by age group (2017-2021).

The most common tissue biopsy site was lymph nodes (55%). Among the extra nodal sites; the gastrointestinal tract and nasopharyngeal were the most frequent (9.9% and 6.9% respectively) (Table 1).

Table 1. Distribution of 131 Non-Hodgkin Lymphoma cases in ALWH by nature of specimen (2017-2021).

Nature of Specimen	No. of patients (n)	% of NHL
A. Nodal site (lymph nodes)		
Non-specified anatomical site	66	50.4
Submandibular	3	2.3
Axilla	2	1.5
Inguinal	1	0.8
Total	72	55.0
B. Extra-nodal site		
Gastrointestinal tract	13	9.9
Nasopharyngeal	9	6.9
Oral cavity	8	6.1
Skin	6	4.6
Neck mass	5	3.8
Breast	5	3.8
Adnexa including ovarian tissue	2	1.5
Vulva	2	1.5
Arm mass	1	0.8
Back mass	1	0.8
Chest mass	1	0.8
Conjunctival growth	1	0.8
Intra-orbital tissue	1	0.8
Retroperitoneal mass	1	0.8
Total	56	42.7
C. Unknown		
Total	3	2.3

3.2 Distribution of NHL by Subtype

NHLs of B cell origin were the most common and accounted for 121/131 (92.4%) while the T-cell NHLs were 10 (7.6%). DLBCL was the most common of the B-NHLs (N=76, 58.0%) followed by PBL (N=32, 24.4%). Other subtypes identified were BL, follicular lymphoma (FL), chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), and mantle cell lymphoma (MCL) which accounted for 3.8%, 3.1%, 2.3% and 0.8%, respectively (Figure 2, Table 2). The most common T-NHL subtypes were PTCL/NOS, accounting for 5 cases (3.8%), and anaplastic large cell lymphoma (ALCL) (n=4, 3.1%).

Fisher's exact test was used to determine if there was any significant association between sex and the NHL subtype. There was no statistically significant association between gender and NHL subtypes which were identified in the study including DLBCL and PBL (two-tailed, p =0.158).

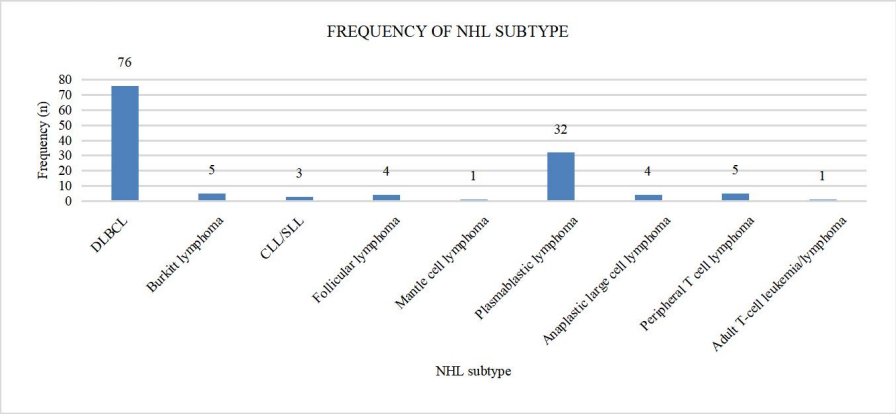

Figure 2. Distribution of 131 Non-Hodgkin Lymphoma cases in ALWH by histopathological and immunophenotype (2017-2021).

3.3 Immunohistochemical Analysis of NHL in Botswana

All DLBCLs were positive for both CD19 and CD20, while all T-NHL were CD3 positive. DLBCL had a high proliferation index as indicated by high Ki67/MIB index with a median value of 80%. The PBLs were 32 (24.4%). They tested CD138 and MUM1 positive. Five cases of BL were recorded; they all had very high proliferation rate indices (>95%) with expression of BCL6, CD10, and MYC, while BCL2 was never expressed. In fact, 1 case was initially misdiagnosed as squamous cell carcinoma after a wide local excision, based on morphology only but were later recognized to be NHL by immunophenotyping.

Table 2. Immunophenotypic pattern of NHLs.

Lymphoma type	# of cases	CD 3	CD 5	CD 10	CD 19	CD 20	CD 23	CD 30	CD 38	CD 79a	CD 138	BCL1/ CCND1	BCL 2	BCL 6	MUM1 /IRF4	TdT	ALK 1	Ki67
		% of positive cases																Average %
DLBCL	76	24	11	25	22	91	3	11	ND	20	1	ND	20	29	17	1	1	75
Burkitt lymphoma (BL)	5	0	20	80	0	100	0	0	ND	0	0	ND	0	80	0	0	0	97.5
CLL/SLL	3	67	100	0	67	100	33	0	ND	33	0	ND	17	33	0	0	0	25
Follicular lymphoma (FL)	4	75	0	75	75	75	50	0	ND	25	0	ND	75	75	25	0	0	41
Mantle cell lymphoma (MCL)	1	0	100	0	100	100	0	0	ND	0	0	ND	100	0	0	0	0	ND
Plasmablastic lymphoma (PBL)	32	34	3	13	0	9	3	9	ND	19	31	ND	6	0	47	3	0	89.2
Anaplastic large cell lymphoma (ALCL)	4	25	25	0	0	25	0	100	ND	25	0	ND	0	0	0	0	0	80
Peripheral T cell lymphoma	5	60	40	60	0	20	0	0	ND	0	20	ND	20	0	0	0	0	99
Adult T-cell leukemia/lymphoma	1	100	100	0	0	0	0	100	ND	0	0	ND	100	0	0	0	0	ND
ND - Not done																		

4. Discussion

The global incidence of lymphoma has increased by 3-4% annually, and in developing countries the increase has been largely driven by the HIV/AIDS pandemic [1]. The national ART policy in Botswana was introduced in 2002, extending the eligibility for ART to all ALWH [14]. In countries with a high prevalence of HIV like Botswana, NHL contributes to increased cancer-related morbidity and mortality in ALWH [7-9]. Despite Botswana being a high HIV prevalence country, NHL has not had much attention in regard to research done when compared to other AIDS-related malignancies such as cervical cancer and KS. KS has dramatically decreased with ART therapy and cervical cancer ahas received tremendous attention for control through the anti-HPV vaccination school administration for teenage girls in Botswana as well as extensive screening and testing using VIA and colposcopy as well as biopsy and

cytology were indicated. Current practice demands that for hematological malignancies, there must be incorporation of clinical, morphologic, immunologic and genetic data in reporting lymphomas as described in the WHO classification [13] which information supports comprehensive targeted treatment modalities currently available. In Western countries, the general outlook for lymphomas has improved drastically with these therapies. This was demonstrated to translate into significantly better clinical outcomes providing reduced unwanted toxicities of chemotherapy. In the current study, the majority of patients were over 40 years of age, this is in line with what others have found that HIV-related malignancies are more common in adults and elderly when compared to children and adolescents. Males were more affected than females (M:F ratio 1.5:1), this compares well with what other authors have found [15]. Similar results have been found in a South African and Nigerian studies with 57.5% (vs. 59.5%) of males affected and a median age of 41 years (vs. 45 years) [5] and male: female ratio was 2:1 and a mean age 44.4 years, respectively [16]. The former study was included three institutions in two countries in Southern Africa including South Africa (Cape Town and Johannesburg) and Zimbabwe (Harare) while the latter study data was collected from tertiary facilities of three different geopolitical areas in Nigeria: University College Hospital, Ibadan, Oyo State, Enugu State University of Science and Technology Teaching Hospital (ESUTH), and Meena Histopathology and Cytology Laboratory, Jos, Plateau State. A higher male preponderance has been noted in studies India of 2.2-2.8:1 [17].

Recent studies on HIV in Botswana have shown prevalence rates of 16.4% in adults aged 15 to 49, of which, 21.1% are female and 11.8% are male (Male to female ratio of 1:2) [2]. This strongly indicates that the occurrence of lymphomas in males is not related to a higher frequency of HIV infection but should be rather referred to other (intrinsic or extrinsic) factors that need to be assessed. However, previous studies have shown that males tend to have a higher likelihood of cancer when compared to females [2]. The higher male preponderance as far as cancer incidence is concerned has been related to chromosome Y increases cancer risk for men. Caceres and colleagues analysed extreme down-regulation of chromosome Y (EDY) and cancer status association in 19 studies involving 9336 individuals [18]. They found a strong association between EDY gene expression and cancer risk in men (odds ratio [OR] 3·66 [95% CI 1.58-8.46]; p=0.002), particularly strongest when comparing EDY in tumour versus normal tissue (OR 8.33 [95% CI 3.30-20.89]; p<0.0001), using transcriptomic data [18]. However, interpretation of these results warrants caution. First, the analysis spans multiple studies with varied cancer types, which introduces heterogeneity that may not directly apply to lymphoma specifically. The stronger association observed in tumor versus normal tissue samples might reflect tumor-specific genomic alterations but does not establish causality. Moreover, the exclusive focus on transcriptomic data leaves out epigenetic, immunological and hormonal factors that may also contribute to the sex disparities in cancer. The biological complexity of lymphoma, particularly its interaction with the immune system, may not be fully captured by EDY analysis alone. Other important confounding variables acknowledged but not addressed in-depth include, differences in ART adherence, con-infections with EBV and behavioural factors (e.g., tobacco use, health-seeking behaviour, sexual activity) may all independently influence lymphoma risk.

Therefore, while EDY may offer mechanistic insight into male vulnerability to certain malignancies, it is insufficient as a stand-alone explanation for the observed male predominance in lymphoma. Future research should incorporate multifactorial models that consider genetic, behavioural, viral, and socio-structural influences in tandem to more accurately explain sex-based differences in lymphoma incidence.

A slight majority of NHLs recorded in this study were of nodal origin (50.4%). This is consistent with what was found in previous studies. Whereas the extra-nodal location accounted for 24-48% of all HIV-associated NHL, with higher prevalence in China and Japan [15]. Unlike our findings, which identified the gastrointestinal tract as the most frequent site of extranodal involvement, other studies have reported the central nervous system (CNS) as the predominant extranodal site, followed by the gastrointestinal tract [19]. Unfortunately, Botswana lacks a dedicated neurosurgery practice and most patients with brain tumours are referred to other countries for neurosurgical care, this could account to the lack of CNS lymphomas in our study. HIV-associated lymphomas are usually aggressive B-cell malignancies such as DLBCL, BL and PBL [20]. This study reported B-cell lineage NHL as the most common, with DLBCL accounting for 63% of cases, followed by PBL (26%).

However, the distribution of NHL subtypes was slightly different from what we observed. In their series, in fact, while DLBCL was the most common subtype (38.2% vs. 58%), it was followed by FL (18.1% vs. 3.1%), PTCL (9.7% vs. 3.8%), and CLL/SLL (8.4% vs. 2.3%) [5]. However, this study did not consider the patient's HIV status, thus reflecting the overall frequency of lymphomas in the Southern African population, of course affected by HIV as relevant risk factor. A review of different lymphoma subsets showed BL as the most common childhood lymphoma accounting for 82% of cases, while DLBCL was the most common lymphoma in adult (55% of all cases) [3]. Our study only focused on patients aged >18 years which explains why a sparingly and rare finding of only one BL. In our study, PBL was quite frequent (24% of all cases) second only to DLBCL, confirming its high incidence in HIV-positive patients [20,21]. The most common site of NHL was nodal with 55% of all the cases, this was followed by gastrointestinal tract with 9.9% and nasopharyngeal with 69%. This compares well with multiple studies in which most common extranodal sites were GI tract (40/122) mainly in severely immunosuppressed patients [22,23]. FL and CLL/SLL, by contrast, seems to be more common in countries with a higher socioeconomic status and in the non-HIV setting [6,15].

A study conducted in Botswana on primary cutaneous lymphoma, reported as a heterogenous collection of non-Hodgkin lymphomas originating in the skin [24]. They identified 27 cases of cutaneous lymphoma and some of the common subtypes identified included mycosis fungoides (81.5%), PBL (7.4%) and PTCL/NOS (3.7%). A prospective observational study from Botswana reported that 58.7% of NHL cases amongst 104 patients were DLBCL [8] and a retrospective analysis involving 2225 cases of lymphoproliferative disorders in South Africa had shown that 29.1% were DLBCL of which 80% were infected with HIV [9,25] These findings compare well with what our study found that DLBCL was the most common adult NHL (in general, in Southern Africa, and in HIV-positive patients). A study was conducted between October 2010 and August 2016 and 104 patients were enrolled, 72% of which were ALWH [9]. At that time, ARV was not well distributed in Botswana yet. Interestingly, the present study, enrolling cases from 2017 to 2021, expanded way beyond the pre-ARV era, and showed that HIV-associated lymphomas did not significantly change over time. This confirms that the pathobiology of NHL in the HIV setting is more complex and not limited to the decreased immunosurveillance. HIV viremia and the depth of CD4 nadir both raise the risk of lymphoma, also driving the exposure to antigen stimulation, and the (re)emergence of latent pathogens like herpes viruses (most but EBV). In fact, co-infection with HHV8, HBV/HCV, and EBV, as well as the loss of EBV-specific immunity are well established risk factors [26]. In addition, there is also compelling evidence that HIV may directly induce lymphomagenesis [26].

Among T-cell lymphomas, PTCL/NOS was the most common subtype (3.8%) and this is supported by a comparative review study of 487 cases done in Southern Africa (9.7%) [5]. In addition, a recent study on 32 PTCLs from 3 Sub-Saharan countries (Kenya, Uganda and Botswana) found that 94% of those cases were PTCL/ NOS, and half of the patients being HIV positive [27]. Supplementary Table 1 shows a comparison of the frequesncy of different NHL subtypes across African countries and India.

A study in Botswana that described trends in the incidence of cancer in Botswana during implementation of the first ART program and analysis using surveys and data from 2003-2008, during active cancer surveillance. The authors found that 45.4% of all malignancies in males and 36.4% of all cancers in women over this period were related to HIV, with 61.6% of cancer diagnoses being made among ALWH. In the PLWH population, age-adjusted cancer incidence dropped by 8.3% per year (95% CI -14.1 to -2.1%). Nonetheless, the annual number of cancer diagnoses was steady (0.0% annually, 95% CI -4.3 to +4.6%) despite an increasingly older and larger HIV population [7]. This indicated an overall increase of HIV-independent cancers. In particular, the incidence of NHL (+11.5% yearly, 95% CI +6.3 to +17.0%) and HPV-associated malignancies increased (+3.9% annually, 95% CI +1.4 to +6.5%) in the general population, while the incidence of KS declined (4.6% annually, 95% CI -6.9 to -2.2) [7].

A similar program was implemented in Malawi in 2016 and a study to explore the impact or ART pre and post ART universal therapy was done. Individuals who have histological confirmation of incident lymphoproliferative disorders were included in a clinical observation cohort and at the time of diagnosis, a comprehensive clinicopathological assessment was performed. A total of 412 participants were divided into 156 (38%) pre-universal ART (2013-June 2016) and 256 (62%) post-universal ART (July 2016-2020) and half of each group was HIV-positive [28]. They found no significant differences in pre- and post-ART lymphoma distribution, the most common entities being DLBCL (48% vs. 43%), indolent NHL (12% vs. 11%), HL (11% vs. 8%), and BL (8% vs. 11%) ($p = 0.61$) [28].

Despite the notable success of ART scale-up and viral suppression efforts in many high-burden countries-including Botswana-HIV-associated malignancies such as NHL continue to pose a significant clinical challenge, particularly among ALWH. This study is important because it highlights that HIV control alone does not eliminate the risk of oncogenic complications, especially in individuals with long-standing immune dysregulation, delayed ART initiation, or co-infections. Moreover, emerging data-including findings from this study-suggest that NHL can and does occur even in the setting of viral suppression, although risk may be somewhat reduced. This indicates that immune restoration may be incomplete or delayed, and factors such as chronic immune activation, past immune damage, and oncogenic viral co-infections (e.g., EBV) may continue to drive lymphomagenesis in this population. Therefore, NHL remains a concern even in well-managed HIV cases. Lastly, there is limited data on the spectrum and characteristics of NHL among ALWH in sub-Saharan Africa, particularly in the context of improved ART coverage. Most existing studies focus on adults, with adolescent-specific data remaining sparse. This study fills a critical local gap by:

- Providing recent data on NHL subtypes.
- Offering insight into whether current HIV management strategies are translating into reductions in NHL burden in this age group, but more research is required to further explore this.
- Informing clinicians and policymakers about the need for ongoing cancer surveillance, early diagnosis, and targeted lymphoma care models even in the ART era.

5. Conclusion

In conclusion, this study found that aggressive B-cell lymphomas-particularly DLBCL and PBL-remain the predominant subtypes of NHL among ALWH in Botswana during the study period from 2017 to 2022, similar to that seen at the beginning of the pandemic. Males were more affected than females. Indolent subtypes were rare, while PTCL/NOS was the most common T-cell lymphoma subtype.

Abbreviations

AIDS: Acquired immunodeficiency syndrome

ALCL: Anaplastic large cell lymphoma

ALWH: Adults living with HIV

ART: Anti-retroviral therapy

ARV: Anti-retroviral drugs

BAIS V: The Fifth Botswana AIDS Impact Survey

BL: Burkitt lymphoma

CI: Confidence interval

CLL/SLL: Chronic lymphocytic leukemia/ small lymphocytic lymphoma

CNS: Central nervous system

DLBCL: Diffuse large B-cell lymphoma

EBV: Epstein barr virus

EDY: Extreme down-regulation of chromosome Y

eMTCT: Elimination of mother-to-child transmission of HIV

FL: Follicular lymphoma

GAM: Gaone Abigail Moalosi

HIV: Human immunodeficiency virus

HPDME: Health & Wellness Research and Development Committee

HPV: Human papilloma virus

H&E: Hematoxylin and eosin

IHC: Immunohistochemical

IPMS: Integrated patient management system

IQR: Interquartile range

KS: Kaposi sarcoma

LTK & PPP: Lynette tumwine kyokunda and pier paulo piccaluga

MCL: mantle cell lymphoma

NHL: Non-hodgkin lymphoma

NHLs: Non-hodgkin lymphomas

OR: Odds ratio

PBL: Plasmablastic lymphoma

PLWH: People living with HIV/AIDS

PTCL/NOS: Peripheral T-cell lymphoma not otherwise specified

SD: Standard deviation

VIA: Visual Inspection with Acetic acid

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Conflict of Interest

The authors declare no conflicts of interest.

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Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

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Supplementary Data

Supplementary Table 1. Comparison of the frequency of different NHL subtypes across African Countries and India.

Source	Study Area	B-cell NHL	T-cell NHL
Current Study	*Botswana*	*92.4%*	*7.6%*
Perry *et al.* (2015) [5]	Southern Africa	85.8%	14.2%
Mantina *et al.* (2010) [25]	South Africa	83%	3.5%
Polepole *et al.* (2021) [1]	Zambia	92.5%	7.5%
Padhi *et al.* (2012) [19]	India	96%	4%
Roy *et al.* (2013) [29]	India	54%	38%
Sharma *et al.* (2014) [30]	India	89.3%	10.7%