DOI:10.1093/jnci/djt158
Advance Access publication July 26, 2013

ARTICLE

Temporal Trends in Presentation and Survival for HIV-Associated Lymphoma in the Antiretroviral Therapy Era

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Manuscript received October 25, 2012; revised May 1, 2013; accepted May 2, 2013.

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Background Lymphoma is the leading cause of cancer-related death among HIV-infected patients in the antiretroviral therapy (ART) era.

Methods We studied lymphoma patients in the Centers for AIDS Research Network of Integrated Clinical Systems from 1996 until 2010. We examined differences stratified by histology and diagnosis year. Mortality and predictors of death were analyzed using Kaplan–Meier curves and Cox proportional hazards.

Results Of 23 050 HIV-infected individuals, 476 (2.1%) developed lymphoma (79 [16.6%] Hodgkin lymphoma [HL]; 201 [42.2%] diffuse large B-cell lymphoma [DLBCL]; 56 [11.8%] Burkitt lymphoma [BL]; 54 [11.3%] primary central nervous system lymphoma [PCNSL]; and 86 [18.1%] other non-Hodgkin lymphoma [NHL]). At diagnosis, HL patients had higher CD4 counts and lower HIV RNA than NHL patients. PCNSL patients had the lowest and BL patients had the highest CD4 counts among NHL categories. During the study period, CD4 count at lymphoma diagnosis progressively increased and HIV RNA decreased. Five-year survival was 61.6% for HL, 50.0% for BL, 44.1% for DLBCL, 43.3% for other NHL, and 22.8% for PCNSL. Mortality was associated with age (adjusted hazard ratio [AHR] = 1.28 per decade increase, 95% confidence interval [CI] = 1.06 to 1.54), lymphoma occurrence on ART (AHR = 2.21, 95% CI = 1.53 to 3.20), CD4 count (AHR = 0.81 per 100 cell/μL increase, 95% CI = 0.72 to 0.90), HIV RNA (AHR = 1.13 per $\log_{10}$copies/mL, 95% CI = 1.00 to 1.27), and histology but not earlier diagnosis year.

Conclusions HIV-associated lymphoma is heterogeneous and changing, with less immunosuppression and greater HIV control at diagnosis. Stable survival and increased mortality for lymphoma occurring on ART call for greater biologic insights to improve outcomes.

J Natl Cancer Inst;2013;105:1221–1229

HIV infection increases risk of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) (1–3). In the antiretroviral therapy (ART) era, NHL incidence initially declined but has since stabilized, whereas HL incidence has remained stable and even increased in some cohorts (1,2,4). Additionally, cancer has increased as a proportional cause of mortality among HIV-infected persons, now accounting for 25% to 35% of HIV-associated deaths, with lymphoma being the most frequent cancer-related cause (5–8).

Risk factors for NHL include lower CD4 count and greater HIV viremia (9–13). However, risk is heterogeneous across NHL categories, with risk for Burkitt lymphoma (BL) being highest with modest rather than severe immunosuppression (14). Risk for HL may also be highest with modest immunosuppression and soon after ART initiation (15,16). Variable risk by CD4 count across lymphoma subtypes may lead to histologic shifts over time with earlier use of ART (17).

In the ART era, chemotherapy clinical trials have demonstrated comparable outcomes for patients with HIV-associated NHL and HL as for patients without HIV (18–22). European observational studies have also reported survival after NHL and HL for HIV-infected individuals similar to that for HIV-uninfected individuals (23–26). However, observational studies in the United States have found HIV to be independently associated with mortality after NHL (27). Existing studies have examined NHL and HL separately and have not studied trends since the modern ART era began. We therefore studied a large HIV-infected cohort in the United States to define temporal trends in the current ART era.

Methods

Patients

The Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) provides a clinical data repository for

point-of-care electronic medical record systems (28). The CNICS cohort includes more than 25 000 HIV-infected adults aged older than 18 years, receiving care from January 1, 1995, to the present, at eight United States CFAR sites (Case Western Reserve University; University of Alabama at Birmingham; University of California, San Francisco; University of Washington; University of California, San Diego; Fenway Health, affiliated with Harvard University; University of North Carolina; and Johns Hopkins University). CNICS is a dynamic cohort with approximately 1400 new patients enrolling and 13% of existing patients leaving care each year. Institutional review boards at each university have approved study protocols. We examined all individuals in CNICS with NHL or HL diagnosed between January 1, 1996, and December 31, 2010. Follow-up was administratively censored on December 31, 2010.

Procedures

After informed consent, standardized demographic and historical information, including prior diagnoses and antiretroviral treatment, are collected upon CNICS entry. Once enrolled, data, including medications, laboratory values, and AIDS-defining and non-AIDS-defining conditions, are prospectively collected at each site and verified by medical record review. A standardized cancer diagnosis verification procedure has been established at all sites (8). Incident cancer diagnoses are reviewed for confirmation and to collect information regarding type, histology, staging, and treatment from the medical record. If more than one lymphoma diagnosis or relapse was recorded, we analyzed only the first occurrence. Patients must attend HIV clinics at network sites to be enrolled in CNICS, although once enrolled, data are frequently available before cohort entry. To increase generalizability, we included individuals diagnosed with lymphoma before and after CNICS entry to avoid exclusion of patients newly diagnosed with HIV, out of care, or transferring HIV care at the time of lymphoma diagnosis. Mortality data in CNICS are obtained from clinic sources and confirmed by the Social Security Death Index. CD4 count and HIV RNA values at lymphoma diagnosis were defined as values closest to diagnosis date beginning 3 months before until 3 months after. Nadir CD4 count was defined as the lowest CD4 count at any time on or before the date of CD4 at lymphoma diagnosis. Suppressed HIV RNA was defined as a value less than 400 copies/mL. Hepatitis B coinfection was defined as any positive hepatitis B surface antigen or DNA result, and hepatitis C coinfection was defined as any positive hepatitis C antibody or RNA result before or until 6 months after lymphoma diagnosis. Lymphoma developing on ART was defined as receipt of any antiretroviral medication from 24 weeks before lymphoma diagnosis until 4 weeks before lymphoma diagnosis. Patients with remote ART exposure ending more than 24 weeks before lymphoma diagnosis or with ART initiated less than 4 weeks before lymphoma diagnosis were classified as having lymphoma not occurring on ART.

Statistical Analysis

Differences in proportions, means, and medians between lymphoma categories were assessed using χ^2 or Fisher exact tests, one-way analysis of variance, and Kruskal–Wallis tests, respectively. Trends in proportions, means, and medians across calendar years were assessed using the Cochran–Armitage and Spearman rank correlation tests. Mortality rates were calculated as number of deaths per 100 person-years of follow-up. Follow-up time was calculated from date of lymphoma diagnosis until administrative censoring, death, or loss to follow-up. Loss to follow-up date was assigned based on last date of any clinical activity in CNICS, including outpatient visits, medication prescriptions, or laboratory and radiologic studies. To minimize survival bias, patients with lymphoma diagnosed before CNICS enrollment were treated as late entries and contributed follow-up time only after cohort entry (29). Kaplan–Meier cumulative mortality curves were used to estimate probability of death for 5 years after lymphoma diagnosis. Differences in survival across lymphoma categories and diagnosis years were evaluated using the log-rank test. Cox proportional hazards modeling was used to examine risk factors for mortality, including sex, race/ethnicity, age, diagnosis year, HIV transmission risk factor, hepatitis B/C coinfection, prior AIDS illness, ART status, CD4 count, HIV RNA, and histology. The proportional hazards assumption was assessed graphically for each variable by examining the log–log survival plot and inclusion of interaction term by time. Detailed information regarding lymphoma treatment, stage, and other prognostic features were not available. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). A two-sided alpha value of 0.05 was used to assess statistical significance. Patients were excluded from analyses that included variables for which data were missing. Sensitivity analyses, as well as analyses restricted to patients with lymphoma diagnosis after CNICS enrollment, were performed. Sex and race/ethnicity were included as covariables in all analyses. We did not do separate analyses by sex or racial/ethnic group.

Results

Among 23 050 HIV-infected individuals enrolled in CNICS, 476 (2.1%) individuals were diagnosed with lymphoma between 1996 and 2010 (79 [16.6%] HL; 201 [42.2%] diffuse large B-cell lymphoma [DLBCL]; 56 [11.8%] BL; 54 [11.3%] primary central nervous system lymphoma [PCNSL]; 86 [18.1%] other NHL). Of these, 199 (41.8%) were diagnosed a median of 4.5 months (interquartile range [IQR] = 1.2–24.2) before CNICS enrollment. At lymphoma diagnosis, CD4 count and HIV RNA measurements differed from lymphoma diagnosis date by a median of 12 days (IQR = 4–27) and 13 days (IQR = 4–29), respectively. Patients with lymphoma diagnosed before CNICS enrollment were more likely to have missing data regarding CD4 count at diagnosis, nadir CD4 count, or HIV RNA at diagnosis compared with patients for whom lymphoma was diagnosed after cohort entry (44.7% vs 11.9%; $P < .001$). Lymphoma developed on ART in 223 (47.0%) patients. At lymphoma diagnosis, these patients had a higher proportion with prior AIDS illness (89.2% vs 74.6%; $P < .001$), similar median CD4 count (157 vs 103 cells/μL; $P = .18$), similar nadir CD4 count (52 vs 67 cells/μL; $P = .19$), lower HIV RNA (2.30 vs 4.91 $\log_{10}$copies/mL; $P < .001$), and higher proportion with suppressed HIV RNA (57.2% vs 5.3%; $P < .001$), compared with patients not on ART.

Baseline characteristics by lymphoma category are shown in Table 1. Pairwise comparisons demonstrated that HL patients were more likely than NHL patients at diagnosis to have black race/ethnicity, be on ART, have higher CD4 counts, have lower HIV RNA,

Table 1. Characteristics of 476 HIV-infected adults in the Center for AIDS Research Network of Integrated Clinical Systems cohort with lymphoma between 1996 and 2010

Characteristics	HL	NHL					*P* HL vs NHL‡	*P* NHL categories§
		All	DLBCL	PCNSL	BL	Other		
Total, No. (%)	79 (16.6)	397 (83.4)	201 (42.2)	54 (11.3)	56 (11.8)	86 (18.1)	—	—
Age, years, at lymphoma diagnosis, mean (SD)	42.1 (8.7)	42.4 (8.8)	42.8 (8.7)	40.7 (7.7)	40.3 (8.5)	43.7 (9.5)	.81	.06
Male, No. (%)	71 (89.9)	350 (88.2)	182 (90.6)	38 (70.4)	53 (94.6)	77 (89.5)	.66	<.001
Race/ethnicity, No. (%)†								
White	30 (38.0)	208 (53.1)	110 (55.3)	15 (27.8)	32 (59.3)	51 (60.0)	.01	<.001
Black	35 (44.3)	117 (29.9)	54 (27.1)	27 (50.0)	13 (24.1)	23 (27.1)	.01	.006
Other	14 (17.7)	67 (17.1)	35 (17.6)	12 (22.2)	9 (16.7)	11 (12.9)	.89	.56
HIV transmission risk factor, No. (%)								
MSM	44 (55.7)	180 (45.3)	93 (46.3)	20 (37.0)	25 (44.6)	42 (48.8)	.09	.57
IDU	8 (10.1)	71 (17.9)	35 (17.4)	12 (22.2)	6 (10.7)	18 (20.9)	.09	.36
MSM and IDU	1 (1.3)	12 (3.0)	10 (4.9)	1 (1.9)	0 (0.0)	1 (1.2)	.70	.13
Heterosexual	26 (32.9)	134 (33.8)	68 (33.8)	25 (46.3)	20 (35.7)	21 (24.4)	.89	.064
Other/Unknown	6 (7.6)	51 (12.9)	26 (12.9)	5 (9.3)	7 (12.5)	13 (15.1)	.19	.80
Hepatitis B/C coinfection, No. (%)	9 (11.4)	88 (22.8)	42 (20.9)	16 (29.6)	10 (17.9)	20 (23.3)	.03	.46
AIDS illness before lymphoma diagnosis, No. (%)	67 (84.8)	321 (80.9)	160 (79.6)	48 (88.9)	48 (85.7)	65 (75.6)	.41	.18
ART at lymphoma diagnosis, No. (%)	55 (69.6)	168 (42.4)	84 (41.8)	26 (49.1)	18 (32.1)	40 (46.5)	<.001	.26
CD4 count, cells/μL, at lymphoma diagnosis, median (IQR)†	165 (78–308)	119 (29–282)	123 (37–294)	14 (5–77)	207 (89–442)	137 (52–258)	.01	<.001
CD4 percentage at lymphoma diagnosis, median (IQR)†	16.9 (11.0–28.0)	11.0 (4.8–20.0)	11.6 (5.0–20.0)	2.5 (1.0–9.1)	18.5 (9.7–26.2)	10.0 (6.0–14.1)	<.001	<.001
CD4 count, cells/μL, nadir, median (IQR)†	75 (38–211)	52 (12–157)	68 (25–153)	5 (3–22)	118 (41–225)	60 (16–177)	.03	<.001
HIV RNA, $\log_{10}$copies/mL, at lymphoma diagnosis, median (IQR)†	2.30 (1.40–4.08)	4.53 (2.30–5.30)	4.67 (2.30–5.30)	4.62 (2.67–5.38)	4.32 (3.31–5.46)	3.41 (2.04–4.87)	<.001	.27
HIV RNA <400 copies/mL at lymphoma diagnosis, No. (%)†	33 (55.0)	84 (28.3)	44 (27.7)	10 (23.8)	8 (18.6)	22 (41.5)	<.001	.07

* Differences in proportions, means, and medians between lymphoma categories were assessed using χ^2 or Fisher exact tests, one-way analysis of variance, and Kruskal–Wallis tests, respectively. All statistical tests reported are two-sided. ART = antiretroviral therapy BL = Burkitt lymphoma; DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; IDU = injection drug use; IQR = interquartile range; MSM = men who have sex with men; NHL = Non-Hodgkin lymphoma; PCNSL = primary central nervous system lymphoma; SD = standard deviation.

† Missing observations: Race/ethnicity = 5 (1%); CD4 count at lymphoma diagnosis = 97 (20%); CD4 percentage at lymphoma diagnosis = 123 (26%); CD4 count nadir = 65 (14%); HIV RNA at lymphoma diagnosis = 19 (25%).

‡ *P* value for pairwise comparison between HL and all NHL.

§ *P* value for overall comparison between NHL categories.

and have suppressed HIV RNA. Among NHL categories, PCNSL patients were more likely to be male ($P < .001$), be black ($P = .003$), have lower nadir CD4 count ($P < .001$), and have lower CD4 count at diagnosis ($P < .001$) than NHL patients without PCNSL. BL patients had higher nadir CD4 count ($P = .006$) and CD4 count at diagnosis ($P < .001$) than NHL patients without BL.

Proportional distribution of lymphoma categories by diagnosis year is shown in Figure 1. No statistically significant trend was observed in proportional distribution of HL vs NHL ($P = .32$). Among NHL categories, a statistically significant proportional increase over time in BL was observed.

Table 2 demonstrates presenting characteristics among all patients stratified by lymphoma diagnosis year. More recently diagnosed patients were older and more likely to be male, of nonwhite/nonblack ethnicity, and men who have sex with men. Additionally, more recently diagnosed patients were more likely to have prior AIDS illness and be on ART at lymphoma diagnosis, with higher CD4 counts and lower HIV RNA.

Among all 476 patients with HIV-associated lymphoma, 225 deaths occurred during 1525 person-years of follow-up, yielding a mortality rate of 14.8 deaths per 100 person-years (95% confidence interval [CI] = 12.9 to 16.8). Mortality rates, along with estimated 2-year and 5-year overall survival, stratified by lymphoma category are shown in Table 3. Five-year survival was 61.6% for HL, 50.0% for BL, 44.1% for DLBCL, 43.3% for other NHL, and 22.8% for PCNSL. Cumulative mortality for NHL vs HL, as well as for NHL categories, is shown in Figure 2, with statistically significant differences observed between NHL and HL ($P < .001$) and among NHL categories ($P < .001$). No statistically significant cumulative mortality differences were observed for patients stratified by lymphoma diagnosis year (1996–2000 vs 2001–2005 vs 2006–2010) among all patients ($P = .10$) or when patients with NHL ($P = .12$) and HL ($P = .95$) were examined separately.

Results of Cox proportional hazards modeling including all listed covariables are shown in Table 4. Results are shown for the full cohort, as well as the restricted cohort with lymphoma diagnosed after CNICS enrollment. Independent risk factors for mortality included older age (adjusted hazard ratio [AHR] = 1.28 per decade increase, 95% CI = 1.06 to 1.54), lymphoma occurrence during ART (AHR = 2.21, 95% CI = 1.53 to 3.20), lower CD4 count at lymphoma diagnosis (AHR = 0.81 per 100 cell/μL increase, 95% CI = 0.72 to 0.90), higher HIV RNA (AHR = 1.13 per $\log_{10}$copies/mL, 95% CI = 1.00 to 1.27), and histologic category. More recent diagnosis year was not associated with decreased mortality. The association of lymphoma occurring on ART with increased mortality was consistent even when ART exposure was defined as beginning 48 rather than 24 weeks before lymphoma diagnosis (AHR = 2.27, 95% CI = 1.58 to 3.28 in full cohort; AHR = 2.58, 95% CI = 1.62 to 4.11 in restricted cohort) and when nadir CD4 count was included in the model in place of CD4 count at diagnosis (AHR = 2.12, 95% CI = 1.46 to 3.08 in full cohort; AHR = 2.16, 95% CI = 1.38 to 3.37 in restricted cohort). When dichotomous HIV RNA less than 400 copies/mL at diagnosis (ie, suppressed vs unsuppressed) was included in place of continuous HIV RNA $\log_{10}$copies per milliliter, lymphoma occurrence on ART was associated with an adjusted hazard ratio of 2.27 (95% CI = 1.46 to 3.16) in the full cohort and an adjusted hazard ratio of 2.35 (95% CI = 1.52 to 3.65) in the restricted cohort, and HIV RNA suppression was associated with an adjusted hazard ratio of 0.63 (95% CI = 0.43 to 0.93) in the full cohort and an adjusted hazard ratio of 0.66 (95% CI = 0.43 to 0.99) in the restricted cohort. Other model results were similarly consistent across all sensitivity analyses.

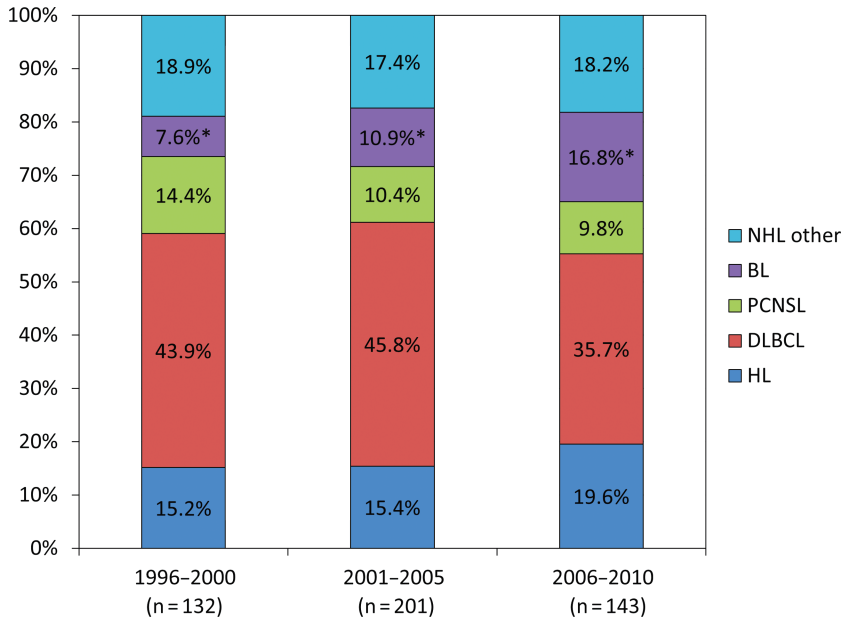


Figure 1. Proportional distribution of 476 HIV-associated lymphomas in the Center for AIDS Research Network of Integrated Clinical Systems cohort by lymphoma diagnosis year, 1996 to 2010. *Cochran–Armitage P_{trend} for Burkitt lymphoma (BL) proportion relative to diffuse large B-cell lymphoma (DLBCL) is .01, BL relative to primary central nervous system lymphoma (PCNSL) is .02, and BL relative to all non-BL Non-Hodgkin lymphoma (NHL) is .02. For all other pairwise comparisons between lymphoma categories, Cochran–Armitage P_{trend} is greater than .05. All reported statistical tests are two-sided. HL = Hodgkin lymphoma.

Table 2. Characteristics of 476 HIV-infected adults in the Center for AIDS Research Network of Integrated Clinical Systems cohort with lymphoma between 1996 and 2010, stratified by year of diagnosis*

Characteristics	1996–2000	2001–2005	2006–2010	*P*
Total, No. (%)	132 (27.7)	201 (42.2)	143 (30.0)	—
Age, years, at lymphoma diagnosis, mean (SD)	40.2 (7.6)	42.1 (8.7)	44.6 (9.4)	<.001
Male, No. (%)	109 (82.6)	182 (90.6)	130 (90.9)	.03
Race/ethnicity, No. (%)†				
White	77 (58.8)	90 (44.8)	71 (51.1)	.22
Black	43 (32.8)	71 (35.3)	38 (27.3)	.32
Other	11 (8.4)	40 (19.9)	30 (21.6)	.005
HIV transmission risk factor, No. (%)				
MSM	53 (40.2)	95 (47.3)	76 (53.2)	.03
IDU	26 (19.7)	34 (16.9)	19 (13.3)	.15
MSM and IDU	4 (3.0)	7 (3.5)	2 (1.4)	.39
Heterosexual	46 (34.9)	69 (34.3)	45 (31.5)	.55
Other/Unknown	19 (14.4)	25 (12.4)	13 (9.1)	.17
Hepatitis B/C coinfection, No. (%)	22 (16.7)	46 (22.9)	29 (20.3)	.48
AIDS illness before lymphoma diagnosis, No. (%)	100 (75.8)	162 (80.6)	126 (88.1)	.008
ART at lymphoma diagnosis, No. (%)	54 (40.1)	93 (46.5)	76 (53.2)	.04
CD4 count, cells/μL, at lymphoma diagnosis, median (IQR)†	85 (25–217)	120 (41–277)	166 (52–346)	.004
CD4 percentage at lymphoma diagnosis, median (IQR)†	9.4 (3.0–18.2)	11.0 (5.0–21.0)	15.8 (7.0–22.0)	.005
CD4 count, cells/μL, nadir, median (IQR)†	50 (13–145)	54 (14–158)	73 (20–195)	.32
HIV RNA, $\log_{10}$copies/mL, at lymphoma diagnosis, median (IQR)†	4.56 (2.66–5.29)	4.36 (2.30–5.24)	3.26 (1.40–4.97)	.001
HIV RNA <400 copies/mL at lymphoma diagnosis, No. (%)†	18 (24.7)	45 (28.9)	54 (42.2)	.006

* Differences in proportions, means, and medians across calendar years were assessed using the Cochran–Armitage and Spearman rank correlation tests. All statistical tests reported are two-sided. ART = antiretroviral therapy; IDU = injection drug use; IQR = interquartile range; MSM = men who have sex with men; SD = standard deviation.

† Missing observations by respective calendar periods 1996–2000/ 2001–2005/ 2006–2009: Race/ethnicity = 1 (1%)/0 (0%)/4 (3%); CD4 count at lymphoma diagnosis = 49 (37)/39 (19%)/9 (6%); CD4 percentage at lymphoma diagnosis = 64 (49%)/46 (23%)/13 (9%); CD4 count nadir = 36 (27%)/26 (13%)/3 (2%); HIV RNA at lymphoma diagnosis = 59 (45%)/45 (22%)/15 (10%).

Table 3. Mortality rates and 2- and 5-year survival estimates for 476 HIV-infected adults in the Center for AIDS Research Network of Integrated Clinical Systems cohort with lymphoma between 1996 and 2010*

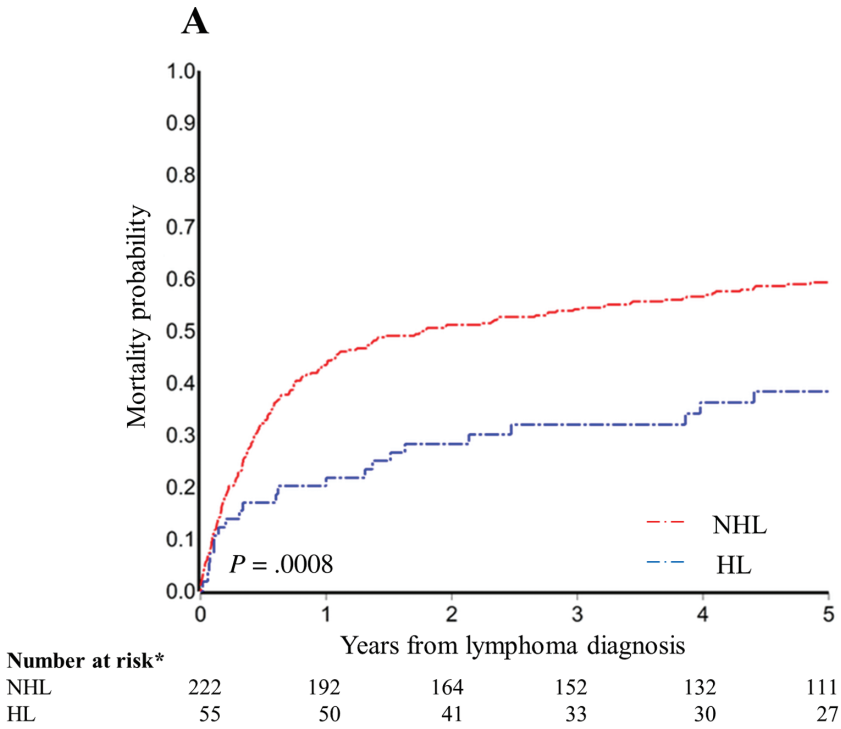
Type of lymphoma	No. of persons	Deaths	Person-years	Mortality rate per 100 person-years (95% CI)	2-year survival % (95% CI)	5-year survival % (95% CI)
All lymphoma	476	225	1525	14.8 (12.9 to 16.8)	52.5 (47.7 to 57.9)	44.0 (39.2 to 49.3)
HL	79	23	292	7.9 (5.2 to 11.9)	71.7 (61.3 to 83.9)	61.6 (50.2 to 75.6)
All NHL	397	202	1233	16.4 (14.3 to 18.8)	48.8 (43.6 to 54.7)	40.6 (35.6 to 46.5)
BL	56	22	151	14.5 (9.6 to 22.1)	53.1 (40.2 to 70.1)	50.0 (37.0 to 67.5)
PCNSL	54	41	117	35.0 (25.8 to 47.5)	24.4 (15.5 to 38.6)	22.8 (14.2 to 36.7)
DLBCL	201	100	674	14.8 (12.2 to 18.0)	55.6 (48.5 to 63.8)	44.1 (37.2 to 52.4)
Other NHL	86	39	290	13.4 (9.8 to 18.4)	50.5 (39.1 to 65.2)	43.3 (32.5 to 57.8)

* BL = Burkitt lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; NHL = Non-Hodgkin lymphoma; PCNSL = primary central nervous system lymphoma.

Discussion

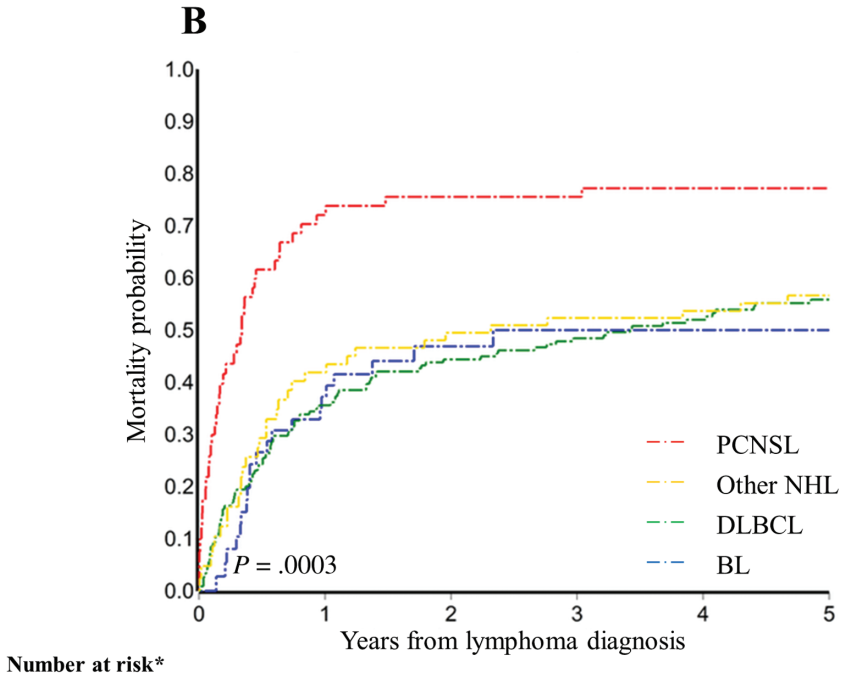
Our results, from a large, multicenter United States HIV-infected cohort, demonstrate that HIV-associated lymphoma is changing in the modern ART era. First, patients are older, with an increasing proportion having nonwhite/nonblack ethnicity, a group primarily comprised of Latino patients, reflecting trends in the United States HIV-infected population as a whole (30,31). Second, patients continue to have severe antecedent immunosuppression evidenced by static nadir CD4 counts over time. However, CD4 counts and HIV RNA suppression at lymphoma diagnosis are steadily improving. Third, histologic shifts are occurring with an increasing proportion of BL relative to other NHL categories. These findings are consistent with data from the HIV/AIDS Cancer Match Study, which reported stable BL incidence and declining DLBCL and PCNSL incidence among persons with AIDS (17).

Our results also confirm statistically significant variations in presentation and survival across lymphoma categories. HL patients had higher CD4 counts and more frequent HIV RNA suppression at diagnosis than NHL patients. PCNSL was associated with greater immunosuppression and BL lesser immunosuppression at diagnosis compared with other NHL categories. Regarding survival, 61.6% of patients with HIV-associated HL were alive 5 years after lymphoma diagnosis, compared with 50.0% for BL, 44.1% for DLBCL, 43.3% for other NHL, and 22.8% for PCNSL. These survival differences correlated with CD4 count differences at diagnosis, although histology was independently associated with mortality in adjusted analyses. By comparison, 5-year survival for all United States adults aged less



Number at risk*

NHL	222	192	164	152	132	111
HL	55	50	41	33	30	27



Number at risk*

PCNSL	40	16	14	15	12	9
Other NHL	42	37	36	33	34	28
DLBCL	115	110	97	88	74	62
BL	25	29	17	16	12	12

Figure 2. Cumulative mortality over time for Hodgkin lymphoma vs non-Hodgkin lymphoma (**A**) and non-Hodgkin lymphoma categories (**B**). *Number at risk may increase over time as a result of patients enrolled in Center for AIDS Research Network of Integrated Clinical Systems after lymphoma diagnosis who were treated as late entries. BL=Burkitt lymphoma; DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; NHL = Non-Hodgkin lymphoma; PCNSL = primary central nervous system lymphoma.

than 65 years with HL, BL, and DLBCL diagnosed between 2001 and 2007 were 88.4%, 50.5%, and 68.7%, respectively (32). Our data therefore suggest that patients in CNICS with HL and DLBCL fare worse than HIV-uninfected patients, whereas BL patients may have comparable survival with nonelderly adult BL patients, although up to 40% of such patients may be HIV-infected (17).

Our analyses also suggest that despite improvements in CD4 counts and HIV RNA suppression between 1996 and 2010, more

Table 4. Adjusted mortality hazard ratios for HIV-infected adults in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort with lymphoma between 1996 and 2010*••

Characteristics	All patients (n = 350)†		Patients with lymphoma diagnosed after CNICS entry (n = 242)‡	
	Adjusted hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI)	*P*
Male sex	1.12 (0.62 to 2.01)	.70	0.99 (0.51 to 1.94)	.98
Non-white ethnicity	0.89 (0.64 to 1.23)	.48	1.05 (0.71 to 1.55)	.83
Age at lymphoma diagnosis, per decade	1.28 (1.06 to 1.54)	.009	1.21 (0.97 to 1.52)	.09
Lymphoma diagnosis year				
1996–2000	Referent	—	Referent	—
2001–2005	1.06 (0.73 to 1.56)	.75	1.26 (0.78 to 2.00)	.35
2006–2009	0.93 (0.60 to 1.46)	.76	1.00 (0.57 to 1.73)	.99
HIV transmission risk factor				
Heterosexual	Referent	—	Referent	—
MSM and IDU	0.58 (0.24 to 1.39)	.22	0.59 (0.22 to 1.60)	.30
IDU	1.19 (0.68 to 2.09)	.55	0.95 (0.45 to 2.04)	.90
MSM	1.97 (0.66 to 1.42)	.87	1.01 (0.64 to 1.58)	.97
Other/ unknown	1.49 (0.90 to 2.48)	.12	1.20 (0.58 to 2.51)	.62
Hepatitis B/C coinfection	1.06 (0.72 to 1.54)	.78	1.02 (0.58 to 2.51)	.93
AIDS illness prior to lymphoma diagnosis	1.16 (0.76 to 1.78)	.49	1.24 (0.68 to 2.27)	.49
ART at lymphoma diagnosis	2.21 (1.53 to 3.20)	<.001	2.24 (1.44 to 3.49)	<.001
CD4 count at lymphoma diagnosis, per 100 cells/μL	0.81 (0.72 to 0.90)	<.001	0.79 (0.69 to 0.89)	<.001
HIV RNA, $\log_{10}$copies/mL, at lymphoma diagnosis	1.13 (1.00 to 1.27)	.05	1.11 (0.97 to 1.27)	.13
Lymphoma category				
PCNSL	Referent	—	Referent	—
HL	0.30 (0.16 to 0.56)	<.001	0.21 (0.10 to 0.44)	<.001
BL	0.72 (0.37 to 1.39)	.32	0.66 (0.29 to 1.49)	.32
DLBCL	0.51 (0.32 to 0.83)	.007	0.41 (0.24 to 0.71)	.002
Other NHL	0.58 (0.33 to 1.02)	.59	0.50 (0.26 to 0.94)	.03

* Statistical significance testing for Cox proportional hazard model estimates were assessed using the Wald χ^2 test. All statistical tests reported are two-sided. ART = antiretroviral therapy; BL = Burkitt lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; NHL = Non-Hodgkin lymphoma; PCNSL = primary central nervous system lymphoma.

† One hundred twenty-six of 476 patients (26%) with missing data excluded from Cox proportional hazards modeling.

‡ Thirty-five of 277 patients (13%) with missing data excluded from Cox proportional hazards modeling.

recent lymphoma diagnosis was not associated with improved survival among HIV-infected patients. Our study may have lacked sufficient follow-up time for more recently diagnosed patients to demonstrate survival differences, although multivariable modeling resulted in adjusted mortality hazard ratios for lymphoma diagnosis year very near the null value.

If survival has indeed remained static and inferior to HIV-uninfected patients, there are many possible explanations. Patients in our cohort represent a large and diverse HIV-infected population in routine care across the United States and may differ substantially from smaller, more homogeneous, uniformly treated clinical trial populations. Additionally, observational studies suggesting outcomes for HIV-infected lymphoma patients similar to those for HIV-uninfected patients in the ART era are largely from Europe (23–26), whereas our results are similar to a large observational study of NHL patients in the United States demonstrating worse outcomes for those with HIV (27). Discordant findings may partially reflect differences in the HIV-infected populations and health-care systems in the United States and Europe, respectively. Other reasons for a lack of survival improvement may include continued presentation with advanced stage and poor performance status (25,27,33), difficulty achieving stage-appropriate chemotherapy cumulative dose and dose intensity (25,33), reduced effectiveness or greater toxicity of chemotherapy due to ART interactions (34), discontinuity or suboptimal concentrations of ART due to chemotherapy interactions (33,34), diminished immunologic response against malignant lymphocytes, intrinsically aggressive tumor biology, and mortality from lymphoma-unrelated causes. Treatment incorporating more intensive first-line and salvage chemotherapy, immunotherapy, radiotherapy, and high-dose therapy with autologous stem cell rescue may also be less frequently used in HIV-infected patients (33). However, most patients in CNICS were treated in academic settings where treatment likely tends toward greater intensity.

The association of lymphoma occurring on ART with increased mortality is also noteworthy. The reasons for this are unclear. Importantly, patients on ART at lymphoma diagnosis may not benefit from positive effects on survival conferred by ART initiation in addition to lymphoma treatment. Exposure to ART at lymphoma diagnosis may also be a marker for more advanced HIV illness, although we adjusted for measures of HIV disease severity. Social and behavioral differences impacting survival, including adherence to treatment, may additionally exist between patients developing lymphoma on and off ART.

However, lymphoma that develops on ART may also be biologically different from lymphoma that occurs in the context of uncontrolled HIV. In an analogous condition, posttransplant

lymphoproliferative disorder occurring more than 2 years after transplant is more frequently negative for Epstein–Barr virus, with a distinct gene expression pattern, and worse clinical outcome compared with early posttransplant lymphoproliferative disorder (35–38). Such differences have not been adequately investigated for HIV-associated lymphoma, and our findings highlight a need for continued basic investigations comparing tumors before and after ART to characterize molecular features and therapeutic targets for lymphoma occurring in both contexts.

Biologic mechanisms underlying histologic shifts are similarly unclear and likely involve complex interactions between viral oncogens such as Epstein–Barr virus (34), immune surveillance of transformed lymphocytes in the germinal center (4,15), activation of cell signaling pathways such as nuclear factor-κB (4,15), and chronic B-cell activation (14,39), all of which likely vary in relative contribution across histologic subtypes (29). Changes in lymphoma diagnostic methods have also occurred during the period studied, including increased use of fluorescence in situ hybridization to detect *c-myc* translocation in BL. These advances likely influence changes in histologic classifications over time.

Our research has several limitations. First, data are observational, and associations may be due to unmeasured confounding. Second, we included patients with lymphoma preceding CNICS enrollment, as well as those with missing data. We sought to maintain generalizability to patients typically seen, including those not receiving HIV care or newly diagnosed with HIV at lymphoma diagnosis. We minimized bias by analyzing follow-up time only after CNICS entry and sought to ensure that immortal person-time between lymphoma diagnosis and cohort entry was not inappropriately counted. However, results remain susceptible to survival bias because survival for patients with lymphoma before CNICS enrollment may not be accurately reflected. Additionally, we performed sensitivity analyses and restricted analyses to patients with lymphoma diagnosed after CNICS enrollment and found consistent results. Third, detailed information regarding lymphoma presentation and treatment were not analyzed. We are implementing a centralized abstraction to collect detailed lymphoma data on all patients to examine correlations between lymphoma presentation, treatment, and outcomes. Fourth, ART effects after lymphoma diagnosis were not analyzed. Correlations between HIV treatment and survival, including timing of ART initiation and differential effects of various ART regimens, are the focus of ongoing analyses. Finally, cause of death was unknown, and our analyses focused on overall survival, although HIV-infected patients are at risk for competing causes of death.

Despite these limitations, our study has several strengths. To our knowledge, this is the first study from a large, multicenter cohort to describe temporal changes in presentation and outcomes among patients with HIV-associated NHL and HL since the beginning of the modern ART era. Patients studied represent a large and diverse HIV-infected population in routine care across the United States, undergoing regular assessment, in whom lymphoma diagnoses were rigorously verified to minimize misclassification. Additionally, mortality assessment used active and passive surveillance, leading to near-complete ascertainment.

In conclusion, HIV-associated lymphoma is highly heterogeneous in the current era, and important demographic, immunologic, virologic, and histologic shifts are occurring. In our analyses of a large US HIV-infected cohort, survival after lymphoma diagnosis has not statistically significantly improved since the modern ART era began, and outcomes remain inferior to registry data for the general population. These results highlight an ongoing need to elucidate lymphoma biology and optimize treatment for this challenging population to reduce deaths from one of the leading causes of mortality in the modern ART era.

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Funding

These findings are presented on behalf of CNICS, a National Institutes of Health (NIH)–funded program (R24 AI067039) made possible by the National Institute of Allergy and Infectious Diseases. This research was also supported by the University of North Carolina CFAR, an NIH-funded program (P30 AI50410); the University of Alabama at Birmingham CFAR (P30 AI027767); and the Case Western Reserve University CFAR (P30 AI36219). Additional support was provided by a UNC Lineberger Comprehensive Cancer Center Developmental Research Award and the Bristol-Myers Squibb Virology Fellows Research Training Program. SG is additionally supported by the Fogarty International Center of the NIH through the Fogarty Global Health Fellows Program (1R25TW009340-01) and an International Scientist Development Award (1K01TW009488-01), as well as an AIDS Malignancy Consortium Fellowship Award.

Notes

S. Gopal and M.R. Patel contributed equally to this work. S. Gopal worked closely with S. Napravnik, C.J. Achenbach, K.L. Richards, and J.J. Eron to design the study. S. Gopal, S. Napravnik, and M.R. Patel acquired the data from the CNICS data management core. M.R. Patel compiled the study database. S. Gopal, M.R. Patel, E.L. Yanik, S.R. Cole, and S. Napravnik collaborated on statistical analyses. S. Gopal and M.R. Patel participated in writing the manuscript. All authors reviewed and commented on the manuscript, and approved its final submission. We declare that we have no conflicts of interest.

The study sponsors had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; nor the decision to submit the manuscript for publication.

We would like to thank all CNICS investigators and data management teams from the eight sites who contributed to the completion of this study at Case Western Reserve University; University of Alabama at Birmingham; University of California, San Francisco; University of Washington; University of California, San Diego; Fenway Health; University of North Carolina; and Johns Hopkins University. The authors additionally wish to acknowledge Donna Porter for her important contributions.

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