Changing Pattern of Lymphoma Subgroups at a Tertiary Academic Complex in a High-Prevalence HIV Setting: A South African Perspective

Tracey M. Wiggill, MBBCh, MMed (Haem), Hamakwa Mantina, MD,* Pascale Willem, MD, PhD,* Yvonne Perner, MBBCh, FCPath (Anat Path),† and Wendy S. Stevens, MBBCh, MMed (Haem), FCPath (Haem)**

Background: HIV infection has been associated with an increased risk of non-Hodgkin lymphoma, particularly in the first world. Despite the high burden of HIV infection in sub-Saharan regions, published data on HIV and malignancies are sparse from these areas.

Materials and Methods: We recently published data on lymphomas diagnosed from January 2004 to December 2006, at a single center in Johannesburg, to serve as a baseline for long-term comparison during the period of highly active antiretroviral therapy rollout. We report a retrospective analysis of the follow-up data collected from January 2007 to December 2009 at the Johannesburg academic hospital complex (Gauteng, South Africa).

Results: There were 2225 new diagnoses of lymphoproliferative disorders made during 2007–2009 as compared with 1897 cases diagnosed during 2004–2006. A significant increase in both high-grade B-cell lymphomas and Hodgkin lymphoma was documented during 2007–2009. This was associated with a statistically significant increase in HIV prevalence in those tested (from 44.3% in 2004–2006 to 62.0% in 2007–2009). HIV-positive patients presented at a statistically significantly younger median age and showed a relative overrepresentation of females when compared with HIV-negative patients. HIV-positive patients were diagnosed at later stages of HIV infection when compared with patients in the first world.

Conclusions: The pattern of lymphoma subtypes and the demographics of the patients diagnosed have altered in association with significantly increased HIV prevalence. These changes have important public health implications. In particular, scale-up and earlier access to highly active antiretroviral therapy is essential with continued monitoring as access to therapy improves.

Key Words: lymphoma, HIV, South Africa, third world

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INTRODUCTION

The link between HIV infection and an increased risk of non-Hodgkin lymphoma has been well described, particularly in first world settings. Before the introduction of highly active antiretroviral therapy (HAART), the increase in relative risk was estimated to be greater than 100-fold overall for all subtypes of lymphoma and greater than 600-fold for diffuse large B-cell lymphoma (DLBCL) in the developed world.[1,2] Approximately 67% of individuals living with HIV reside within the sub-Saharan African region.[3] Despite this, there are little published data on HIV-related lymphomas in this population with available data suggesting an increase of only five- to 10-fold.[4–7] The limited literature available on HIV-associated malignancies is compounded by other weaknesses in this region such as poorly resourced national cancer registries[8–10]; inaccuracies in data collection[2]; failure to link cancer registry data with HIV databases as has been described in the Western world[7,10,11]; and the lack of diagnostic capability in resource-constrained settings.[5,10,12]

South Africa has a number of features that make it valuable to assess HIV-associated lymphomas in this region. It has the highest number of HIV-infected people worldwide, estimated to be 5.7 million people in 2008.[3] The national HIV prevalence among women attending antenatal clinics aged 15 to 49 years is reported as 29.3% and the prevalence in the 15-to 49-year age group has been estimated to be approximately 16.9% (2008 data).[13,14] HAART has only recently become accessible to patients in this region and was only rolled out nationally in 2004.[14,15] UNAIDS data for 2007 suggested that only approximately 28% of those requiring HAART were actually on therapy in South Africa[16]; thus, a large proportion of our patients is HAART-naïve and a malignancy may still be the presenting diagnosis.

We recently published data on lymphoproliferative disorders (LPD), diagnosed from January 2004 to December 2006, at a single academic center in Johannesburg, South

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From the Departments of *Molecular Medicine and Haematology and †Anatomical Pathology, National Health Laboratory Service and University of the Witwatersrand, Johannesburg, South Africa.
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Correspondence to: Tracey M. Wiggill, MBBCh, MMed (Haem), Room 3B18, 3rd floor Wits Medical School, 7 York Road, Parktown, Johannesburg, 2000, South Africa. e-mail: tracey.wiggill@nhls.ac.za.
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Africa,[12] to serve as a baseline for long-term comparison during the period of HAART rollout. The current article reports the follow-up data collected from January 2007 to December 2009 and extends the research to the Johannesburg academic hospital complex (Gauteng, South Africa).

METHODS

Study Design, Sample Population, and Data Collection

A retrospective study was performed that screened all pathology reports for samples referred to the Departments of Molecular Medicine and Haematology and Anatomical Pathology at the Johannesburg Academic Complex of Hospitals (South Africa) during the period under review (January 2007 to December 2009). This complex includes the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH, a major quaternary referral hospital, which accepts referral work from other centers), Helen Joseph Hospital (a secondary level hospital with oncology services, which refers all histopathology and immunophenotyping samples to CMJAH), and Chris Hani Baragwanath Hospital (a tertiary hospital serving the Soweto region with histopathology services but not immunophenotyping facilities; immunophenotyping is referred to CMJAH). This report concentrates primarily on data collected from 2007 to 2009 at CMJAH and Chris Hani Baragwanath Hospital but uses previously published data from January 2004 to December 2006[12] as a baseline for comparison (cases that were diagnosed only on a histopathologic basis at Chris Hani Baragwanath Hospital were not included in the 2004–2006 data). The major inclusion criterion into the study was a new diagnosis of a LPD (including plasma cell dyscrasia [PCD] and acute lymphoblastic leukemia) made on histopathologic biopsies or hematologic/flow cytometric material. Data were collected through a comprehensive database search of each hospital's laboratory information system (DisaLab Version 04.16.04.373) and through the www.disa database search tool (web site https://labresults.nhls.ac.za/) hosted by the National Health Laboratory Service, allowing access to data on referred samples.

Limited demographic and clinical information was collected for each newly diagnosed patient, including age, sex, referral site, and comprehensive pathology findings. Where available, the following data were collected from the Laboratory Information system: 1) HIV status: based on history provided by the referring clinician and/or results of enzyme-linked immunosorbent assay HIV serology and/or on a quantitative RNA-based HIV-viral load and/or on a qualitative DNA-based HIV polymerase chain assay; 2) CD4 count at presentation measured through a variety of flow cytometric platforms using the PanLeucogating method (Beckman Coulter, Miami, FL)[17,18]; 3) viral load at presentation measured by a variety of techniques including Easy-Q (Biomerieux, Lyon, France) and Roche Amplicor HIV-1 RNA test Version 1.5 (Roche Molecular Systems, Branchburg, NJ); and 4) history of HAART therapy.

Ethics approval was given by the Ethics Committee of the University of the Witwatersrand (ethics approval numbers: M0-61110: 2006-2011 and M090441: 2009-2014).

Tumor Classification

All LPDs were classified using the World Health Organization criteria published in 2001.[19] An updated classification system was introduced in 2008,[20] but we used the 2001 system throughout to prevent introduction of lymphoma classification bias. Results of all diagnostic investigations (morphology, histopathology, immunophenotyping, conventional cytogenetics, fluorescence in situ hybridization, and other molecular investigations) were correlated if available. Where comprehensive investigations were unavailable and accurate classification was not possible, cases were assigned to the subgroups of LPD not otherwise specified (BLPD NOS), or BLPD, low or high grade. Many of these diagnoses were based on immunophenotypic data alone, because no histopathology samples were received on these cases.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism Version 4.03 for Windows (GraphPad Software, San Diego, CA; www.graphpad.com). The Mann-Whitney or two-sample *t* test were used to assess differences between two groups where data were continuous. One-way analysis of variance tests were performed when assessing more than two groups of data with Bonferroni posttest comparison. Categorical variables were assessed using chi-squared or Fisher exact test. Differences between the results of comparative tests were considered statistically significant if the two-sided *P* value was <0.05.

RESULTS

Lymphoproliferative Disorders Diagnosed

During the 3-year period of January 2007 to December 2009, 2225 cases of LPDs were diagnosed as compared with 1897 cases diagnosed during the previously published period (January 2004 to December 2006).[12] DLBCL remained the most commonly diagnosed LPD in our setting with 648 (29.1%) new cases diagnosed during the period of review. Other LPDs also increased during the later time period when compared with the 2004–2006 period. These include the aggressive high-grade B-cell lymphomas (DLBCL, DLBCL plasmablastic variant and Burkitt leukemia/lymphoma [BL]); Hodgkin lymphoma (HL); PCDs; and some of the T-cell lymphoproliferative disorders. Conversely, the number of cases of low-grade LPDs, including small lymphocytic lymphoma/chronic lymphocytic leukemia, diagnosed has decreased. See Figure 1 and Supplemental Figure 1 (**Supplemental Digital Content 1**, http://links.lww.com/QAI/A133) and Table 1.

HIV Prevalence in the Patient Cohort

The overall HIV prevalence in the 2007–2009 patient cohort where an HIV result was available (n = 1233) was 62.0% (95% confidence interval [CI], 59.3–64.7). This is a statistically significant increase when compared with the patient cohort with an HIV result available during 2004–2006 (n = 709), in which 44.3% (95% CI, 40.7–48) of patients tested were HIV-positive ($P < 0.0001$). Statistically significant increases in HIV prevalence between the two cohorts were also

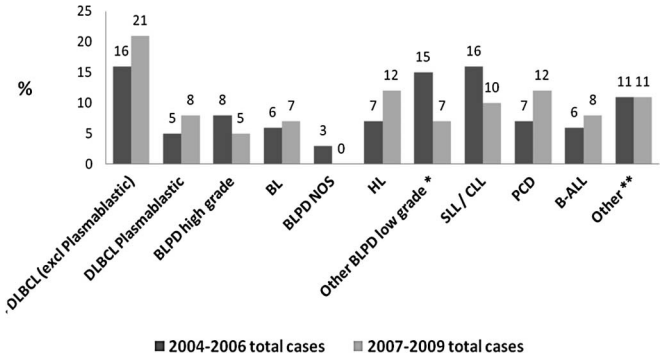

FIGURE 1. Column chart demonstrating the percentages of the different lymphoma subgroups diagnosed during 2004–2006 as compared with 2007–2009. During 2007–2009, the percentage of high-grade lymphomas and Hodgkin lymphoma had increased, whereas low-grade lymphomas had decreased. *Other BLPD low-grade cases include: BLPD low grade; follicular lymphoma; mantle cell lymphoma; mucosa-associated lymphoid tissue (MALT) lymphoma; and lymphoplasmacytic lymphoma. **Other cases include: precursor T-cell acute lymphoblastic leukemia; other ALL; anaplastic large cell lymphoma; T-cell lymphoproliferative disorder; and primary effusion lymphoma. DLBCL, diffuse large B-cell lymphoma; DLBCL (excluding plasmablastic): DLBCL (excluding plasmablastic lymphoma); BLPD NOS, B-cell lymphoproliferative disorder not otherwise specified; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; HL, Hodgkin lymphoma; PCD, plasma cell dyscrasia; BL, Burkitt leukemia/lymphoma; B-ALL, precursor B-cell acute lymphoblastic leukemia.

noted for the DLBCL ($P = 0.005$) and the BLPD NOS ($P = 0.02$) subgroups. Of note, the HIV prevalence in the HL subgroup ($P = 0.06$) fell just short of statistical significance.

Demographic Data of the Patient Cohort

The median age at diagnosis for all patients diagnosed during 2007–2009 was 41 years, which is statistically significantly younger than the median age of 46 years for patients diagnosed during the earlier period ($P < 0.0001$). Interesting patterns emerged when these data were further subdivided on the basis of HIV infection and sex. HIV-positive patients presented at a median age of 36 years, whereas their HIV-negative counterparts presented at a statistically significantly older median age of 47 years ($P < 0.0001$). The sex (male:female) ratios were also statistically significantly different when comparing HIV-positive (male:female ratio = 1:1) and -negative (male:female ratio = 1.4:1) patients ($P = 0.0012$) as were the peak ages of presentation. HIV-negative patients present with a bimodal age peak pattern with peaks occurring in those less than 15 years of age and then again in the 50- to 59-year age group. HIV-positive patients showed a single modal peak in the 30- to 39-year age group. These data are shown in Figure 2.

Analysis of HIV-positive patients demonstrated that HIV-positive females presented with lymphoma at a statistically significantly younger median age of 35 years when compared with HIV-positive males (median age 38 years; $P = 0.0004$). Analysis of the data using age ranges showed that in the 15- to 29-year age group, HIV-positive females predominate when compared with HIV-positive males (male:female ratio = 0.6:1) and equal ratios (male:female=1:1) were noted in the 30- to 39-year age group. These data are presented in Figure 3. In HIV-negative patients with lymphoma, this pattern was reversed with females presenting at an older age (median, 52 years) when compared with HIV-negative males (median age at presentation 43 years; $P = 0.0001$).

Overview of the Viral Status of the HIV-Positive Patient Cohort

The median CD4 count at diagnosis for those patients with a result available (n = 784) for the entire study period (2004–2009) was 118 $\times$ 10^6 cells/L (mean, 165.4 $\times$ 10^6 cells/L). No statistically significant difference in CD4 count was noted for those diagnosed during 2004–2006 (median CD4, 107; n = 181) as compared with those diagnosed during 2007–2009 (median CD4, 122; n = 603). There were also no statistically significant differences noted in median CD4 count when comparing values for those diagnosed during 2007, 2008, or 2009. Likewise, the CD4 count at presentation was not statistically significantly different for males (median CD4, 122; n = 402) compared with females (median CD4, 116; n = 382).

The median viral load (VL) at presentation in those patients who had an available result and a detectable viral load (n = 296) was 70,000 copies/mL (mean VL, 336,931 copies/mL; range, 27–4,800,000 copies/mL). Twenty-nine percent of all patients tested showed evidence of viral suppression (VL less than 1000), whereas 60% of those tested had a VL greater than 10,000 copies/mL. Viral suppression (VL less than 1000) at presentation showed a statistically significant increase over the years under review (2007–2009): from 22% in 2007 to 38% in 2009 ($P = 0.03$).

Different patterns were noted for the different lymphoma subgroups: patients with DLBCL were statistically significantly older (median age, 38 years) than their counterparts with BL (median age, 33 years) ($P < 0.001$) and HL (median age, 35 years) ($P < 0.01$). Considering only patients with CD4 counts available, patients with DLBCL showed statistically significantly lower CD4 counts at presentation (median CD4, 109 $\times$ 10^6/L) than those with BL (median CD4, 176 $\times$ 10^6/L) ($P < 0.001$). Patients with HL were the most likely subgroup to be virologically suppressed at presentation (50% of those tested had a VL less than 1000), whereas only 13% of patients with BL and 26% of patients with DLBCL had VL less than 1000, respectively ($P = 0.0006$). Refer to Figure 4 for further information.

DISCUSSION

We recently reported baseline data on LPDs diagnosed during 2004–2006 at an academic center in Johannesburg, South Africa.[12] The current article presents the follow-up data collected from 2007 to 2009, allowing comparison of the trends noted during the early period of HAART rollout. The pattern of lymphomas and the demographics of the patients diagnosed in our setting have shown differences in association with statistically significantly increased HIV prevalence during 2007–2009. HIV prevalence in those tested for the

TABLE 1. Lymphoproliferative Disorders (LPD) and Associated HIV Prevalences in Each Category of Lymphoma Diagnosed During 2004–2006 and 2007–2009

	2004–2006			2007–2009		
LPD	New Cases No. (%)	Cases With HIV Results No. (%)	HIV Prevalence in Those Tested No. (%) 95% CI	New Cases No. (%)	Cases With HIV Results No. (%)	HIV Prevalence n Those Tested No. (%) 95% CI
DLBCL	401 (21.1%)	169 (42.1%)	135 (79.9%) 73.2–85.3§	648 (29.1%)	453 (69.9%)	411 (90.7%) 87.7–93.1§
BLPD*	330 (17.4%)	105 (31.8%)	62 (59.0%) 49.5–68.0‖	154 (6.9%)	71 (46.1%)	54 (76.1%) 64.9–84.6‖
SLL/CLL	294 (15.5%)	79 (26.9%)	4 (5.1%) 1.6–12.7	230 (10.3%)	50 (21.7%)	3 (6.0%) 1.4–16.8
HL	137 (7.2%)	52 (38.0%)	24 (46.2%) 33.3–59.5¶	264 (11.9%)	194 (73.5%)	118 (60.8%) 53.8–67.4¶
PCD/myeloma	127 (6.7%)	62 (48.8%)	5 (8.1%) 3.1–17.9	259 (11.6%)	136 (52.5%)	19 (14.0%) 9.1–20.9
BL	117 (6.2%)	72 (61.5%)	62 (86.1%) 76.1–92.5	150 (6.7%)	115 (76.7%)	106 (92.2%) 85.6–96.0
B-ALL	117 (6.2%)	55 (47.0%)	2 (3.6%) 0.3–13.0	172 (7.7%)	67 (39.0%)	3 (4.5%) 1.0–12.9
T-ALL	87 (4.6%)	34 (39.1%)	4 (11.8%) 4.1–27.2	74 (3.3%)	29 (39.2%)	3 (10.3%) 2.8–27.2
FCL	93 (4.9%)	22 (23.7%)	0 (0%)	51 (2.3%)	20 (39.2%)	2 (10.0%) 0.5–17.4
MCL	31 (1.6%)	9 (29.0%)	0 (0%)	17 (0.8%)	3 (17.6%)	1 (33.3%)
ALCL	27 (1.4%)	3 (11.1%)	1 (33.3%)	31 (1.4%)	18 (58.1%)	13 (72.2%) 48.8–87.8
TLPD	44 (2.3%)	10 (22.7%)	2 (20.0%) 4.6–52.1	94 (4.2%)	41 (43.6%)	14 (34.1%) 21.5–49.5
PEL	5 (0.3%)	5 (100.0%)	5 (100%)	7 (0.3%)	6 (85.7%)	6 (100%)
Other†	87 (4.6%)	32 (36.8%)	8 (25.0%) 13.0–42.3	74 (3.3%)	30 (40.5%)	12 (40.0%) 24.6–57.7
Total	1897 (100%)	709 (37.4%)	314 (44.3%) 40.7–48.0‡	2225 (100%)	1233 (55.4%)	765 (62.0%) 59.3–64.7‡

*BLPD includes: BLPD NOS, BLPD high grade, and BLPD low grade.
†Other cases include: other acute leukemias, hairy cell leukemia (HCL), MALT lymphoma, and lymphoplasmacytic lymphoma.
P value for increase in HIV prevalence between 2007–2009 cohort compared with 2004–2006 cohort: ‡< 0.0001; §0.005; ‖0.02; ¶0.06.
CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; BLPD NOS, B-cell lymphoproliferative disorder not otherwise specified; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; HL, Hodgkin lymphoma; PCD, plasma cell dyscrasia; BL, Burkitt leukemia/lymphoma; B-ALL, precursor B-cell acute lymphoblastic leukemia; T-ALL, precursor T-cell acute lymphoblastic leukemia; FCL, follicular lymphoma; MCL, mantle cell lymphoma; ALCL, anaplastic large cell lymphoma; TLPD, T-cell lymphoproliferative disorder; PEL, primary effusion lymphoma.

entire lymphoma cohort showed a statistically significant increase from 44.3% in 2004–2006 to 62.0% in 2007–2009 ($P < 0.0001$). This was associated with a decreasing age at presentation, decrease in the male:female ratios in the patient cohort, and an increase in aggressive BLPDs and HL.

The 2007–2009 period was notable for increases in the total number and proportion of high-grade B-cell lymphomas diagnosed (including DLBCL, DLBCL plasmablastic variant, and BL) when compared with cases diagnosed during 2004–2006. This was accompanied by an overall decrease in the number and proportion of low-grade lymphomas diagnosed. Our data for the entire period 2004–2009 were compared with previously published international data,[20,21] which highlighted the excess of high-grade tumors.

In 1997, the International Lymphoma Study Group published an assessment of the distribution of lymphomas diagnosed histopathologically in a multicenter international

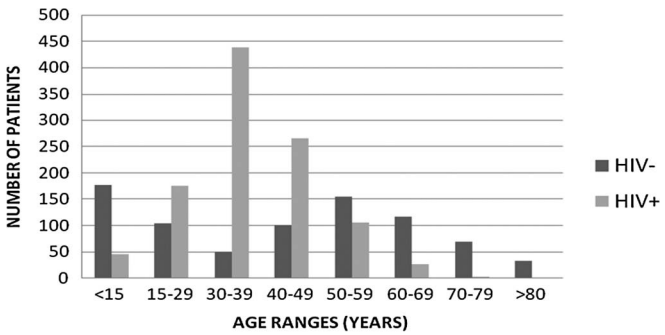

FIGURE 2. Age ranges at presentation: comparison of HIV-negative and HIV-positive patients. HIV-positive patients show a single peak in the age range 30 to 39 years, whereas HIV-negative patients have a bimodal pattern with peaks in the less than 15-year and in the 50- to 59-year age groups.

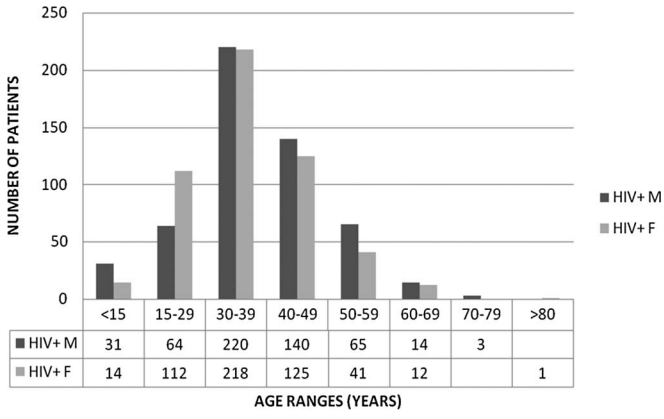

FIGURE 3. Age ranges at presentation: comparison of HIV-positive male and female patients. A predominance of males is seen at some ages in HIV-positive patients; however, in the 15- to 29-year age group, females predominate (male:female [M:F] ratio: 0.6:1) and in the 30- to 39-year age group, the M:F ratio is approximately 1:1. The M:F ratio for all HIV-positive patients of all ages during 2004–2009: 1:1; M:F ratio for all HIV-negative patients of all ages 2004–2009: 1.4:1.

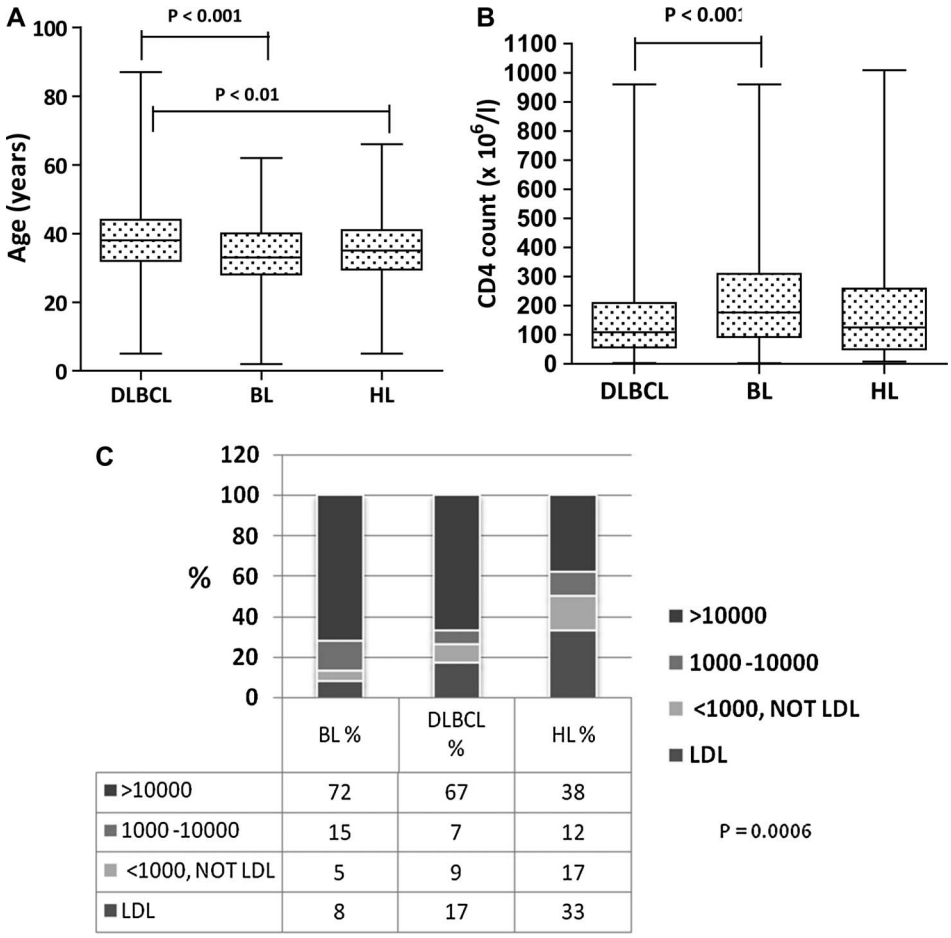

FIGURE 4. Age and virologic factors in HIV-positive patients with BL, DLBCL, or HL: results at presentation. (A) Age distribution by lymphoma subgroup (box and whisker plot). Median, interquartile, and range of age demonstrated. DLBCL: n = 530, median age = 38 years; BL: n = 169, median age = 33 years; HL: n = 140, median age = 35 years. (B) CD4 count distribution in HIV-positive patients by lymphoma subgroup (box and whisker plot). Median, interquartile, and range of CD4 count demonstrated. DLBCL: n = 400, median CD4 = 109 × -10^6/l; BL: n = 129, median CD4 = 176 × -10^6/l; HL: n = 102, median CD4 = 125 × -10^6/l. (C) Viral load (VL, copies/mL) distribution (by percentages) in HIV-positive patients by lymphoma subgroup. BL: n = 60; DLBCL: n = 202; HL: n = 52. LDL, viral load less than detectable limits of assay.

study.[20,21] Considering only B-cell tumors (excluding PCD and acute lymphoblastic leukemias), approximately 40% of cases in this study were diagnosed as DLBCL and less than 45% of cases were of high-grade nature.[20,21] Review of our data showed that high-grade B-cell lymphomas accounted for 82% of all B-cell cases in the 2007–2009 period (increased from 64% in the 2004–2006 data). For the high-grade lymphomas, those tested in the later time period show greater than 90% prevalence of underlying HIV infection. These findings have important public health implications: younger patients with aggressive lymphoma will require inpatient, intensive therapies. Elderly patients with indolent disease are more likely to be managed on an outpatient "watch and wait" basis.[22,23] From a public health perspective, consideration of resource (including human resource) and hospital bed allocation needs to be based on changing disease profiles to accommodate increased numbers of highly aggressive B-cell malignancies.

Other interesting patterns noted in the data include the presence of a trimodal age peak at presentation, as shown in Figure 2. HIV-negative patients showed bimodal peaks in the less than 15-year age group (predominantly acute lymphoblastic leukemia) and then again in the 50- to 59-year age group (predominantly low grade LPDs and PCD). HIV-positive patients show a single modal peak in the 30- to 39-year age group comprised largely of high-grade B-cell lymphomas. A trimodal pattern has been described previously in the setting of BL[24] but may be applicable to other LPDs in a high prevalence HIV setting. The age of diagnosis of LPDs in HIV-positive patients (modal peak in the 30- to 39-year age group) can be correlated with peak ages of HIV infection. This has been described in the 25- to 29-year-old age group for young females and 30- to 34-year age group for males.[14,25]

Not only has the lymphoma subtype and age of onset changed within the setting of HIV disease, but significant changes have also been noted in the gender preponderance of the disease. Males have historically been at higher risk for lymphoma,[21,26] including in international studies with a higher infection risk noted for HIV-positive men who have sex with men.[27,28]

In Southern Africa, the epidemic predominantly affects the heterosexual population and females are disproportionately infected with approximately 60% of HIV infections occurring in young women.[14,25,29] The epidemiology of the epidemic is reflected with a 1:1 gender ratio noted overall in HIV-positive patients diagnosed from 2004–2009 as compared with 1.4:1 in the HIV-negative cohort (P = 0.0012). In our study, young HIV-positive women presented with lymphomas at a statistically significantly younger median age than males (35 years versus 38 years, respectively; P = 0.0004) and in the 15- to

29-year age, females predominated (see Fig. 3). These findings are likely to reflect the overall pattern of relationships described within southern Africa, where age-disparate relationships are common.[25] Clearly targeting young females, in particular, for educational, preventive, and social reforms is an important approach to controlling the HIV epidemic and associated lymphoma diagnoses.

The diagnosis of HL has increased associated with an increasing HIV prevalence in those patients tested (46.2% in 2004–2006; increased to 60.8% in 2007–2009; $P = 0.06$). Previous publications have demonstrated a moderately increased risk of HL in HIV-infected patients (odds ratio ranging from 1.6 to 30).[5,30] An increase in HL has also been noted specifically in the early post-HAART period.[31] Although the literature in this area remains controversial, HL is reported in HIV-positive patients with moderate immunosuppression and in patients with a history of recent HAART initiation[30] leading to the suggestion that HL may be associated with immune reconstitution. Our data support this notion with 33% of patients with HL (in whom VL testing was performed at presentation, total n = 52) showing evidence of full virologic suppression (VL less than assay detectable limits [LDL]) and 50% presenting with a VL less than 1000 copies/mL. This is statistically significantly different from the pattern in BL (8% of those tested present with VL LDL) and DLBCL (17% of patients tested at presentation have VL LDL) ($P = 0.0006$). See Figure 4.

Although South Africa only initiated HAART rollout nationally in 2004,[14] significant progress has been made in increasing the numbers of patients on therapy. Recently published data suggest that approximately 28% (UNAIDS data 2007/2008) to 40% (2008–2009 data)[32] of patients requiring HAART are actually on therapy countrywide.[16,33] This has increased from less than 5% in 2004.[16,34] Our data reflect this in showing a different pattern of VL in patients presenting in 2007 when compared with 2009: statistically significantly more patients were virologically suppressed at presentation in 2009 when compared with both 2008 and 2007 ($P = 0.03$). Despite this, there is no statistically significant difference in CD4 count at presentation between the different time periods and no overall significant difference in CD4 count when stratified by VL (median CD4 count for those with VL LDL is statistically significantly higher at 175 when compared with those with VL greater than 10,000 with a median CD4 count of 97 [$P < 0.05$], but no other statistically significant differences were noted on stratification). This finding supports the suggestion that HAART is started at a late stage of disease in South Africa, when significant immunosuppression has already occurred.[35,36]

Comparison of CD4 counts at presentation for all HIV-positive patients with LPD tested at diagnosis (median CD4, 118 in 2004–2009 cases; 70% CD4 less than 200, 43% CD4 less than 100) with international data suggests our patients are much more severely immunosuppressed at presentation when compared with their international counterparts.[27] In a study from the United Kingdom, patients with non-Hodgkin lymphoma had a median CD4 count of 216 to 225 at presentation[27] and in an American study, the median CD4 count was 157×10^6/L and only 23% of patients had a CD4 count less than 200.[37] The risk of B-cell lymphoma in the setting of HIV has been clearly linked to the severity of immunosuppression with low CD4 count and nadir CD4 count emerging as the strongest risk predictors.[27,38,39] It is thus essential for South Africa not only to scale up the number of patients on HAART therapy, but also to start HAART therapy earlier before patients are severely immunocompromised. The South African government has recently expressed a willingness to offer HAART therapy at CD4 counts of less than 350 in some patient subgroups[14] (as has been advocated internationally[40,41]); has embarked on a policy of HIV counseling and testing[14]; and has also recognized human resources as a huge limitation to this process. The potential of task-shifting to nurses is also an option under consideration.[14,42] It remains to be seen what impact the changes in HAART management will have on the general well-being of HIV cohorts and on the patterns of cancers seen in South Africa.

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