Original Article

Human Immunodeficiency Virus-Associated Lymphomas in the Antiretroviral Therapy Era: Analysis of the National Cancer Data Base

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BACKGROUND: Antiviral therapy has altered the prognosis of patients with human immunodeficiency virus (HIV)-associated non-Hodgkin lymphoma (NHL), but patterns of lymphoma-directed therapy in the community are unknown. **METHODS:** The authors analyzed the National Cancer Data Base records of 10,769 patients who were diagnosed with HIV-associated lymphoma from 2004 through 2012. Changes in clinical characteristics and chemotherapy delivery over time were evaluated. Factors that were associated with not receiving chemotherapy were studied using multivariable logistic regression, reporting odds ratios (ORs) with 95% confidence intervals (CIs). **RESULTS:** The proportion of black or Hispanic patients with HIV-associated NHL increased from 41% in 2004 to 55% in 2012 ($P<.0001$). Chemotherapy was received by 81% of patients with diffuse large B-cell lymphoma, 90% of those with Burkitt lymphoma, 61% of those with primary effusion lymphoma (PEL), and 35% of those with primary central nervous system lymphomas (PCNSL). Between 2004 and 2012, this proportion increased only for patients with PCNSL ($P<.00001$). Chemotherapy was less likely to be received by patients who were older, black, or without private insurance. It was delivered more frequently in hospitals designated as academic (OR for nonreceipt, 0.68; 95% CI, 0.51-0.92) or in hospitals that had ≥3 HIV-positive cases per year (OR, 0.71; 95% CI, 0.58-0.86). Survival improved in patients with diffuse large B-cell lymphoma ($P=.007$), Burkitt lymphoma ($P=.0002$), and PCNSL ($P=.019$), but not in those with PEL ($P=.94$). Receipt of chemotherapy in patients with PEL was not associated with better survival. **CONCLUSIONS:** Disparities in chemotherapy delivery need attention, because a majority of HIV-positive patients with NHL in the United States are now black or Hispanic. Higher volume centers were associated with an increased likelihood of chemotherapy administration. Survival gains in patients with PCNSL parallel an increase in chemotherapy use, supporting its role in therapy. [See Editorial on pages 000-000, this issue.] ***Cancer* 2016;122:2689-97.** © *2016 American Cancer Society.*

KEYWORDS: acquired immunodeficiency syndrome (AIDS), epidemiology, human immunodeficiency virus, National Cancer Data Base, non-Hodgkin lymphoma, outcomes research.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is 1 of the most serious complications of infection with the human immunodeficiency virus (HIV) because of its aggressive course and need for intensive chemotherapy. Combination antiretroviral therapy (CART) has enhanced clinicians' ability to apply rituximab-containing curative regimens, thus changing the prognosis of patients with HIV-associated NHL.[1] This aggressive malignancy typically presents as diffuse large B-cell lymphoma (DLBCL), Burkitt or Burkitt-like lymphoma (BL), primary central nervous system lymphoma (PCNSL), or rare entities that include primary effusion lymphoma (PEL) and plasmablastic lymphoma.[2] The histologic subtypes differ in prognosis and associated phase of the HIV infection: PCNSL and PEL occur in severely immunocompromised individuals,[3] whereas BL is more common among those with higher cluster of differentiation 4 (CD4 [T-helper]) cell counts.[4] Indolent B-cell and T-cell lymphomas are often excluded from clinicopathologic series, although their incidence is also elevated among patients with HIV.[5,6]

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The data used in this study are derived from a de-identified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigator.

See editorial on pages 2621-23, this issue.

Additional supporting information may be found in the online version of this article

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Population-based research on HIV-associated lymphoma is hampered by limited identification of cases in cancer registries. Prior studies relied on pooled data from clinical trials, observational cohorts of HIV-positive patients (such as the one from Centers for Acquired Immunodeficiency Syndrome [AIDS] Research Network of Integrated Clinical Systems [CNICS]), or linkages between cancer and HIV registries (the HIV/AIDS Cancer Match Study [HACM]).[1,7-9] They demonstrated decreasing incidence of HIV-associated NHL, improved survival in the post-CART era, and an association between survival and CD4 cell count, but did not assess the use of chemotherapy in the community. Recent data indicate disparities in cancer treatments among HIV-infected patients that are particularly important in the setting of curative chemotherapy for NHL.[10]

We hypothesized that the evolving epidemiology of HIV/AIDS would alter clinical characteristics and chemotherapy delivery in HIV-associated lymphoma. Our objectives were to compare recent trends in demographics, chemotherapy use, and associated survival using a nationwide registry.

MATERIALS AND METHODS

Data Source and Cohort Selection

This study used de-identified data from the National Cancer Data Base (NCDB) and was exempt from oversight of the institutional review board. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It collects registry records from >1500 facilities and captures approximately 85% of all patients with lymphoma in the United States.[11] Participating institutions must collect survival data on >90% of known living patients annually. The NCDB contains information about cancer histology, staging, and the first course of treatment, including chemotherapy. Since 2004, HIV status was recorded for patients with NHL, with the exception of mycosis fungoides or Sezary syndrome, which were excluded from our study. We extracted data on 359,731 lymphomas diagnosed between 2004 and 2012. We excluded 35,130 patients (including 5.6% of HIV-positive patients) who were treated entirely outside of the reporting facility (for whom data collection was not required), and 2751 from hospitals that never reported HIV status on their patients.

Variables and Endpoints

NHL histology was assigned according to the World Health Organization classification.[12] We distinguished the following categories: DLBCL, BL, PCNSL, PEL, B-cell lymphoblastic, indolent B-cell lymphoma (follicular, mantle cell, marginal zone, lymphoplasmacytic, and small lymphocytic lymphomas), T-cell lymphoma, and unspecified lymphomas. Plasmablastic lymphoma (N = 269) and NHL arising from human herpesvirus-8–positive, multicentric Castleman disease (N = 46) were distinguished only since 2010, so we grouped them with unspecified NHL. Race/ethnicity was categorized as white non-Hispanic, white Hispanic, black, and Asian/other. Socioeconomic status was approximated by median income in patients' zip codes of residence (linked from the American Community Survey) and by individual health insurance status. Stage was assigned according to the American Joint Committee on Cancer schemas. The type of cancer program was designated by the Commission on Cancer based on annual case volume and available oncology services in the facility.[11] Facility case volume was calculated as the average number of HIV-associated lymphomas per year.

Chemotherapy administration was recorded without details of specific drugs, doses, duration, or response to treatment. Overall survival (OS) was calculated from the date of diagnosis until death or last follow-up by the registry. OS was not reported for 2012 cases, and they were excluded from the survival analysis. There were no data on CD4 cell counts, viral load, opportunistic infections, CART, or virologic control. The timing between the HIV and NHL diagnoses also was unrecorded.

Statistical Methods

Trends in characteristics were described using crude case numbers and proportions. Nonreceipt of chemotherapy was studied in a multivariable, mixed-effects logistic regression model, assuming a facility-specific random intercept that corresponds to local propensity to administer chemotherapy. Trends in OS between the periods 2004 through 2006, 2007 through 2009, and 2010 through 2011 were assessed by jointly testing coefficients from Cox models stratified by histology, sex, race, and quartiles of age. The proportional hazard assumption was verified using Schoenfeld residuals. Missing data (race, 2%; insurance, 2%; stage, 4%; B symptoms, 15%; receipt of chemotherapy, 2%) were multiply imputed by chained equations, creating 20 imputed data sets. Proportions of patients receiving chemotherapy, coefficients, and standard errors for regression models were then averaged using Rubin rules, incorporating uncertainty resulting from data missing at random.[13] Two-sided P values with an α

TABLE 1. Comparison of Human Immunodeficiency Virus (HIV)-Positive and HIV-Negative Patients With Non-Hodgkin Lymphoma

	No. of Patients (%)	
Variable	HIV-Positive, n = 10,769	HIV-Negative, n = 311,081[a]
Age group, y		
18-39	2711 (25.2)	19,049 (6.1)
40-59	6157 (57.2)	82,425 (26.5)
60-74	1282 (11.9)	111,662 (35.9)
≥75	619 (5.7)	97,945 (31.5)
Sex		
Female	2530 (23.5)	147,882 (47.5)
Male	8239 (76.5)	163,199 (52.5)
Race/ethnicity		
White non-Hispanic	5252 (48.8)	258,954 (83.2)
White Hispanic	1473 (13.7)	16,466 (5.3)
Black	3578 (33.2)	21,705 (7)
Asian/other	182 (1.7)	8214 (2.6)
Unrecorded	284 (2.6)	5742 (1.8)
Health insurance		
Private	4156 (38.6)	119,918 (38.5)
Medicaid	2674 (24.8)	14,225 (4.6)
Medicare	2358 (21.9)	157,519 (50.6)
Uninsured	1183 (11)	10,722 (3.4)
Other	88 (0.8)	2782 (0.9)
Unknown	310 (2.9)	5915 (1.9)
Annual income		
<$38,000	3150 (29.3)	48,253 (15.5)
$38,000-$47,999	2602 (24.2)	71,420 (23)
$48,000-$62,999	2474 (23)	83,361 (26.8)
≥$63,000	2290 (21.3)	101,355 (32.6)
Unknown	253 (2.3)	6692 (2.2)
Histology		
Diffuse large B-cell	5003 (46.5)	113,898 (36.6)
Burkitt	1588 (14.7)	4556 (1.5)
Primary central nervous system	977 (9.1)	8312 (2.7)
Primary effusion	106 (1)	75 (<0.1)
B-lymphoblastic	21 (0.2)	630 (0.2)
Indolent B-cell	1071 (9.9)	126,854 (40.8)
T-cell	568 (5.3)	20,905 (6.7)
Unspecified subtype	1435 (13.3)	35,851 (11.5)
Stage		
I	2325 (21.6)	85,804 (27.6)
II	1248 (11.6)	48,159 (15.5)
III	1663 (15.4)	52,027 (16.7)
IV	5193 (48.2)	113,710 (36.6)
Unrecorded	340 (3.2)	11,381 (3.7)
B symptoms		
Absent	4491 (41.7)	196,920 (63.3)
Present	5066 (47)	68,521 (22)
Unrecorded	1212 (11.3)	45,640 (14.7)
Primary site		
Nodal	7261 (67.4)	216,786 (69.7)
Extranodal	3508 (32.6)	94,295 (30.3)
Cancer program		
Community/other	843 (7.8)	33,971 (10.9)
Comprehensive community	4353 (40.4)	167,576 (53.9)
Academic/research	5573 (51.8)	109,534 (35.2)

[a] In this large data set, all chi-square *P* values were < .00001.

level of .05 and 95% confidence intervals (CIs) were calculated using the Stata/MP 14.0 statistical software package (StataCorp LP, College Station, Tex).

RESULTS

Patient Characteristics

Among 321,850 patients with NHL, 3.4% (10,769) were HIV-positive. Patients who had negative (56%) or unrecorded (40.7%) HIV status had very similar clinical characteristics (Supporting Table 1; see online supporting information). We grouped them as HIV-negative, because cancer registry flagging correctly identifies the majority of HIV-associated lymphomas,[14] and because this method was used in previous population-based studies to account for patients who did not get tested for HIV.[5,15] We validated this approach by repeating all relevant comparisons for only unequivocally HIV-positive or HIV-negative patients, with consistent results (data not shown). On average, HIV-positive patients were younger (median age, 47 years; interquartile range, 40-55 years), more often male, nonwhite, uninsured or with Medicaid insurance (indicating poverty or disability), and resided in poorer areas (Table 1). Their lymphomas were characterized more often by advanced stage or B symptoms. The most common histologies were DLBCL (47%), BL (15%), unspecified NHL (13%), indolent B-cell lymphomas (10%), and PCNSL (9%). Patients with PEL were almost exclusively male, and those with PCNSL included the highest proportion of black (43%) and white Hispanic (18%) individuals (Supporting Table 2; see online supporting information).

Trends in Clinical Characteristics

Between 2004 and 2012, the number of reported HIV-associated lymphomas decreased from 1329 to 896 per year (Fig. 1a). The median age did not change during this period, but the proportion of men increased from 75% to 81%. The decline in cases was significantly larger (by > 50%, from 729 to 357 cases) among white non-Hispanic patients compared with white Hispanic patients (17% decrease, from 178 to 147) and black patients (7% decrease, from 374 to 348; $P < .00001$). Consequently, in 2012, 50% of men and 77% of women with HIV-associated lymphoma were black or Hispanic. Such shifts were not evident in the HIV-negative cohort.

The decline in HIV-associated lymphomas was most pronounced for DLBCL, PCNSL, indolent B-cell, and T-cell histologies (Fig. 1b). In contrast, the number of BL cases (167 in 2004 vs 170 in 2012) remained relatively unchanged, thus significantly increasing the proportion of BL from 13% to 19% ($P < .00001$).

Delivery of Chemotherapy

Altogether, 74% of HIV-positive patients received chemotherapy. This proportion varied by histology: it was 81%

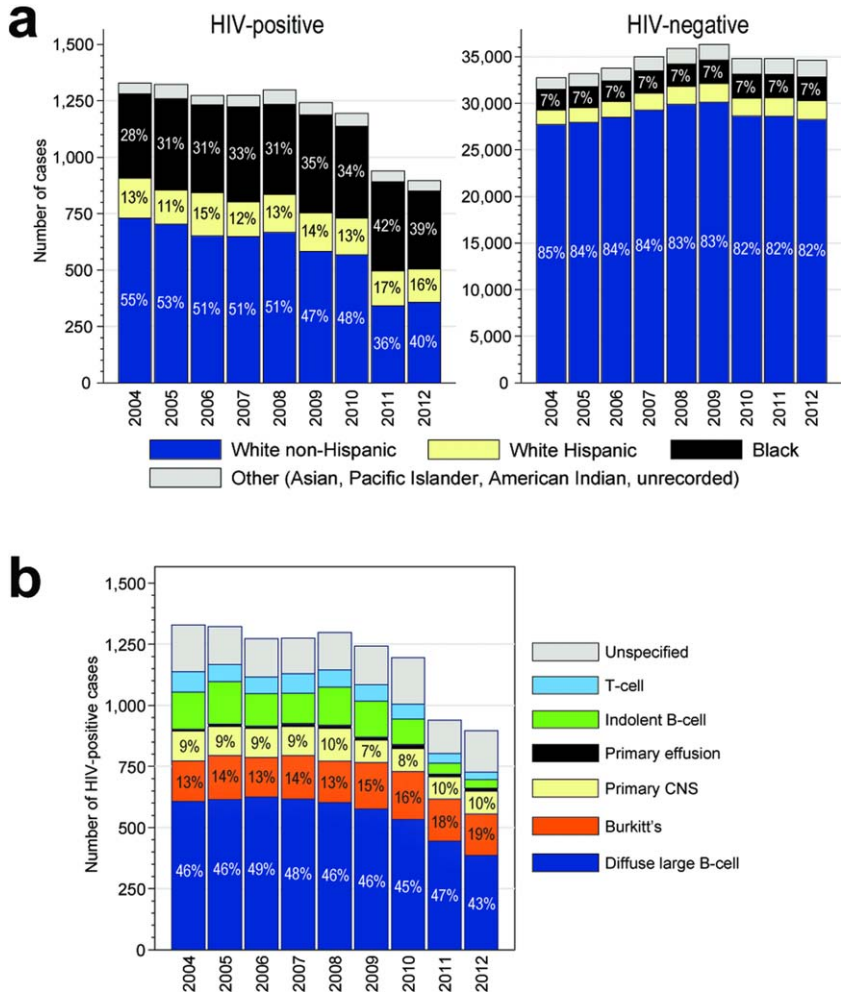

Figure 1. Charts illustrate trends in the crude numbers and proportions of patients with non-Hodgkin lymphoma in the National Cancer Data Base stratified by (a) race/ethnicity and (b) histologic subtype. Note the different scale on the y-axis for human immunodeficiency virus (HIV)-positive and HIV-negative populations. CNS indicates central nervous system.

for DLBCL, 90% for BL, 61% for PEL, but only 35% for PCNSL. Furthermore, chemotherapy was delivered to 70% of patients with T-cell lymphoma, 64% of those with indolent B-cell lymphoma, and 64% of those with unspecified lymphomas. Among HIV-negative patients, these proportions were similar for those with DLBCL (83%) and BL (89%), lower for those with PEL (49%), and twice as high for those with PCNSL (70%; $P < .00001$). Between 2004 and 2012, the proportion of HIV-positive patients who received chemotherapy did not change significantly for those with DLBCL, BL, or PEL, whereas it increased significantly for those with PCNSL after 2009 (Fig. 2).

We evaluated the factors associated with nonreceipt of chemotherapy among HIV-positive patients with DLBCL or BL—2 subtypes that require immediate systemic treatment (Table 2). In a multivariable model, the odds of not receiving chemotherapy increased with age and were higher in patients who were black, without private insurance, had DLBCL (rather than BL), or had stage I lymphoma. The risk was significantly lower in hospitals that were designated as academic/research institutions and those that reported $\geq$3 HIV-associated NHL cases per year. These higher volume facilities constituted 7.5% of 1340 unique cancer programs but cared for 46% of HIV-positive (and 19% of HIV-negative) patients. They were more commonly located in metropolitan counties with a population of >1 million (72% vs 45%, $P = .00003$), and proportionally treated more black patients (14% vs 6%) or Hispanic patients (10% vs 5%; $P < .00001$). A statistically significant variation in chemotherapy use between individual hospitals was confirmed by a positive intraclass correlation.

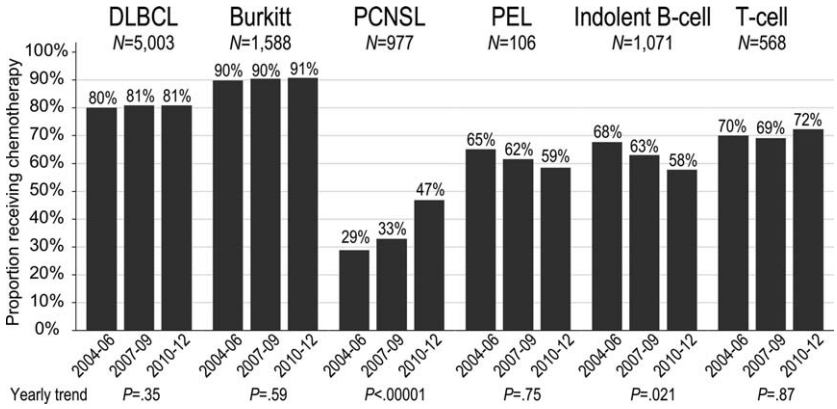

Figure 2. Trends in the proportions of human deficiency virus (HIV)-positive patients who received chemotherapy are illustrated. DLBCL indicates diffuse large B-cell lymphoma; PCNSL, primary central nervous system lymphoma; PEL, primary effusion lymphoma.

Survival Outcomes

OS was analyzed for 4 classic HIV-associated lymphomas: DLBCL, BL, PCNSL, and PEL (Fig. 3a). The median follow-up among censored patients was 4 years (interquartile range, 2-6 years). The median OS was 2 years (95% CI, 1.8-2.4 years) for DLBCL, 2.2 years (95% CI, 1.4-3.5 years) for BL, 0.3 years (95% CI, 0.26-0.33 years) for PCNSL, and 0.4 years (95% CI, 0.2-0.7 years) for PEL. Estimates at 5 years were 42% (95% CI, 41%-44%) for DLBCL, 45% (95% CI, 42%-48%) for BL, 22% (95% CI, 19%-25%) for PCNSL, and 28% (95% CI, 19%-37%) for PEL. Respective estimates in the HIV-negative cohort were 54%, 52%, 29%, and 10%.

Survival was better among HIV-positive patients who received chemotherapy (Fig. 3b), with a median OS of 4.1 years (95% CI, 3.3-4.8 years) for DLBCL, 3.9 years (95% CI, 2.4-5.7 years) for BL, 1.5 years (95% CI, 0.8-3.1 years) for PCNSL, and 0.7 years (95% CI, 0.4-1.1 years) for PEL. The OS rate at 5 years was 48% (95% CI, 46%-49%) for DLBCL, 48% (95% CI, 45%-51%) for BL, 40% (95% CI, 34%-47%) for PCNSL, and 28% (95% CI, 17%-41%) for PEL. Those estimates were significantly higher compared with those for patients who did not receive chemotherapy in all subtypes except PEL (28% with and 25% without chemotherapy) (Supporting Table 3; see online supporting information). In the trend analysis, OS significantly improved for patients with DLBCL, BL, and (after 2009) for PCNSL, whereas no improvement was detectable for those with PEL (Fig. 3c-f).

DISCUSSION

In this comprehensive study, which included the majority of HIV-associated lymphomas in the United States from 2004 to 2012, we demonstrated significant shifts in epidemiology, the application of chemotherapy, and survival. Receipt of chemotherapy varied by histology, sociodemographic features, and type of treating hospital. These findings are important, because most Americans with HIV-associated lymphoma are now black or Hispanic, and the ability to deliver chemotherapy closely correlates with survival outcomes.

Proportions of racial/ethnic subgroups mirror the incidence of HIV in the United States. Blacks constituted 13% of the country's population in 2013, but they accounted for 42% of new HIV infections among men and 63% among women.[16] The incidence of HIV-associated lymphoma has decreased overall since the 1990s, although prior studies did not analyze it in racial subgroups.[9] We observed an uneven decline, which was markedly more pronounced in the white non-Hispanic population, possibly reflecting disparities in patients' immune status, considering the higher rate of virologic failure on CART among blacks.[17] Similar shifts in proportions of different races are evident in HIV-associated Hodgkin lymphoma.[18] Compared with our more recent data, the HACM study (1996-2010) demonstrated a similar proportion of DLBCL (50%), but less BL (9%), and more PCNSL (16%).[6] The CNICS study (1996-2010) reported an increasing proportion of BL over time, but our data indicated that this was because of a reciprocal decrease in DLBCL and other subtypes rather than an increase in BL.[8]

We also placed survival outcomes in the context of chemotherapy application, although chemotherapy use was only identified as a binary variable, without distinguishing specific regimens. The HACM researchers

TABLE 2. Factors Associated With Nonreceipt of Chemotherapy Among Human Immunodeficiency Virus-Positive Patients With Diffuse Large B-Cell or Burkitt Lymphoma in a Multivariable Logistic Model, N = 6591

Variable	OR (95% CI)	*P*
Age group, y		
18-39	Reference	< .00001
40-59	1.43 (1.20-1.71)	
60-74	1.63 (1.24-2.14)	
≥75	2.27 (1.58-3.26)	
Sex		
Female	Reference	.77
Male	1.03 (0.86-1.22)	
Race		
White non-Hispanic	Reference	.0018
White Hispanic	1.22 (0.99-1.54)	
Black	1.41 (1.18-1.68)	
Asian/other	1.03 (0.57-1.86)	
Histology		
Diffuse large B-cell	Reference	< .00001
Burkitt	0.51 (0.42-0.62)	
Stage		
I	Reference	<.00001
II	0.50 (0.39-0.65)	
III	0.38 (0.30-0.50)	
IV	0.69 (0.57-0.84)	
B symptoms		
Absent	Reference	.74
Present	0.97 (0.84-1.14)	
Annual income		
<$38,000	1.23 (0.99-1.52)	.15
$38,000-$47,999	1.21 (0.97-1.51)	
$48,000-$62,999	1.03 (0.83-1.28)	
≥$63,000	Reference	
Health insurance		
Private	Reference	< .00001
Medicaid	1.55 (1.29-1.87)	
Medicare	1.55 (1.26-1.92)	
Uninsured	2.11 (1.67-2.67)	
Other insurance	1.22 (0.55-2.72)	
Facility case volume per y		
<3	Reference	.0005
≥3	0.71 (0.58-0.86)	
Cancer program		
Community/other	Reference	.016
Comprehensive community	0.86 (0.65-1.13)	
Academic/research	0.68 (0.51-0.92)	
Year of diagnosis (per 1 y)	0.99 (0.96-1.01)	.29
Individual hospital intraclass correlation = 6.4%[a]	(3.7%-10.8%)	

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] This is a random effect for measuring variation among all treating hospitals; an intraclass correlation of 0% indicates no significant variation.

previously demonstrated higher rates of nontreatment among HIV-positive individuals with various cancers.[10] Another registry-based case-control study indicated a high risk of dose reductions in lymphoma chemotherapy.[19] Advanced immunodeficiency, AIDS-related infections, and comorbidities are among the barriers to administering curative systemic regimens in patients with HIV-associated lymphoma. Because rituximab-containing chemotherapy exhibited high toxicity among patients with low CD4 cell counts in the initial randomized trial, clinicians were hesitant about using immunochemotherapy in the HIV-positive population.[20] Subsequent studies demonstrated safety of this approach in less compromised patients,[21,22] and rituximab repeatedly conferred survival benefits for HIV-positive patients who had CD20-expressing NHL.[23,24] We observed no change in the proportion of patients receiving chemotherapy for DLBCL and BL between 2004 and 2012, whereas OS improved during that period. Better management of HIV itself, including access and adherence to CART, and better supportive care likely contribute to these favorable trends. An advantage may also be in the quality of chemotherapeutic regimens, because the application of novel infusional regimens is associated with better OS.[22,24,25] We corroborated no significant difference in survival between patients with DLBCL and BL, as previously suggested in the CNICS report (44% and 50% at 5 years, respectively) and in a German observational study (63% and 69% at 2 years, respectively).[8,26]

We observed a significant association between receipt of chemotherapy for HIV-associated lymphoma and certain patient-specific and hospital-specific factors. We acknowledge a lack of important confounders in the NCDB (the presence of AIDS, CART, performance status, and psychosocial barriers to treatment) that limited the interpretation of our findings. Substance abuse, homelessness, and mental health disorders are prevalent among individuals with HIV and influence their health outcomes.[27-29] Advanced immunodeficiency may correlate with race or insurance-related disparities, although cancer treatment was less likely among black patients even after adjustment for CD4 count and the mode of HIV transmission in the HACM study.[10] Sociodemographic disparities in treatment and survival have been widely reported in patients with HIV-negative lymphomas.[30,31] A study focused on adolescents and young adults suggested that racial disparities in NHL survival were attenuated after excluding HIV-positive patients from the cohort.[32] Our study highlights the importance of addressing correctible disparities in a disease in which the majority of patients are black or Hispanic and thus vulnerable to both HIV-related and socioeconomic barriers to curative cancer therapy. Cancer programs could streamline their patient navigation resources, expand psychosocial support services, and focus on coordination of care to assure that HIV-positive patients with lymphoma can receive curative chemotherapy as well as CART. An additional novel finding is that nonreceipt of chemotherapy was nearly 30% less likely for patients who received treatment at

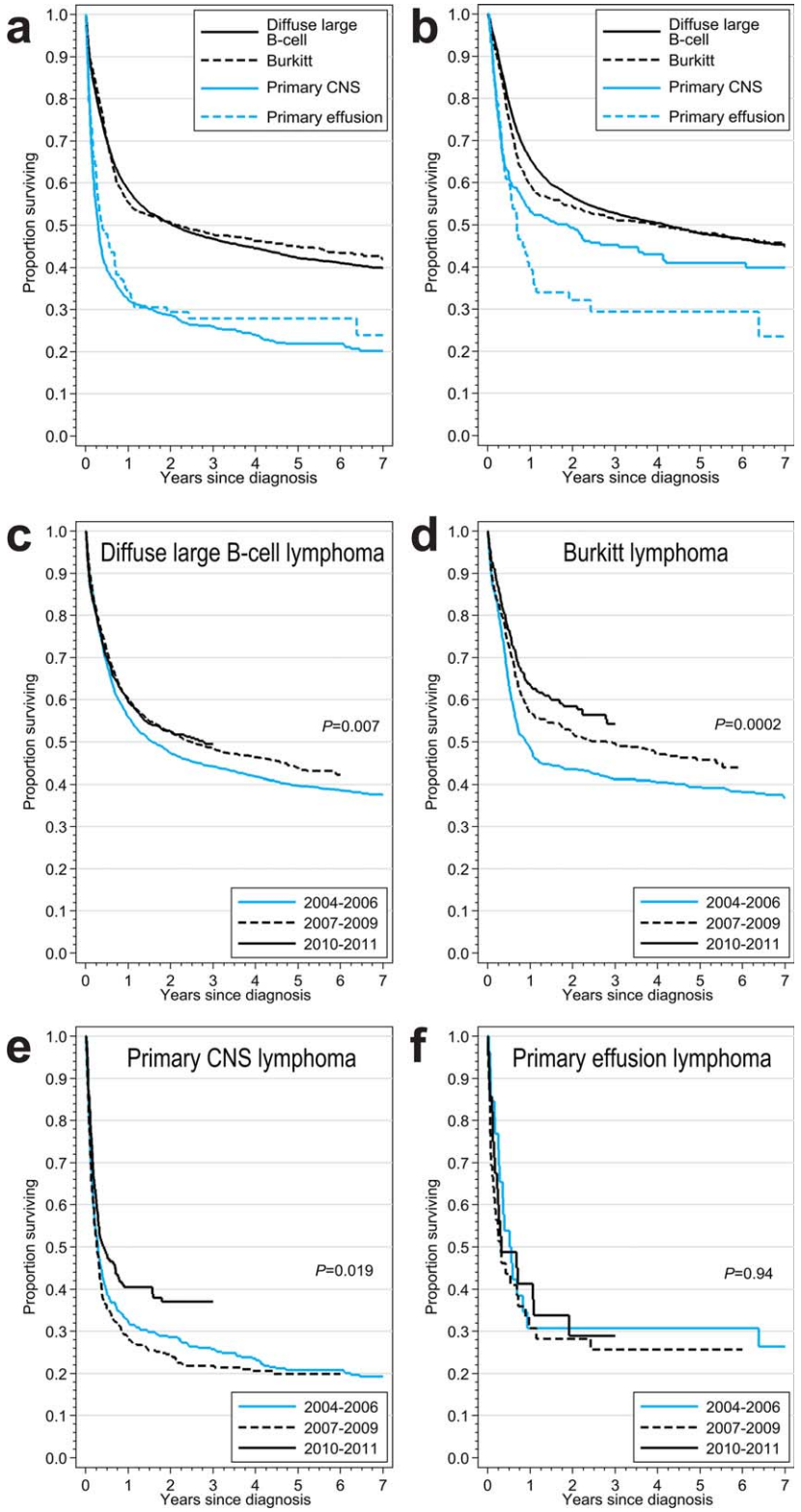

Figure 3. Overall survival curves are shown (a) for all patients with human immunodeficiency virus (HIV)-associated lymphoma and (b) for patients with HIV-associated lymphoma who received chemotherapy. (b-f) Survival curves are shown for subtypes of HIV-associated lymphoma stratified by period of diagnosis. *P* values for period of diagnosis are derived from Cox models adjusting for age, sex, and race. CNS indicates central nervous system.

institutions that treated ≥3 HIV-associated lymphomas per year, even after adjustment for the academic/community setting. Although higher volume centers care disproportionally for metropolitan minority populations, clinicians' experience, availability of supportive services, and infectious disease expertise in the management of interactions between CART and chemotherapy all may contribute to better delivery of cancer treatment. We cannot rule out self-selection of healthier patients to receive care at academic hospitals, so additional research on potential confounding characteristics in various settings is needed. It is noteworthy that, in a recent British report focused on university hospitals, the survival of HIV-positive patients with DLBCL was actually marginally better than that for HIV-negative patients.[33] Centralization of care might have benefits, but we should point out that it may also create an additional burden for vulnerable patients because of the need for referral or travel, posing a risk of undesirable diagnostic or treatment delay.

We distinguished outcomes for PCNSL and PEL—2 less common, yet problematic subtypes driven by oncogenic viruses.[34] PCNSL occurs in individuals with advanced AIDS and is often treated using radiation therapy alone or with supportive care only because of patients' poor clinical condition.[2,35] We observed increased use of chemotherapy in patients with PCNSL after 2009 that was paralleled by increased OS during that period, although expanded use of CART may have caused those gains too, especially because remissions of HIV-associated PCNSL with CART alone have been reported.[36] Survival curves for patients with PCNSL largely overlapped with the curves for those for PEL in the overall cohort, yet the OS of patients with PCNSL who received chemotherapy was closer to the OS of those with DLBCL/BL, generating a hypothesis that the administration of systemic treatment may translate into better outcomes. In line with this, current National Comprehensive Cancer Network guidelines advocate high-dose methotrexate for all HIV-positive patients who have PCNSL, regardless of performance or immune status,[37] although only prospective research can firmly establish the advantage of this approach. In contrast, outcomes in PEL remain poor regardless of chemotherapy receipt and without any evident trend, highlighting the inadequacy of currently available modalities.[38]

Our analysis, which relied on cancer registry data, has several additional limitations. The NCDB reports only information from accredited cancer programs, so it is not completely population-based and does not allow a calculation of standard epidemiologic measures like incidence rates, which limited us to a study of crude numbers and proportions.[39] In addition, as a hospital-based registry, the NCDB may not capture patients treated in private practices, restricting the scope of our analysis. Records of immune status or CART treatment were lacking, in contrast to the CNICS or HACM cohorts. An advantage of our analysis was the ability to study chemotherapy administration in various types of lymphoma, although it would be of further interest to discern treatment regimens, particularly infusional chemotherapy or rituximab use. Because CD4 counts, the presence of AIDS, and exposure to CART are critical confounders of OS in patients with HIV-associated lymphomas,[1,8,40,41] we could not reliably analyze prognostic factors for survival in multivariable models. Response to treatment, cause of death, and progression-free survival also were unavailable in this data set.

In conclusion, most HIV-positive patients with newly diagnosed DLBCL and BL in the United States receive active chemotherapy. OS has increased over the past decade for these patients and does not differ between DLBCL and BL. Significant sociodemographic disparities in treatment delivery need to be addressed in view of the evolving epidemiology. Centralized care may be advantageous in patients with HIV-associated lymphoma considering the correlation of hospital case volume with chemotherapy delivery. PEL continues to be characterized by a markedly worse prognosis and uncertain benefit of standard chemotherapy. Finally, US cancer registries should continue to record the HIV status of patients with NHL or even expand the scope of collected data to enable ongoing epidemiologic surveillance and health outcomes research in this population.

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CONFLICT OF INTEREST DISCLOSURES

Adam J. Olszewski reports personal fees from Bristol-Myers-Squibb and other support from Genentech outside the submitted work. Jorge J. Castillo reports grants and personal fees from Pharmacyclics, grants from Millennium and Gilead, and personal fees from Otsuka and Biogen outside the submitted work.

AUTHOR CONTRIBUTIONS

Adam J. Olszewski designed the study, conducted the analysis, interpreted the data, and wrote the article. **Jaleh Fallah** interpreted the data and wrote the article. **Jorge J. Castillo** designed the study, interpreted the data, and wrote the article.

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