

# HIV Infection and Survival of Lymphoma Patients in the Era of Highly Active Antiretroviral Therapy

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## Abstract

**Background:** Highly active antiretroviral therapy (HAART) has extended the life expectancy of patients with HIV/AIDS to approach that of the general population. However, it remains unclear whether HIV infection affects the survival of patients with lymphoma in the HAART era.

**Methods:** Patients diagnosed with Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, peripheral T-cell lymphoma (PTCL), or follicular lymphoma during 2004–2011 were identified from the National Cancer Database. Survival analyses were conducted, where each HIV-infected patient was propensity score matched to a HIV-uninfected patient on the basis of demographic factors, clinical features, and treatment characteristics.

**Results:** Among 179,520 patients, the prevalence of HIV-infection ranged from 1.0% for follicular lymphoma, 3.3% for PTCL, 4.7% for Hodgkin lymphoma, 5.4% for DLBCL, to 29%

for Burkitt lymphoma. HIV infection was significantly associated with inferior overall survival for patients with each lymphoma subtype: Hodgkin lymphoma [HR, 1.47; 95% confidence interval (CI), 1.25–1.74], DLBCL (HR, 1.95; 95% CI, 1.80–2.11), Burkitt lymphoma (HR, 1.46; 95% CI, 1.24–1.73), PTCL (HR, 1.43; 95% CI, 1.14–1.79), and follicular lymphoma (HR, 1.44; 95% CI, 1.04–2.00).

**Conclusions:** HIV/AIDS continues to be independently associated with increased risk of death among patients with lymphoma in the HAART era in the United States, and the association varies by lymphoma histologic subtype.

**Impact:** Examination of effective management strategies for patients with HIV/AIDS-associated lymphoma and enrollment of patients in prospective clinical trials are needed to improve patient outcomes. *Cancer Epidemiol Biomarkers Prev*; 26(3); 303–11. ©2016 AACR.

## Introduction

Highly active antiretroviral therapy (HAART) introduced in 1996 has turned HIV/AIDS from a rapidly fatal disease to a manageable chronic disease (1). Currently, HIV-infected patients who are treated with HAART have a near-normal life expectancy approaching that of the general population (2–4). HIV infection is the strongest risk factor for lymphoma with a 77-fold associated risk for non-Hodgkin lymphoma (NHL) and an 11-fold risk for Hodgkin lymphoma (5–7). In the HAART era, the incidence of AIDS-defining NHL subtypes decreased in HIV-infected patients (8–10), and changes in the HIV-associated relative risks partly contributed to the decrease (10), whereas the incidence of Hodgkin lymphoma remained stable and even increased in some HIV/AIDS cohorts (10–12). As a result, lymphoma is currently one of the most common cancers and a leading cause of cancer death

among people with HIV/AIDS (7, 13, 14). Among patients with lymphoma, HIV/AIDS status has been strongly associated with poor survival (15, 16); however, it remains unclear to what extent this association has changed in the HAART era.

Several clinical trials (17–21) and observational studies (22–24) with HIV-infected lymphoma cases treated with HAART reported survival outcomes comparable to general patients with lymphoma. However, a few studies directly compared HIV-infected and HIV-uninfected patients with lymphoma and found inconsistent results. Two studies from Europe found no difference (25, 26), one study from the United States found that HIV infection was still negatively associated with NHL survival in the HAART era (27), and another recent study from England found that patients with diffuse large B-cell lymphoma (DLBCL, the most common NHL subtype) with HIV infection had a significantly longer survival (28). Thus, the evidence for an association between HIV infection and lymphoma survival remains elusive, likely due to limitations of previous studies, which include the lack of a well-matched control group, a small sample size, highly selected cases, and short follow-up. To understand this relationship in an adequately designed study with sufficient sample size, we used a national hospital-based cancer registry dataset, which captures approximately 70% of the incident cancer cases in the United States, to examine the association between HIV infection status and survival for Hodgkin lymphoma and major NHL subtypes. As a secondary aim, we also examined the association between HIV infection status and presence of adverse presentation and treatment factors such as diagnosis at an advanced stage, having

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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**doi:** 10.1158/1055-9965.EPI-16-0595

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B-symptoms, comorbidities, and extranodal primary site, which may contribute to poor survival.

## Materials and Methods

### Patients

We used data from the National Cancer Database (NCDB), a nationwide, hospital-based cancer registry jointly sponsored by the American Cancer Society and the American College of Surgeons. The NCDB contains approximately 30 million records from more than 1,500 Commission on Cancer (CoC)-accredited facilities in the United States and Puerto Rico. The NCDB contains standardized information on patient demographics, insurance status, tumor characteristics, comorbidities, zip-code level socioeconomic factors, and the type of facility in which patients were treated. Currently, CoC facilities report patients' vital status and date of death to the NCDB on a yearly basis. More information about NCDB can be found at its webpage (29). All data were de-identified, and the study was considered exempt from Institutional Review Board (IRB) review by the Morehouse University IRB.

Patients diagnosed during 2004 to 2011 with the following lymphoma subtypes as the first primary cancer were identified using the third edition of International Classification of Diseases for Oncology (ICD-O-3) histology codes for: Hodgkin lymphoma (9650–9667), DLBCL (9678–9680, 9684B), Burkitt lymphoma (9687), peripheral T-cell lymphoma (PTCL; 9575T/NK, 9702, 9705, 9708, 9709, 9714, 9716–9718), and follicular lymphoma (9690, 9691, 9695, 9698). DLBCL, Burkitt lymphoma, and PTCL were selected because HIV infection was most prevalent among patients with NHL of these subtypes, and follicular lymphoma was selected as it is a common NHL subtype not strongly associated with HIV/AIDS. Patients with lymphoma were included in the analysis if they were 18 to 84 years old, and if they received all or part of their first course of treatment at the reporting facility. Patients were excluded if sex, stage, primary site, or insurance status was unknown or if they had government insurance other than Medicaid, Medicare, TRICARE, or military. The analyses included a total of 179,520 patients with lymphoma: 36,521 patients with Hodgkin lymphoma, 81,534 patients with DLBCL, 4,684 Burkitt lymphoma, 12,061 patients with PTCL, and 44,720 patients with follicular lymphoma.

### Study variables

All information was captured using standardized codes defined by the Facility Oncology Registry Data Standards (FORDS; ref. 30). A patient was defined as HIV-infected if either the Collaborative Staging Site-Specific Factor 1 indicated an association with HIV/AIDS or if HIV/AIDS was reported as a comorbidity. Age at diagnosis was classified into 5 categories: 18–34 years, 35–44 years, 45–54 years, 55–64 years, and 65–84 years. Race/ethnicity was coded as nonHispanic white, nonHispanic black, Hispanic, nonHispanic other, and unknown. Zip-code level education was measured as the proportion of adults without high school diploma obtained through linkage to the 2000 U.S. Census data and was grouped as <14%, 14%–19.9%, 20%–28.9%, 29%+ or unknown. Insurance status was coded as uninsured, Medicaid, younger Medicare (age 18–64 years), older Medicare (age 65+ years), or privately insured (including TRICARE and military insurance). Stage at diagnosis (I, II, III, and IV) was defined according to the sixth edition of the American Joint Committee

on Cancer (AJCC) Staging Manual (31). Presence of B-symptoms was recorded in the Collaborative Staging Site-Specific Factor 2. Preexisting medical conditions and/or complications were recorded, and a modified Charlson Deyo Score (32) was calculated excluding cancer and HIV/AIDS from the score construction; the comorbidity score was then coded into 3 categories: 0, 1,  $\geq 2$ . The first course of treatment was grouped into 3 categories: no treatment, chemotherapy-based treatment, and other/unknown. Time to treatment for those who received treatment was calculated from diagnosis date to the date of first course of treatment. Overall survival was calculated from the date of diagnosis to December 31, 2011, 5 years after diagnosis, the date of death, or the date of last contact, whichever occurred first.

### Statistical analyses

For each lymphoma subtype, the prevalence of HIV infection was examined. Distribution of demographic and clinical factors was described by HIV infection status, and a  $\chi^2$  test was used to assess the differences by HIV infection status. We used a propensity score matching approach in analysis to control for the underlying differences between HIV-infected and -uninfected patients. To examine the relationship between HIV infection status and lymphoma presentation, we matched an HIV-uninfected patient to each HIV-infected patient with the same lymphoma subtype by propensity score on the basis of sociodemographic factors including year of diagnosis, sex, age, race/ethnicity, zip-code level education, and insurance status and fitted log-binomial regression models to calculate the prevalence ratios (PR) and 95% confidence intervals (95CI) of adverse clinical presentations [advanced stage at diagnosis (III/IV), presence of B-symptoms, presence of comorbidities, and extranodal primary site] associated with HIV infection, controlling for the sociodemographic factors mentioned above. To examine the association of HIV infection with treatment, we again matched each HIV-infected patient to an HIV-uninfected patient with the same lymphoma subtype by propensity score on the basis of the sociodemographic factors above and presentation factors including stage at diagnosis, presence of B-symptoms, comorbidity score, and primary site and fitted log-binomial regression models for 2 treatment outcomes: receipt of chemotherapy-based treatment and receiving treatment within 2 weeks of diagnosis, still adjusting for the matching factors.

Finally, for survival analysis, we created 1-to-1 matched dataset for each lymphoma subtype on the basis of propensity scores constructed from the above sociodemographic and presentation factors, plus treatment and time to treatment ( $\leq 2$  or  $> 2$  weeks), and limited analysis to those patients diagnosed in 2004–2009 to ensure adequate follow-up time. Survival status through year 3 following diagnosis was available for 79% of patients. We then plotted Kaplan–Meier survival curves for each subtype by HIV infection status and used log-rank tests to compare differences. We also fitted Cox proportional hazard models to calculate adjusted HRs and 95% CI associated with HIV infection controlling for all the matching variables, in total and stratified by treatment. The proportional hazard assumption was checked by plotting the  $\log[-\log(\text{survival})]$  versus  $\log(\text{time})$  curves and the assumption was met for all covariates except treatment, thus a treatment-by-time interaction term was included in the Cox models for total patients. All the propensity score matched datasets were balanced in terms of all the variables used in the propensity score construction.

**Table 1.** Characteristics of HIV-uninfected and HIV-infected lymphoma patients, NCDB 2004–2011

	HL		DLBCL		BL		PTCL		FL	
	HIV-uninfected, n (%)	HIV-infected, n (%)	HIV-uninfected, n (%)	HIV-infected, n (%)	HIV-uninfected, n (%)	HIV-infected, n (%)	HIV-uninfected, n (%)	HIV-infected, n (%)	HIV-uninfected, n (%)	HIV-infected, n (%)
Total	34,792	1,729	77,110	4,424	3,336	1,348	11,665	396	44,285	435
Year of diagnosis										
2004	4,229 (12.2)	207 (12)	9,096 (11.8)	618 (14)	386 (11.6)	163 (12.1)	1,325 (11.4)	63 (15.9)	5,562 (12.6)	70 (16.1)
2005	4,321 (12.4)	223 (12.9)	9,290 (12)	562 (12.7)	356 (10.7)	170 (12.6)	1,404 (12)	51 (12.9)	5,555 (12.5)	73 (16.8)
2006	4,398 (12.6)	197 (11.4)	9,442 (12.2)	578 (13.1)	420 (12.6)	155 (11.5)	1,436 (12.3)	52 (13.1)	5,904 (13.3)	62 (14.3)
2007	4,445 (12.8)	203 (11.7)	9,864 (12.8)	587 (13.3)	425 (12.7)	172 (12.8)	1,490 (12.8)	57 (14.4)	5,929 (13.4)	61 (14)
2008	4,585 (13.2)	264 (15.3)	10,132 (13.1)	599 (13.5)	455 (13.6)	162 (12)	1,511 (13)	42 (10.6)	5,981 (13.5)	54 (12.4)
2009	4,566 (13.1)	223 (12.9)	10,028 (13)	543 (12.3)	467 (14)	186 (13.8)	1,635 (14)	59 (14.9)	5,617 (12.7)	65 (14.9)
2010	4,176 (12)	204 (11.8)	9,610 (12.5)	497 (11.2)	417 (12.5)	190 (14.1)	1,517 (13)	48 (12.1)	4,918 (11.1)	37 (8.5)
2011	4,072 (11.7)	208 (12)	9,648 (12.5)	440 (9.9)	410 (12.3)	150 (11.1)	1,347 (11.5)	24 (6.1)	4,819 (10.9)	13 (3)
Age group, y										
18–34	15,073 (43.3)	431 (24.9)	4,608 (6)	568 (12.8)	716 (21.5)	277 (20.5)	1,161 (10)	52 (13.1)	1,143 (2.6)	23 (5.3)
35–44	6,275 (18)	545 (31.5)	5,495 (7.1)	1,393 (31.5)	453 (13.6)	511 (37.9)	1,195 (10.2)	132 (33.3)	3,574 (8.1)	80 (18.4)
45–54	4,773 (13.7)	474 (27.4)	10,902 (14.1)	1,469 (33.2)	618 (18.5)	408 (30.3)	2,075 (17.8)	103 (26)	8,716 (19.7)	124 (28.5)
55–64	3,694 (10.6)	188 (10.9)	17,259 (22.4)	588 (13.3)	632 (18.9)	126 (9.3)	2,601 (22.3)	58 (14.6)	11,969 (27)	98 (22.5)
65–84	4,977 (14.3)	91 (5.3)	38,846 (50.4)	406 (9.2)	917 (27.5)	26 (1.9)	4,633 (39.7)	51 (12.9)	18,883 (42.6)	110 (25.3)
Sex										
Male	18,537 (53.3)	1,384 (80)	40,850 (53)	3,419 (77.3)	2,224 (66.7)	1,154 (85.6)	6,809 (58.4)	278 (70.2)	21,594 (48.8)	278 (63.9)
Female	16,255 (46.7)	345 (20)	36,260 (47)	1,005 (22.7)	1,112 (33.3)	194 (14.4)	4,856 (41.6)	118 (29.8)	22,691 (51.2)	157 (36.1)
Race										
NonHispanic white	24,449 (70.3)	675 (39)	57,096 (74)	1,846 (41.7)	2,458 (73.7)	654 (48.5)	7,853 (67.3)	167 (42.2)	35,002 (79)	280 (64.4)
Hispanic	2,625 (7.5)	288 (16.7)	5,175 (6.7)	652 (14.7)	291 (8.7)	205 (15.2)	787 (6.7)	42 (10.6)	2,180 (4.9)	30 (6.9)
NonHispanic black	3,997 (11.5)	630 (36.4)	5,538 (7.2)	1,585 (35.8)	196 (5.9)	393 (29.2)	1,718 (14.7)	152 (38.4)	2,047 (4.6)	77 (17.7)
NonHispanic other	1,181 (3.4)	51 (2.9)	3,227 (4.2)	117 (2.6)	144 (4.3)	39 (2.9)	509 (4.4)	14 (3.5)	1,094 (2.5)	10 (2.3)
Unknown	2,540 (7.3)	85 (4.9)	6,074 (7.9)	224 (5.1)	247 (7.4)	57 (4.2)	798 (6.8)	21 (5.3)	3,962 (8.9)	38 (8.7)
Zip-code level median % of without high school diploma										
<14%	12,142 (34.9)	376 (21.7)	26,283 (34.1)	971 (21.9)	1,188 (35.6)	306 (22.7)	3,987 (34.2)	87 (22)	16,374 (37)	110 (25.3)
14%–19.9%	7,776 (22.3)	296 (17.1)	17,824 (23.1)	746 (16.9)	739 (22.2)	234 (17.4)	2,560 (21.9)	63 (15.9)	10,370 (23.4)	100 (23)
20%–28.9%	7,335 (21.1)	435 (25.2)	16,849 (21.9)	1,042 (23.6)	690 (20.7)	332 (24.6)	2,453 (21)	110 (27.8)	9,154 (20.7)	113 (26)
29% +	5,409 (15.5)	527 (30.5)	11,894 (15.4)	1,438 (32.5)	488 (14.6)	391 (29)	1,958 (16.8)	116 (29.3)	5,840 (13.2)	84 (19.3)
Unknown	2,130 (6.1)	95 (5.5)	4,260 (5.5)	227 (5.1)	231 (6.9)	85 (6.3)	707 (6.1)	20 (5.1)	2,547 (5.8)	28 (6.4)
Insurance status										
Uninsured	3,044 (8.7)	199 (11.5)	3,664 (4.8)	523 (11.8)	223 (6.7)	149 (11.1)	635 (5.4)	47 (11.9)	1,556 (3.5)	31 (7.1)
Medicaid	3,511 (10.1)	469 (27.1)	4,719 (6.1)	1,236 (27.9)	315 (9.4)	376 (27.9)	957 (8.2)	108 (27.3)	1,761 (4)	57 (13.1)
Younger Medicare	1,140 (3.3)	233 (13.5)	3,337 (4.3)	602 (13.6)	152 (4.6)	115 (8.5)	550 (4.7)	30 (7.6)	1,845 (4.2)	35 (8)
Older Medicare	4,137 (11.9)	67 (3.9)	32,643 (42.3)	323 (7.3)	775 (23.2)	21 (1.6)	3,895 (33.4)	39 (9.8)	15,905 (35.9)	90 (20.7)
Private	22,960 (66)	761 (44)	32,747 (42.5)	1,740 (39.3)	32,747 (42.5)	1,871 (56.1)	5,628 (48.2)	172 (43.4)	23,218 (52.4)	222 (51)
Primary site										
Lymphnodes	33,666 (96.8)	1,647 (95.3)	50,039 (64.9)	2,817 (63.7)	2,328 (69.8)	1,062 (78.8)	6,934 (59.4)	278 (70.2)	37,711 (85.2)	370 (85.1)
Extranodal	1,126 (3.2)	82 (4.7)	27,071 (35.1)	1,607 (36.3)	1,008 (30.2)	286 (21.2)	4,731 (40.6)	118 (29.8)	6,574 (14.8)	65 (14.9)
Comorbidity score <sup>b</sup>										
0	30,310 (87.1)	1,456 (84.2)	57,015 (73.9)	3,525 (79.7)	2,606 (78.1)	1,145 (84.9)	9,238 (79.2)	322 (81.3)	36,320 (82)	361 (83)
1	3,462 (10)	180 (10.4)	12,962 (16.8)	612 (13.8)	502 (15)	135 (10)	1,669 (14.3)	47 (11.9)	5,756 (13)	55 (12.6)
≥2	1,020 (2.9)	95 (5.4)	7,133 (9.3)	287 (6.5)	228 (6.8)	68 (5)	758 (6.5)	27 (6.8)	2,209 (5)	19 (4.4)
B-symptom presence										
No	17,569 (50.5)	468 (27.1)	45,921 (59.6)	1,754 (39.6)	1,787 (53.6)	581 (43.1)	6,296 (54)	139 (35.1)	30,019 (67.8)	210 (48.3)
Yes	13,889 (39.9)	1,112 (64.3)	21,813 (28.3)	2,149 (48.6)	1,139 (34.1)	621 (46.1)	3,978 (34.1)	208 (52.5)	7,824 (17.7)	196 (45.1)
Unknown	3,334 (9.6)	149 (8.6)	9,376 (12.2)	521 (11.8)	410 (12.3)	146 (10.8)	1,391 (11.9)	49 (12.4)	6,442 (14.5)	29 (6.7)

(Continued on the following page)

**Table 1.** Characteristics of HIV-uninfected and HIV-infected lymphoma patients, NCDB 2004–2011 (Cont'd)

Stage	HL			DLBCL			BL			PTCL			FL		
	HIV-uninfected, n (%)	HIV-infected, n (%)	P <sup>a</sup>	HIV-uninfected, n (%)	HIV-infected, n (%)	P <sup>a</sup>	HIV-uninfected, n (%)	HIV-infected, n (%)	P <sup>a</sup>	HIV-uninfected, n (%)	HIV-infected, n (%)	P <sup>a</sup>	HIV-uninfected, n (%)	HIV-infected, n (%)	P <sup>a</sup>
I	5,911 (17)	214 (12.4)	<0.0001	21,537 (27.9)	996 (22.5)	<0.0001	683 (20.5)	190 (14.1)	<0.0001	3,754 (32.2)	79 (19.9)	<0.0001	11,906 (26.9)	87 (2.0)	<0.0001
II	15,573 (44.8)	384 (22.2)		15,833 (20.5)	619 (14)		518 (15.5)	141 (10.5)		1,561 (13.4)	55 (13.9)		7,591 (17.1)	58 (13.3)	
III	7,321 (21)	405 (23.4)		13,539 (17.6)	785 (17.7)		361 (10.8)	164 (12.2)		2,308 (19.8)	90 (22.7)		11,386 (25.7)	121 (27.8)	
IV	5,987 (17.2)	726 (42)		26,201 (34)	2,024 (45.8)		1,774 (53.2)	853 (63.3)		4,042 (34.7)	172 (43.4)		13,402 (30.3)	169 (38.9)	
Initial treatment															
No treatment	2,773 (8)	271 (15.7)	<0.0001	8,672 (11.2)	718 (16.2)	<0.0001	281 (8.4)	111 (8.2)	0.69	2,160 (18.5)	98 (24.7)	<0.0001	11,060 (25)	95 (21.8)	0.005
Other/unknown	1,508 (4.3)	48 (2.8)		2,891 (3.7)	344 (7.8)		50 (1.5)	16 (1.2)		1,836 (15.7)	31 (7.8)		5,542 (12.5)	37 (8.5)	
Chemotherapy	30,511 (87.7)	1,410 (81.6)		65,547 (85)	3,362 (7.6)		3,005 (90.1)	1,221 (90.6)		7,669 (65.7)	267 (67.4)		27,683 (62.5)	303 (69.7)	
Days to initial treatment, d															
No treatment	2,773 (8)	271 (15.7)	<0.0001	8,672 (11.2)	718 (16.2)	<0.0001	281 (8.4)	111 (8.2)	0.055	2,160 (18.5)	98 (24.7)	<0.0001	11,060 (25)	95 (21.8)	<0.0001
0–14	6,699 (19.3)	371 (21.5)		22,639 (29.4)	1,497 (33.8)		1,660 (49.8)	732 (54.3)		2,537 (21.7)	113 (28.5)		5,447 (12.3)	90 (20.7)	
15–30	10,466 (30.1)	429 (24.8)		21,061 (27.3)	968 (21.9)		792 (23.7)	302 (22.4)		2,333 (20)	86 (21.7)		8,132 (18.4)	78 (17.9)	
31–60	9,197 (26.4)	376 (21.7)		15,369 (19.9)	711 (16.1)		359 (10.8)	119 (8.8)		2,335 (20)	45 (11.4)		10,500 (23.7)	100 (23)	
>60	4,330 (12.4)	225 (13)		6,157 (8)	342 (7.7)		124 (3.7)	37 (2.7)		1,752 (15)	35 (8.8)		7,187 (16.2)	58 (13.3)	
Missing	1,327 (3.8)	57 (3.3)		3,212 (4.2)	188 (4.2)		120 (3.6)	47 (3.5)		548 (4.7)	19 (4.8)		1,959 (4.4)	14 (3.2)	

Abbreviations: BL, Burkitt lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma.

<sup>a</sup>P values from  $\chi^2$  tests comparing HIV-uninfected patients versus HIV-infected patients.

<sup>b</sup>Modified weighted Charlson Deyo Score with cancer and HIV/AIDS excluded from the construction of the score.

Several sensitivity analyses were conducted: adding facility type as a covariate did not substantively change the associations of HIV infection status with treatment factors or overall survival. Cox regression models using the full datasets before propensity score matching were run adding covariates in a stepwise fashion to examine the contribution of demographic and clinical factors, in particular insurance status, stage, and treatment, in the association of HIV infection status with overall survival, and the results are presented in Supplementary Table S1. All analyses were conducted using SAS software (version 9.3; SAS Statistical Institute).

## Results

HIV/AIDS was present in 1,729 of 36,521 (4.7%) patients with Hodgkin lymphoma, 4,424 of 81,534 (5.4%) patients with DLBCL, 1,348 of 4,684 (28.8%) patients with Burkitt lymphoma, 396 of 12,061 (3.3%) patients with PTCL, and 435 of 44,720 (1.0%) patients with follicular lymphoma (Table 1). For each lymphoma subtype, HIV infection rates were higher in those who were: 35–54 years old, male, Hispanic, nonHispanic black, living in the least educated areas, insured by Medicaid, <65 years with Medicare, or uninsured (Table 1). HIV-infected patients also were more likely to have B-symptoms, be diagnosed at stage IV, and to receive treatment within 2 weeks of diagnosis compared with HIV-uninfected patients, regardless of lymphoma subtype (Table 1). Compared with HIV-uninfected patients, HIV-infected patients were more likely to be untreated and less likely to receive chemotherapy-based treatment for Hodgkin lymphoma and DLBCL (Table 1).

After controlling for the sociodemographic factors (Table 2), HIV infection was significantly associated with higher likelihood of advanced stage at diagnosis (III/IV) for all lymphoma subtypes except PTCL, with PR (95CI) ranging from 1.11 (1.01–1.23) in follicular lymphoma to 1.38 (1.30–1.47) in Hodgkin lymphoma. HIV infection was also significantly associated with higher likelihood of presence of B-symptoms for all lymphoma subtypes, with PR (95CI) ranging from 1.19 (1.08–1.32) in Burkitt lymphoma to 2.00 (1.63–2.46) in follicular lymphoma. HIV infection did not appear to be associated with the presence of comorbidities. HIV infection was associated with higher risk of extranodal primary site in Hodgkin lymphoma, DLBCL, and follicular lymphoma whereas with lower risk in Burkitt lymphoma and PTCL.

After controlling for sociodemographic and clinical presentation factors, HIV infection was associated with a slightly lower probability of receiving chemotherapy in Hodgkin lymphoma (PR, 0.95; 95CI, 0.93–0.98) and DLBCL (PR, 0.94; 95CI, 0.92–0.95) and a higher probability of receiving treatment within 2 weeks of diagnosis in follicular lymphoma (PR, 1.71; 95CI, 1.26–2.32; Table 3).

The 5-year overall survival rates were lower among HIV infected patients (68% for follicular lymphoma, 67.6% for Hodgkin lymphoma, 47.6% for Burkitt lymphoma, 41.1% for DLBCL, 32.3% for PTCL, and 68.0% for follicular lymphoma) compared with HIV-uninfected patients (74.8% for follicular lymphoma, 72.8% for Hodgkin lymphoma, 60.9% for DLBCL, 58.5% for Burkitt lymphoma, 39.4% for PTCL, and 75.6% for follicular lymphoma). As shown by the survival curves (Fig. 1), those lymphoma patients infected with HIV had a worse survival than those without HIV, regardless of subtype. Similarly, the multivariable Cox proportional hazard models using the propensity

**Table 2.** Number of occurrence and PRs (95% CIs) of presentation characteristics associated with HIV infection status, NCDB 2004–2011

Presentation characteristic	HL (N = 3,442)	DLBCL (N = 8,616)	BL (N = 2,020)	PTCL (N = 780)	FL (N = 870)
Advanced stage (III/IV)	1,919 [ <b>1.38 (1.30–1.47)</b> ]	5,031 [ <b>1.19 (1.14–1.23)</b> ]	1,410 [ <b>1.13 (1.07–1.20)</b> ]	493 [1.07 (0.97–1.19)]	553 [ <b>1.11 (1.01–1.23)</b> ]
Presence of B-symptoms <sup>a</sup>	1,879 [ <b>1.42 (1.33–1.50)</b> ]	3,588 [ <b>1.39 (1.32–1.46)</b> ]	829 [ <b>1.19 (1.08–1.32)</b> ]	358 [ <b>1.33 (1.14–1.54)</b> ]	287 [ <b>2.00 (1.63–2.46)</b> ]
Comorbidities	546 [0.99 (0.85–1.15)]	1,717 [1.02 (0.94–1.10)]	320 [0.90 (0.74–1.09)]	153 [1.00 (0.76–1.32)]	146 [0.96 (0.72–1.28)]
Extranodal primary site	139 [ <b>1.41 (1.02–1.97)</b> ]	2,966 [ <b>1.12 (1.06–1.19)</b> ]	518 [ <b>0.74 (0.64–0.86)</b> ]	265 [ <b>0.75 (0.62–0.92)</b> ]	110 [ <b>1.45 (1.01–2.06)</b> ]

NOTE: HIV-uninfected patients were the reference group in adjusted log-binomial regression in datasets matched on propensity cores with demographic factors. Bold font indicates significance at an  $\alpha = 0.05$  level.

Abbreviations: BL, Burkitt lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma.

<sup>a</sup>Patients with unknown B-symptoms presence were excluded.

score matched datasets showed that HIV infection was associated with a significantly increased risk of death in patients with Hodgkin lymphoma (HR, 1.47; 95CI, 1.25–1.74), DLBCL (HR, 1.95; 95CI, 1.80–2.11), Burkitt lymphoma (HR, 1.46; 95CI, 1.24–1.73), PTCL (HR, 1.43; 95CI, 1.14–1.79), and follicular lymphoma (HR, 1.44; 95CI, 1.04–2.00) for patients diagnosed during the HAART era (Table 4). After stratifying by treatment, the increased risk of death associated with HIV infection persisted for the Hodgkin lymphoma, DLBCL, Burkitt lymphoma, and PTCL among those who received chemotherapy and only for Hodgkin lymphoma and DLBCL among those who received no treatment (Table 4).

### Discussion

Almost two decades after the introduction of HAART, data from a nationwide hospital-based cancer registry showed that HIV infection remains an independent risk factor for increased risk of death among patients diagnosed with Hodgkin lymphoma and NHL subtypes DLBCL, Burkitt lymphoma, PTCL, and follicular lymphoma. HIV infection was also shown to be associated with higher prevalence of advanced stage at diagnosis, presence of B-symptoms, and not receiving chemotherapy for some lymphoma subtypes, which could partly account for the inferior survival of HIV-infected patients.

Only a few previous studies included both HIV-infected and HIV-uninfected patients to examine lymphoma survival differences in the HAART era. Three European studies, including one involving patients with Hodgkin lymphoma (25), one involving patients with Burkitt lymphoma (26), and another one involving DLBCL (28), found similar or better survival associated with HIV infection, although these studies were limited by small number of patients. A larger study from the United States conducted by Chao and colleagues (27), including 259 HIV-infected and 8,230 HIV-uninfected NHL patients diagnosed in 1996 to 2005 at Kaiser Permanente, reported that HIV infection was associated with doubled all-cause mortality (27). We similarly found increased risk of death associated with HIV infection for DLBCL and Burkitt

lymphoma, although the magnitude of the associations was smaller perhaps due to differences in study population and study design. We further found an increased risk of death associated with HIV infection among Hodgkin lymphoma, PTCL, and follicular lymphoma patients, after controlling for sociodemographic, presentation, and treatment-related factors. Our result regarding Hodgkin lymphoma is consistent with a recent study (33) using NCDB, which applied traditional modeling to control for potential confounders and identified an HR of 1.29 among patients with Hodgkin lymphoma who received chemotherapy, compared with 1.34 in our study. Furthermore, complementary to our findings, the study found heterogeneous effect by Hodgkin lymphoma histologic subtype: the association was not statistically significant for the 2 classical Hodgkin lymphoma subtypes nodular sclerosis and mixed cellularity but was highly significant (HR, 1.56; 96CI, 1.31–1.85) among patients with undetermined histology.

There are several possible explanations for this continued survival disparity by HIV status in the HAART era in the United States. First, although HAART substantially improves immune function of patients with HIV and it has transformed HIV infection into a chronic disease for many individuals, it is still not accessible to all patients with HIV. In a study of patients with lymphoma with HIV infection in the Center for AIDS Research Network of Integrated Clinical System cohort, Gopal and colleagues reported that even more than a decade after the introduction of HAART, only about half of HIV-infected patients were taking HAART at the time of their lymphoma diagnosis (34). Those patients with lymphoma who were not on HAART or not taking HAART correctly would not benefit from the improved immune health from HAART. Second, even when taken correctly, HAART does not confer full restoration of the immune function (1), which renders HIV-infected patients more prone to immunodeficiency- and inflammation-associated conditions during and after cancer treatment, thus lowering survival. Third, because of interaction with HAART, chemotherapy in HIV-infected patients may have compromised efficacy and increased toxicity (35). Our findings that the inferior survival associated with HIV infection among Burkitt lymphoma and PTCL

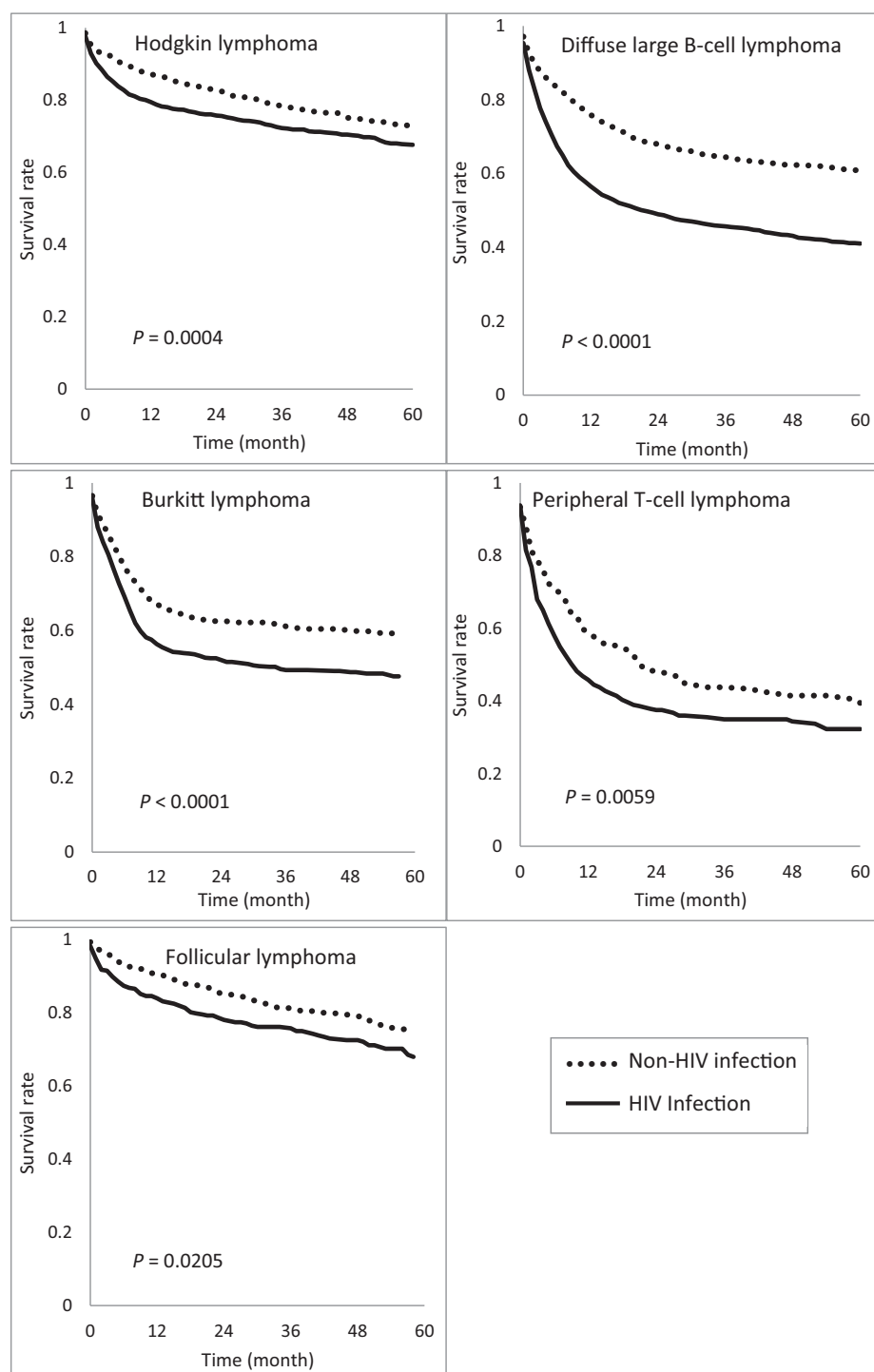
**Table 3.** Number of occurrence and PRs (95% CIs) of initial treatment factors associated with HIV infection status, NCDB 2004–2011

Treatment factor	HL	DLBCL	BL	PTCL	FL
Receipt of chemotherapy	2,825 [ <b>0.95 (0.93–0.98)</b> ]	6,983 [ <b>0.94 (0.92–0.95)</b> ]	1,796 [0.99 (0.96–1.03)]	584 [0.95 (0.89–1.01)]	622 [0.97 (0.91–1.03)]
Receiving treatment within 2 weeks of diagnosis <sup>a</sup>	711 [1.03 (0.91–1.17)]	2,719 [1.05 (0.99–1.11)]	1,050 [1.00 (0.93–1.07)]	220 [1.11 (0.91–1.34)]	139 [ <b>1.71 (1.26–2.32)</b> ]

NOTE: HIV-uninfected patients were the reference group in adjusted log-binomial regression in datasets matched on propensity cores with demographic factors and presentation factors. Bold font indicates significance at an  $\alpha = 0.05$  level.

Abbreviations: BL, Burkitt lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma.

<sup>a</sup>Among patients who received chemotherapy.



**Figure 1.** Survival curves by HIV infection status, patients with lymphoma, NCDB 2004-2009.

patients diminished when analysis was limited to untreated patients partly support this explanation. Finally, behavioral factors that often coexist with HIV infection, such as smoking (36), heavy alcohol intake (36), and diets low in vegetables and fruit (37), may contribute to the low survival rate observed in patients infected with HIV.

DLBCL and Burkitt lymphoma are two AIDS-defining NHL subtypes; PTCL and Hodgkin lymphoma have a high incidence

among HIV-infected patients (8). Unlike previous studies, we intentionally included follicular lymphoma for comparison purposes, which is a common NHL subtype not strongly associated with HIV infection. Follicular lymphoma is also unique from the other 4 types of lymphoma in that no evidence links it to any infection (38), whereas Hodgkin lymphoma, DLBCL, and Burkitt lymphoma are largely related to Epstein-Barr virus (EBV; ref. 39), and PTCL is associated with both human T-cell lymphotropic

**Table 4.** Number of deaths/cases and HRs (95% CIs) associated with HIV infection status, NCDB 2004–2009

Treatment	HL	DLBCL	BL	PTCL	FL
Total	594/2,480 [1.47 (1.25–1.74)]	2,564/6,221 [1.95 (1.80–2.11)]	570/1,410 [1.46 (1.24–1.73)]	324/609 [1.43 (1.14–1.79)]	167/730 [1.44 (1.04–2.00)]
No treatment <sup>a</sup>	195/407 [2.07 (1.50–2.84)]	638/957 [1.87 (1.59–2.21)]	84/118 [1.36 (0.78–2.39)]	102/157 [1.19 (0.78–1.82)]	43/170 [1.95 (0.83–4.57)]
Chemotherapy	424/2,023 [1.31 (1.08–1.59)]	1,943/4,908 [1.86 (1.69–2.04)]	533/1,284 [1.50 (1.26–1.79)]	249/419 [1.47 (1.13–1.91)]	124/499 [1.24 (0.84–1.82)]

NOTE: The numbers for other/unknown treatment were too small to generate adjusted HRs. HIV-uninfected patients were the reference group in adjusted Cox proportional hazard regression in datasets matched on propensity cores with demographic factors, presentation factors, treatment, and time to treatment. Abbreviations: BL, Burkitt lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma.

<sup>a</sup>Time to treatment was not controlled.

virus-1 and EBV (40). We found an increased risk of death associated with HIV infection among all lymphoma subtypes. However, when analysis was limited to patients received chemotherapy, the association persisted for the four infection-related lymphoma subtypes but not for follicular lymphoma.

Our data also showed disparities in sociodemographic factors by HIV infection status among patients with lymphoma. In particular, HIV-infected patients were disproportionately represented in uninsured, Medicaid insured, or Medicare insured (18–64 years old) groups. This may change with the implementation of the Affordable Care Act (ACA), which prohibits insurers from denying coverage because of preexisting health conditions including HIV and expands Medicaid eligibility in states that opt-in so that low-income childless adults with HIV infection do not have to wait for an AIDS diagnosis to be able to enroll in Medicaid. Not only will the ACA increase the insurance coverage for HIV-infected individuals but also it can potentially improve the affordability and quality of care through provisions such as lowering prescription drug costs for Medicare recipients, and eliminating cost-sharing for preventive services (41). Future studies are merited to monitor how these changes from the ACA will affect the survival disparities among patients with lymphoma by HIV status.

Besides overall survival in relation to HIV infection, we also investigated lymphoma presentation and receipt of treatment, which are all prognostic factors influencing survival. We found that HIV infection was generally associated with advanced-stage disease and presence of B-symptoms, but not presence of comorbidities. We also found that compared with HIV-uninfected patients, HIV-infected patients had a slightly lower probability of receiving chemotherapy among patients with Hodgkin lymphoma and DLBCL. These differences in treatment may underlie the disparities in outcomes between HIV-infected and -uninfected patients observed in this study, as these 2 lymphoma subtypes are highly curable with chemotherapy-based treatment. Thus, HIV status may impact treatment decisions rendering these patients less likely to receive standard curative therapy when they are in need of such therapy given they are more likely to have advanced-stage disease and B-symptoms. Interestingly, we observed that for HIV-infected patients with follicular lymphoma, a disease in which chemotherapy is not considered curative and observation can be an appropriate frontline management strategy, had a higher probability of receiving rapid treatment and chemotherapy. This highlights how disparities in practice patterns based on HIV status may influence outcomes in this population that is often excluded from prospective clinical trials.

The strengths of our study include large sample size, thus sufficient power, inclusion of multiple lymphoma subtypes;

availability of insurance status and clinical factors such as presence of B-symptoms and comorbidities; and the propensity-score matching design to minimize the confounding effects from sociodemographic factors and examine the extra risk of death related to HIV infection independent of the known sociodemographic and clinical variations. Our study, however, was not able to consider the following factors due to lack of information: detailed laboratory data such as CD4<sup>+</sup> count, HIV viral load, erythrocyte sedimentation rate, and hematocrit; detailed tumor presentation traits such as extent of abdominal involvement and absolute number of nodal sites of involved; detailed treatment information such as completion of treatment course, receipt of HAART, and specific regimen of chemotherapy; and lifestyle factors such as smoking, obesity and HCV infection (common in injection drug users). We were not able to examine lymphoma-specific survival, which reflects prognosis of lymphoma more accurately and is less susceptible to comorbidities and other competing risks of death, due to lack of information. Interestingly, a recent study linking data from the HIV/AIDS registries and cancer registries in six U.S. states found that HIV infection was associated with elevated cancer-specific mortality for many cancers but not for lymphoma (42). These limitations highlight the importance of performing prospective studies in this underserved population to understand the factors that impact outcomes for patients with HIV and lymphoma and to learn how to best eliminate disparities in outcomes for them, particularly as management of HIV infection in the modern era continues to improve.

In conclusion, using a nationwide hospital-based cancer registry database, our study showed that almost a decade after the HAART was available for patients with HIV/AIDS, HIV infection continued to be associated with worse survival among patients diagnosed with Hodgkin lymphoma and NHL subtypes DLBCL, Burkitt lymphoma, PTCL, and follicular lymphoma in the United States. More research is needed to elucidate the contributions of sociodemographic, lifestyle, and clinical factors to the differences in survival. Providing optimal care to patients with HIV/AIDS-associated lymphoma is warranted as is their inclusion in prospective clinical trials to improve their outcomes.

#### Disclosure of Potential Conflicts of Interest

L. Nastoupil reports receiving Commercial Research Grant from Abbvie, Janssen, and TG Therapeutics; speakers' bureau honoraria from Gilead; and is a Consultant/Advisory Board member for Pharmacyclics, Infinity, and TG Therapeutics. C.R. Flowers reports receiving Commercial Research Grant from Abbvie, Celgene, Acerta, Gilead Sciences, Infinity Pharmaceuticals, Janssen

Pharmaceutical, Eastern Cooperative Oncology Group, Southwest Oncology Group, and Mayo Clinic and is a Consultant/Advisory Board member of Genentech/Roche, Celgene, Seattle Genetics, Gilead, and Abbvie. No potential conflicts of interest were disclosed by the other authors.

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Received July 21, 2016; revised September 29, 2016; accepted October 12, 2016; published OnlineFirst October 18, 2016.

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