Outcomes of HIV-associated Hodgkin lymphoma in the era of antiretroviral therapy

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Objectives: Clinical series suggest favorable outcomes of HIV-associated Hodgkin lymphoma, in conflict with population-based statistics. Our objective was to investigate the proportion of Americans who received curative chemotherapy for this disease, and compare their survival with HIV-negative cases using population data.

Methods: We selected cases of HIV-associated Hodgkin lymphoma diagnosed in 2004–2012 from the National Cancer Data Base. Factors associated with receipt of chemotherapy were analyzed by logistic regression. Overall survival was compared in proportional hazard models adjusting for available confounding factors.

Results: Among 2090 HIV-positive patients, 81% received chemotherapy, but 16% received no treatment. Advanced age, male sex, nonwhite race, poor socioeconomic status, and undetermined histologic subtype were associated with higher risk of nontreatment. In 2012, 49% of HIV-positive patients were black, and 15% were Hispanic. Unadjusted 5-year overall survival was significantly lower for HIV-positive (66%) than for HIV-negative (80%) populations. However, among patients who received chemotherapy, HIV-positive status was not significantly associated with higher mortality in classical histologic subtypes, including nodular sclerosis (hazard ratio, HR, 1.08; 95% confidence interval, CI, 0.88–1.33) and mixed cellularity (HR, 1.06; 95% CI, 0.80–1.40). In contrast, prognosis remained significantly worse for cases with undetermined histology (HR, 1.56; 95% CI, 1.31–1.85), suggesting a more aggressive biology or other high-risk characteristics in this subgroup.

Conclusion: Worse survival statistics for HIV-associated Hodgkin lymphoma are driven by lower rates of chemotherapy administration. The disparity in treatment delivery needs attention because a majority of HIV-positive Americans with Hodgkin lymphoma are now black or Hispanic, and this proportion is increasing.

AIDS 2016, **30**:787–796

Keywords: chemotherapy, epidemiology, healthcare disparities, HIV, Hodgkin lymphoma, National Cancer Data Base, survival

Introduction

The incidence of Hodgkin lymphoma among HIV-positive patients is 5–20 times higher than in the general population [1–5]. Moreover, it has significantly increased after widespread adoption of combination antiretroviral therapy (cART) because, unlike for non-Hodgkin lymphoma, it peaks in groups with relatively better immune function and $CD4^+$ lymphocyte counts of 150–200 cells/μl [6–9]. cART has also improved survival of patients with this disease [10]. HIV-associated Hodgkin lymphoma is characterized by unfavorable clinical presentation, including advanced stage in 60–80% of patients, more frequent constitutional symptoms, extranodal disease and high International Prognostic Score [11,12]. Histologically, it shows a nearly universal

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Received: 28 October 2015; revised: 22 November 2015; accepted: 24 November 2015.

DOI:10.1097/QAD.0000000000000986

expression of the Epstein–Barr virus-encoded genes, and a high prevalence of the mixed cellularity morphologic subtype [13,14].

Several observational cohorts of HIV-positive patients on cART who were treated using paradigms identical to HIV-negative patients have suggested similar survival regardless of HIV status [11,12,15,16]. In contrast, population-based studies from the United States, including the analyses from the Centers for AIDS Research Network of Integrated Clinical Systems [17] and from the National Cancer Institute/Surveillance, Epidemiology and End Results programme [18], demonstrated consistently poor overall survival (OS) with 5-year estimate of about 63%. They were however limited by lack of information about administration of lymphoma-directed therapy and cART. Data from cancer registries indicate that HIV-infected individuals may have nearly double the odds of not receiving therapy for their cancer, although these odds have improved over time for some malignancies [19]. Chemotherapy is an essential treatment modality critical for achieving cure in all forms of classical Hodgkin lymphoma [20,21].

We hypothesized that the unfavorable survival statistics for HIV-associated Hodgkin lymphoma from the United States are related to suboptimal delivery of chemotherapy, and our objective was to evaluate management patterns, trends and associated survival outcomes among HIV-positive patients using comprehensive nationwide data.

Patients and methods

Data source and cohort selection

We obtained records from the National Cancer Data Base (NCDB), a joint programme sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society [22]. The NCDB collects registry records from over 1500 cancer programmes in the United States which meet prespecified quality standards, including mandatory 90% follow-up rate for all cancer cases diagnosed within 5 years. Although a number of facilities, particularly those with limited oncology services, are excluded from the research files, creating potential geographical and demographic bias [23], the database captures over 70% of all incident cancer cases in the country, and duplicate records are eliminated using standardized algorithms. The NCDB contains information about patient demographics, comorbidities, socioeconomic status, cancer histology, stage, and the first course of therapy, defined as all modalities of treatment recorded in the treatment plan and administered before disease progression or recurrence. Details of dose, field and technique of radiation therapy are collected, but specific chemotherapy drugs, regimens, doses or treatment duration are not. OS is the only available endpoint, because response to therapy, cancer recurrences or cause of death are not recorded. OS is calculated from the date of diagnosis until death or censoring at last follow-up obtained by the registry. Participating institutions are required to collect survival data on at least 90% of known living cases annually.

We extracted data on all cases of Hodgkin lymphoma reported to the NCDB between 2004 and 2012 ($N = 50\,748$), with OS available for patients diagnosed up to 2011. During this timeframe, as part of the Collaborative Staging System, the programme recorded HIV status for all patients with Hodgkin lymphoma. Further details of the HIV infection, such as $CD4^+$ cell counts, presence of AIDS, opportunistic infections, or use of cART were not available. We excluded cases treated outside of the reporting facility ($N = 4657$), for which the NCDB does not require collection of treatment or follow-up data, as well as nodular lymphocyte predominant histology ($N = 2156$), because of its specific clinical course and treatment paradigms.

We classified race and ethnicity as white non-Hispanic, white Hispanic, black, and Asian/other. We approximated the commonly used clinical definitions of early favorable (stage I/IIA), unfavorable (I/IIB) or advanced (III/IV) stage Hodgkin lymphoma, although only Ann Arbor stage designation and presence of B-symptoms were available for this purpose, whereas bulky tumor designation, sedimentation rate or number of nodal sites were not. Socioeconomic data were provided as quintiles of median household income in patients' zip code of residence. The type of treating facility was designated according to the Commission on Cancer categories (community, comprehensive community or academic/research programme) based on annual case volume and available oncology services.

Statistical analysis

Patient characteristics were tabulated, and proportions of patients treated with specific modalities were compared by χ^2 test. Trends in proportions over time were assessed by log-binomial regression (separately for groups with or without HIV), reporting average annual percentage change (APC) [24]. Factors associated with nonreceipt of chemotherapy among HIV-positive patients were analyzed using a mixed-effects logistic regression model, thus allowing us to analyze the random effect related to clustering of treatment patterns by facility, reporting odds ratios (OR) and intra-class correlation [25]. For this model, missing data on Hodgkin lymphoma stage (3%), B-symptoms (9%), health insurance (3%), median income (2%) and chemotherapy administration (2%) were multiply imputed into 20 datasets by chained equations to minimize bias [26]. OS at 5 years was calculated using the Kaplan–Meier estimator in strata defined by stage and HIV status. Trends in survival among HIV-positive patients were compared using two methods: log-rank test

for cohort analysis stratified by year of diagnosis, and period survival method using time-at-risk data only from patients entering follow-up during a specific calendar year [27]. For multivariable survival analysis, we fitted proportional hazard models in which HIV status was included as an independent variable, reporting a hazard ratio (HR). The proportional hazard assumption in the models was assessed by the global Grambsch and Therneau test based on scaled Schoenfeld residuals, and by testing the interaction of HIV status with time [28]. The models adjusted for sex, race, year of diagnosis, type of health insurance and median income, whereas age categories (18–39, 40–59, 60–74 and ≥75 years), stage, and presence of B-symptoms were included as stratification variables. We introduced an interaction between sex and race because of its known association with survival, and between the HIV status and histologic subtype, but no other interactions. All estimates are presented with 95% confidence intervals (CI). Analyses were conducted using Stata MP 14.0 (StataCorp LP, College Station, Texas, USA).

Results

Among 43 935 patients with classical Hodgkin lymphoma recorded in the NCDB between 2004 and 2012, 2090 (5%) were HIV-positive. This proportion was unchanged throughout the study period. Thirty-eight percent of cases had unrecorded HIV status. They were included in the HIV-negative group following the methodology from a prior population-based National Cancer Institute study, to avoid potential bias from differential treatment patterns among patients who were or were not tested for HIV [18]. Clinical characteristics and outcomes in groups with HIV-negative or unrecorded status were very similar (Supplemental Table S1, http://links.lww.com/QAD/A848). As a sensitivity analysis, we conducted all comparative analyses using only cases with unequivocal HIV-positive or negative status, and found consistent results. HIV-positive patients were on average older, primarily in the 40 to 59-year-old group (Table 1), with a predominance of men and a significantly higher proportion of white Hispanic or black race. HIV-positive patients resided more frequently in metropolitan areas with low median income, received treatment in academic/research facilities, and had Medicaid health insurance corresponding to their disability or poverty status. Moreover, the proportion of HIV-positive black patients significantly increased from 31% in 2004 to 49% in 2012 (APC, 7.0%, 95% CI, 4.6–9.4%, $P < 0.00001$), which was not observed in the HIV-negative population (Fig. 1a).

Two-thirds of HIV-positive patients had advanced-stage Hodgkin lymphoma, and most had B-symptoms – in reverse of proportions observed within the HIV-negative group. HIV-positive Hodgkin lymphoma was also more frequently extranodal in origin, with most frequent sites being bone marrow (46% of extranodal cases), gastrointestinal tract (28%) and head and neck mucosa (13%). Although nodular sclerosis was the most common histologic subtype identified in both populations, mixed cellularity cases were twice as frequent among HIV-

Table 1. Characteristics of HIV-positive and negative patients with Hodgkin lymphoma.

	HIV-positive	HIV-negative[a]
N	2090	41 845
Age, median (interquartile range)	43 (35–51)	40 (27–59)
Age group, *N* (%)		
18–39 years	772 (36.9)	20 737 (49.6)
40–59 years	1116 (53.4)	11 117 (26.6)
60–74 years	159 (7.6)	5996 (14.3)
>75 years	43 (2.1)	3995 (9.5)
Sex, *N* (%)		
Female	410 (19.6)	19 774 (47.3)
Male	1680 (80.4)	22 071 (52.7)
Race, *N* (%)		
White non-Hispanic	869 (41.6)	32 198 (76.9)
White Hispanic	356 (17.0)	3186 (7.6)
Black	775 (37.1)	4494 (10.7)
Asian or other	90 (4.3)	1967 (4.7)
Stage, *N* (%)		
I/IIA ('early favorable')	310 (14.8)	14 998 (35.8)
I/IIB ('early unfavorable')	303 (14.5)	7123 (17.0)
I/IIB unclassifiable[b]	46 (2.2)	2160 (5.2)
III/IV	1372 (65.6)	16 589 (39.3)
Unrecorded	59 (2.8)	975 (2.3)
B-symptoms, *N* (%)		
Absent	573 (27.4)	21 308 (50.9)
Present	1329 (63.6)	16 437 (39.3)
Unrecorded	188 (9.0)	4100 (9.8)
Histologic subtype, *N* (%)		
Nodular sclerosis	668 (32.0)	23 993 (57.3)
Mixed cellularity	459 (22.0)	4780 (11.4)
Lymphocyte-depleted	71 (3.4)	591 (1.4)
Lymphocyte-rich	63 (3.0)	1634 (3.9)
Undetermined	829 (39.7)	10 847 (25.9)
Primary site, *N* (%)		
Nodal	1982 (94.8)	40 641 (97.1)
Extranodal	108 (5.2)	1204 (2.9)
Health insurance, *N* (%)		
Uninsured	228 (10.9)	3406 (8.1)
Private	856 (41.0)	24 780 (59.2)
Medicaid	522 (25.0)	3928 (9.4)
Medicare	384 (18.4)	7841 (18.7)
Other	33 (1.6)	524 (1.3)
Unrecorded	67 (3.2)	1366 (3.3)
Median income, *N* (%)[c]		
< $38 000	641 (30.7)	6789 (16.2)
$38 000–$47 999	484 (23.2)	9226 (22.0)
$48 000–$62 999	467 (22.3)	11 252 (26.9)
≥ $63 000	451 (21.6)	13 758 (32.9)
Unrecorded	47 (2.2)	820 (2.0)
Type of cancer programme, *N* (%)[d]		
Community	191 (9.1)	4486 (10.7)
Comprehensive community	776 (37.1)	21 570 (51.5)
Academic or research	1123 (53.7)	15 725 (37.6)
Other	–	64 (0.2)

[a]All *P* values for comparisons were <0.00001.
[b]Because of unrecorded B-symptoms.
[c]Median household income in patient's area of residence according to the 2012 American Community Survey data.
[d]According to the designation by the Commission on Cancer Accreditation programme.

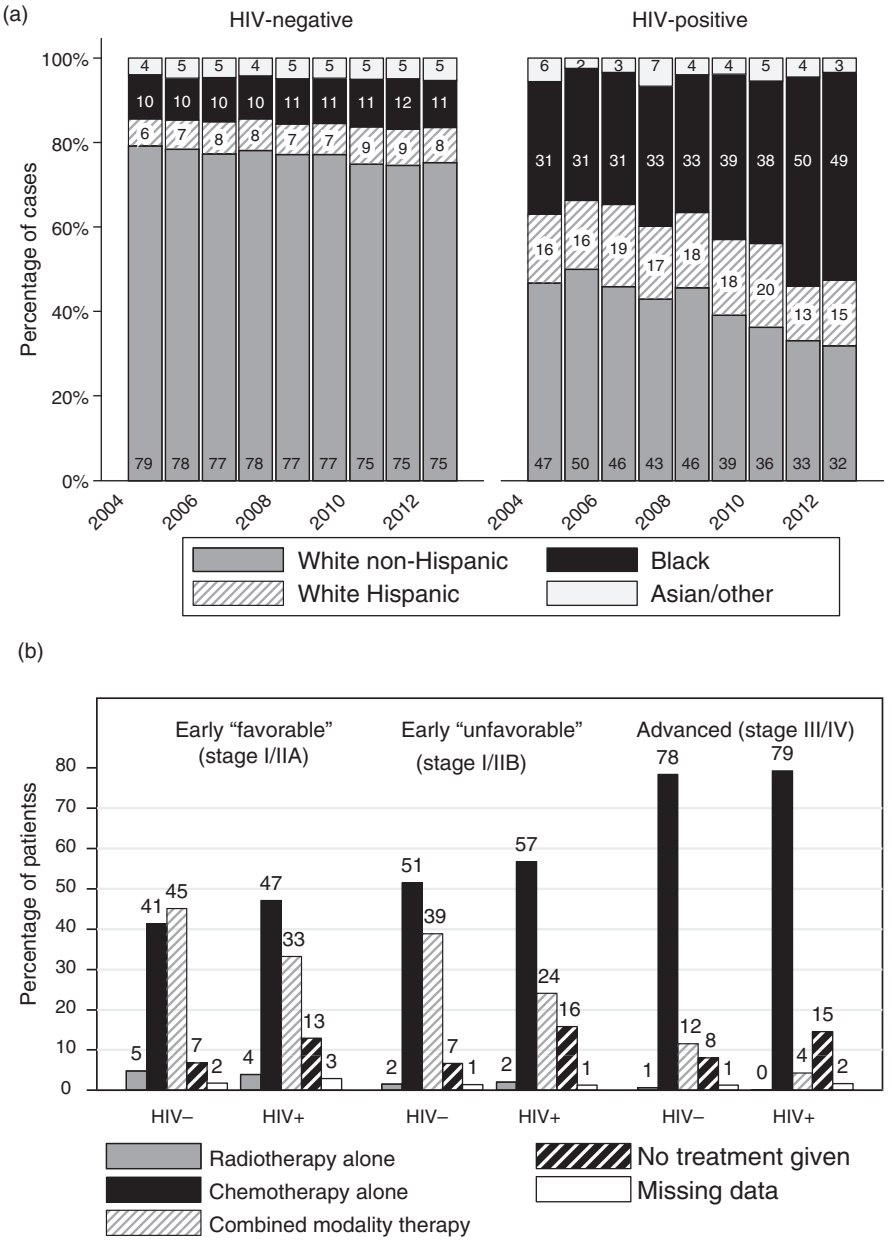

Fig. 1. Distribution of race and treatment modalities among HIV-positive and HIV-negative patients with Hodgkin lymphoma. (a) Trends in the proportion of different races among HIV-positive and HIV-negative patients with Hodgkin lymphoma. (b) Treatment modalities delivered as initial course of therapy in Hodgkin lymphoma, stratified by stage and HIV status. Numbers on bars indicate percentage of cases; cases with undefined stage are not represented.

positive patients, and lymphocyte-depleted histology, whereas rare, was 2.4 times more common in this group. Forty percent of HIV-positive and 26% of HIV-negative cases had undetermined histologic subtype. Between 2004 and 2012, the proportion of nodular sclerosis cases decreased, whereas undetermined histology increased for both HIV-positive and HIV-negative patients (Supplemental Figure S1, http://links.lww.com/QAD/A848).

Treatment modalities

Among HIV-positive patients 81% received chemotherapy (12% in combination with radiation), 13% received any radiation therapy, and 16% received no treatment for their lymphoma. The proportions treated with chemotherapy and radiation were significantly lower compared with the HIV-negative population (87, 31 and 9%, respectively, all $P < 0.00001$). Furthermore, early stage HIV-associated Hodgkin lymphoma was less frequently treated with combined modality therapy (28 vs. 41%, Fig. 1b). Patients without assigned stage, while few, had a very high rate of not receiving any lymphoma-directed therapy (42% for HIV-positive and 38% for HIV-negative cases with unassigned stage). There was no evidence of change in the proportion of

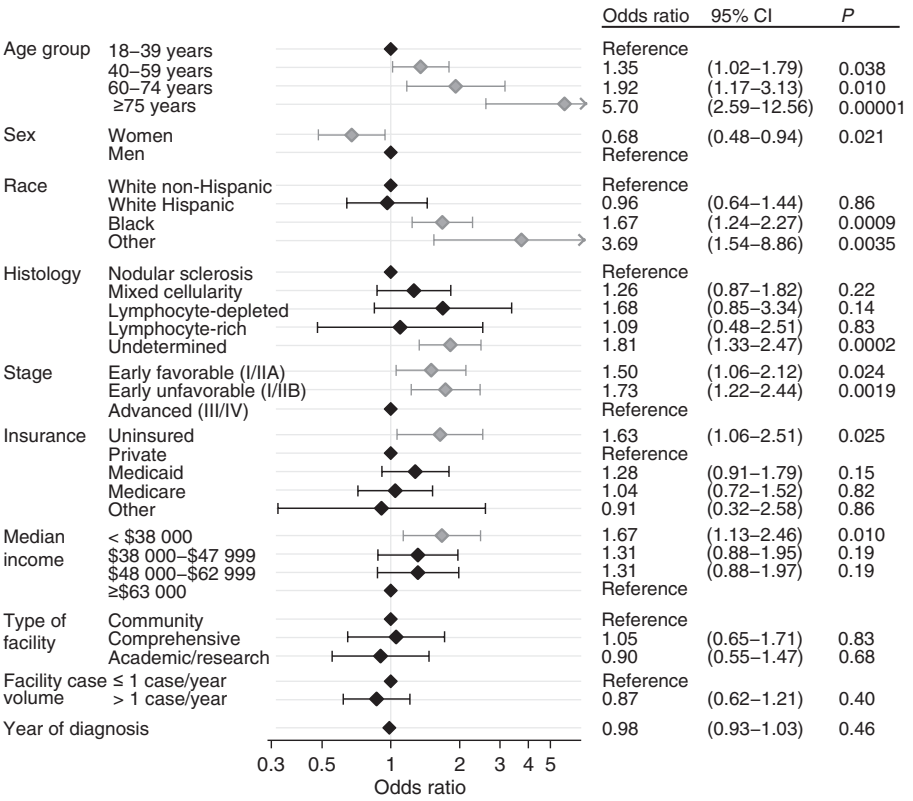

Fig. 2. Multivariable logistic model for nonreceipt of chemotherapy among HIV-positive patients with Hodgkin lymphoma. CI: confidence interval.

HIV-positive patients receiving chemotherapy (APC, 0.2%, 95% CI, −0.6 to 1.0%, $P = 0.61$), whereas a decrease in the utilization of radiation therapy was notable, consistent with nationwide trends (APC, −8.7%, 95% CI, −12.7 to −4.6%, $P = 0.000045$) [29]. Median time from diagnosis to treatment was 27 days, the same for HIV-positive and negative cases ($P = 0.30$). Median dose of radiation was 30.6 Gy (interquartile range, 26–36), also the same regardless of the HIV status ($P = 0.71$), as was the proportion treated with the technically advanced 3D conformal or intensity-modulated radiation therapy (18%, $P = 0.97$).

We studied patient- and disease-related factors associated with the risk of not receiving chemotherapy, the critical component of curative treatment in Hodgkin lymphoma, in the HIV-positive population (Fig. 2). This risk was significantly higher for patients who were older, male, nonwhite, without health insurance, or who lived in areas with the lowest median income, as well as for early stage disease and for undetermined histology. We found a significant random effect related to the variation in treatment delivery in each of the 610 institutions (intra-class correlation, 9.8%, 95% CI, 4.3–20.9%). However, the model did not indicate any significant fixed effect for a difference between community or academic/research centers, or according to average yearly institutional volume, which varied from 0.1 to four HIV-positive Hodgkin lymphoma cases per year. The 55 facilities which reported more than one case per year (9% of institutions) cared for 38% of all patients.

Survival outcomes

With median follow-up of 51 months (interquartile range, 30 to 72 months), unadjusted 5-year OS for HIV-positive Hodgkin lymphoma was 66% (95% CI, 64–68%), significantly lower than for HIV-negative patients (80%, 95% CI, 79–80%, Fig. 3a). Stratified by stage, these estimates among HIV-positive patients were 86% (CI, 81–90%) for 'early favorable' (stage I/IIA), 71% (CI, 64–76%) for 'early unfavorable' (stage I/IIB), and 60% (CI, 57–63%) for advanced stage disease. Among HIV-negative patients, they were 89% (CI, 89–90%), 84% (CI, 83–85%), and 70% (CI, 69–70%), respectively. Unadjusted outcomes in the subcohort who received chemotherapy were also lower for HIV-positive cases (5-year OS 73%, 95% CI, 71–75%) than for HIV-negative ones (83%, 95% CI, 83–84%, Fig. 3b). There was no evidence of a statistically significant trend in OS in the HIV-positive population either in cohort analysis stratified by year of diagnosis (log-rank $P = 0.18$) or in the period survival analysis ($P = 0.95$, Fig. 3c/d). These trends were not significant in the HIV-negative population, either ($P = 0.45$ and $P = 0.99$, respectively).

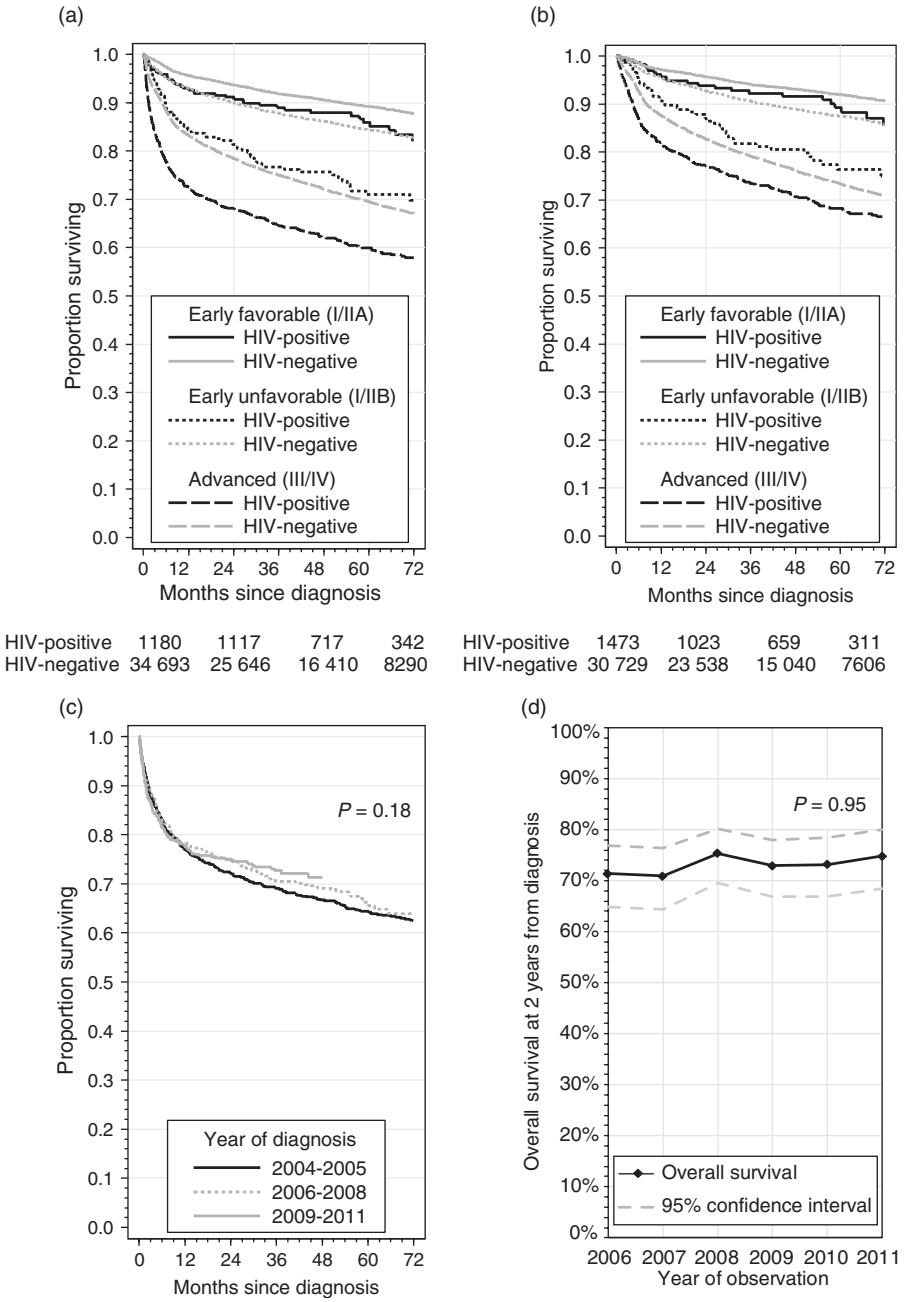

Fig. 3. Survival outcomes in Hodgkin lymphoma. Kaplan–Meier curves of overall survival of all patients (a) and patients who received chemotherapy (b), stratified by stage grouping and HIV status; trends in overall survival of HIV-positive patients using cohort approach by year of diagnosis (c), and using period survival analysis, by year of observation (d).

In multivariable proportional hazard models, we discovered a significant interaction between the HIV status and histologic subtypes ($P = 0.023$). Therefore, separate models were fitted for each morphologic category. Among patients who received chemotherapy, there was no significant difference in the hazard of death between HIV-positive and HIV-negative patients who had one of the defined classical histologic subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich or lymphocyte-depleted Hodgkin lymphoma (Table 2). In contrast, mortality was significantly higher in the group of HIV-positive patients with undetermined histologic subtype, with OS numerically similar to HIV-negative lymphocyte-depleted Hodgkin lymphoma. In models fitted for the entire population regardless of treatment receipt, survival was worse for HIV-positive patients in all subsets (Supplemental Table S2, http://links.lww.com/QAD/A848). In a multivariable prognostic model limited to HIV-positive patients who received chemotherapy, OS was significantly worse with advancing age, for patients

Table 2. Overall survival, and hazard ratio for HIV-positive status among patients with Hodgkin lymphoma who received chemotherapy.

	N		5-year OS (%)		Multivariable model[a]		
Histologic subtype	HIV+	HIV-	HIV+	HIV-	Hazard ratio for HIV status	95% CI	*P*
Nodular sclerosis	616	21 736	80.2	87.2	1.08	0.88–1.33	0.46
Mixed cellularity	407	4303	77.6	77.3	1.06	0.80–1.40	0.68
Lymphocyte-rich	59	1442	71.1	84.0	1.27	0.55–2.93	0.58
Lymphocyte-depleted	63	523	69.0	64.9	1.05	0.54–2.03	0.89
Undetermined	734	9507	63.5	77.0	1.56	1.31–1.85	<0.0001[b]
All histologies	1879	37 511	73.0	83.3	1.29	1.15–1.44	0.0001[c]

[a]Models adjusted for: age, sex, race, stage of the lymphoma, presence of B-symptoms, year of diagnosis, type of health insurance, and median income in the area of residence.
[b]Model with time-varying HR for HIV status: baseline HR, 2.00, time-varying HR: 0.98 ($P = 0.002$).
[c]Model with time-varying HR for HIV status: baseline HR, 1.60, time-varying HR: 0.99 ($P < 0.0001$).
HIV+, HIV-positive; HIV–, HIV-negative; HR, hazard ratio.

with undetermined histology, advanced stage or unfavorable health insurance status (Supplemental Table S3, http://links.lww.com/QAD/A848). There were no significant differences related to sex, race or type of treating facility. HIV-positive cases with undetermined histology had a higher rate of advanced-stage disease (75 vs. 63%) and extranodal disease (9 vs. 2%, particularly bone marrow, 5 vs. 1%) compared with those with defined Hodgkin lymphoma histologies, but there was no significant difference in age, sex or race distribution between those two groups. Additionally, the proportion of cases with undetermined histology was not significantly different between academic/research or community sites ($P = 0.14$).

Discussion

In this observational study, which contained a majority of American Hodgkin lymphoma cases diagnosed between 2004 and 2012, we investigated survival outcomes of HIV-positive patients in the context of treatment delivery. Our results demonstrate that previous unfavorable survival statistics in this group are related to two factors: a higher rate of nontreatment and a poor prognosis in the subgroup with undetermined histologic subtype. For patients with classical Hodgkin lymphoma morphology who were able to receive chemotherapy, OS was similar regardless of the HIV status after adjusting for stage and sociodemographic factors.

The proportions of Hodgkin lymphoma histologic categories in our analysis, which reflect diagnostic patterns in the United States community, and the associated OS, are quite different from some observational case series of HIV-positive Hodgkin lymphoma. In our contemporary NCDB dataset the most common histologic subtype was nodular sclerosis, just like in the HIV-negative population, although mixed cellularity predominated in prior series. The German HIV-Related Lymphoma Study Group prospectively studied 100 patients, excluding those with significant comorbidities, active drug addiction or psychiatric disease [12]. Mixed cellularity constituted 61% of cases, and the undetermined subtype 18%. Treatment involved standard chemotherapy used for HIV-negative Hodgkin lymphoma, with a resulting 2-year OS of 91%. Of note, all patients who relapsed had a baseline $CD4^+$ cell count less than 200 cells/μl. These results were similar to a retrospective series from Spain (76% 5-year OS) [30], and a comparative British analysis of 93 patients, of whom 80% had advanced-stage disease, 55% mixed cellularity, and 26% undetermined histology [11]. In that study all patients received standard Hodgkin lymphoma chemotherapy, and 5-year OS was not significantly different for HIV-positive and negative cases (79 and 88%, respectively). Similarly, investigators from the French Lymphovir observational cohort reported 62% prevalence of mixed cellularity and 21% of undetermined histology among 68 Hodgkin lymphoma cases, with 94% 2-year OS [15].

All of the above studies were limited by a small sample size (≤100 HIV-positive patients), thus lacking statistical power to conclusively compare OS. Contrasting with their optimistic estimates, data from national registries show significantly worse outcomes. A prospective cohort from 15 Spanish institutions captured 104 HIV-positive patients, of whom 83 were on cART and four did not receive any Hodgkin lymphoma therapy, showing 72% 5-year OS among patients on cART, but only 44% for those without antiviral therapy [31]. An analysis from eight American academic institutions in the period of 1996–2010 revealed 5-year OS for Hodgkin lymphoma of only 62%, which was lower for patients with $CD4^+$ cell count less than 100 cells/μl or those not on cART [17]. Shiels *et al.* described survival of Hodgkin lymphoma cases in the United States using the Surveillance, Epidemiology and End Results programme data from 2000–2010, reporting 4% prevalence of the HIV infection (848 cases) [18]. Demographic characteristics of HIV-positive cases were similar to our (partially overlapping) cohort, with higher prevalence of HIV

among black patients (17%), those with mixed cellularity (11%), lymphocyte-depleted (15%) or undetermined Hodgkin lymphoma (11%). OS at 5 years was 73% for the HIV-positive and 83% for the HIV-negative population, but no information about either lymphoma-directed therapy or cART was available in that study. Of note, 66% of deaths among HIV-positive cases were ascribed to HIV/AIDS, and only 6% to Hodgkin lymphoma, although reliability of those designations using death certificates is questionable. A large, international retrospective of 229 patients with advanced-stage HIV-positive Hodgkin lymphoma reported 5-year OS of 78% and identified $CD4^+$ cell count less than 200 cells/μl as a risk factor for progression-free survival and OS, primarily associated with the risk of death from non-Hodgkin lymphoma causes [16].

Similarly to the recent HIV/AIDS Cancer Match Study [19], we found that a significant proportion (18%) of HIV-infected Hodgkin lymphoma patients do not receive treatment for this curable cancer, which was 1.7 times higher than in the HIV-negative population. Nonreceipt of chemotherapy correlated with unfavorable socioeconomic variables, including black race, lack of health insurance and residence in high-poverty areas. These associations are concerning in the context of HIV incidence in the United States, which is nearly 10 times higher in African Americans compared with whites [32], and the fact that according to our data half of currently diagnosed HIV-positive Hodgkin lymphoma patients are of black race. The identified factors may certainly correlate with lower baseline $CD4^+$ cell counts, presence of AIDS, lack of access to cART, or opportunistic infections, or other psychosocial factors influencing the ability to receive lymphoma-directed therapy. Substance abuse, homelessness, and mental health disorders have a higher prevalence in patients affected by HIV [33,34].

Likewise, we could not analyze in depth clinical characteristics of the HIV-positive patients with undetermined Hodgkin lymphoma histology, a group that was identified as high-risk for both nonreceipt of chemotherapy and for subsequent survival. A plausible explanation for these associations might be that those patients were diagnosed by a biopsy of the bone marrow (54% had stage IV disease), another extranodal site, or a suboptimal specimen that precluded adequate classification. This had been the case in some clinical series, which contained between 20 and 40% of cases with undetermined subtype, yet did not detect worse survival for this group [6,10,11,15,16]. Undetermined histology has been associated with worse survival in the general Hodgkin lymphoma population [35]. Failed diagnostic classification may reflect patients' poor clinical condition precluding extensive workup, administration of standard therapy, and consequently leading to poor survival. Another possibility is that unusual morphology correlates with unfavorable prognosis or a more advanced HIV infection, although in the study by Biggar *et al.* median $CD4^+$ cell count of patients with undetermined histology was not different than in other subtypes [6]. This group of patients, whether because of aggressive Hodgkin lymphoma biology or unfavorable baseline patient characteristics, may potentially benefit from novel therapeutic approaches that lower acute toxicity without sacrificing efficacy. For example, the monoclonal antibody-drug conjugate brentuximab vedotin is currently being studied in the front-line setting for HIV-associated Hodgkin lymphoma in the United States and France (NCT01771107, NCT02298257).

Unrecorded lymphoma and treatment-related variables in the NCDB, which include type and duration of chemotherapy, toxicity, response to treatment, Hodgkin lymphoma recurrences, as well as details of immune status and cART administration, pose a significant limitation to our analysis. Current National Comprehensive Cancer Network guidelines encourage testing all Hodgkin lymphoma patients for HIV to allow optimal management of both conditions when they coincide [21], yet we found that 38% of Hodgkin lymphoma cases in the United States were not tested, indicating potential missed diagnostic and therapeutic opportunities. Complete remission after initial therapy and baseline $CD4^+$ cell count are the principal factors affecting survival in the HIV-positive Hodgkin lymphoma population [12,16,31]. We could not determine to what extent the disparities in chemotherapy administration correlate with lack of cART or virologic failure. We also could not disentangle AIDS- and Hodgkin lymphoma-associated mortality, which is difficult even in clinical series because of unclear attribution of many events (e.g. an opportunistic infection during Hodgkin lymphoma chemotherapy). Further research is needed to establish optimal treatment strategy for HIV-associated Hodgkin lymphoma that can balance its curative potential with risks of serious adverse events. In particular, we found that the use of combined modality therapy in early stage disease was less frequent than among HIV-negative patients, although it may offer conceptual benefits in a setting of lower hematologic tolerance of chemotherapy.

The fact that survival with active treatment is not influenced by HIV status in patients with classical histologic subtypes of Hodgkin lymphoma underscores the need for an aggressive approach to obtain an adequate diagnostic sample and to deliver curative therapy, but also for adequate supportive care to assure its safety. This includes granulocyte growth factor for prevention of febrile neutropenia (particularly in cases with bone marrow involvement), multidisciplinary management of infectious prophylaxis and cART (especially considering drug–drug interactions with chemotherapy agents), as well as psychosocial interventions to minimize distress related to disease and treatment toxicity [14,20,36,37]. A majority of HIV-positive patients in the current era

appear to have the favorable nodular sclerosis morphology and should not miss the opportunity of upfront cure. Those with excellent immune function should potentially not be excluded from the upcoming clinical trials involving immunotherapy or checkpoint inhibitors, as had been previously advocated [38,39]. Patients with undetermined histology require particular attention due to worse prognosis and high risk of nontreatment, and may be targeted by novel, alternative approaches.

Acknowledgements

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

Authorship contribution: A.J.O. and J.J.C. designed the research; A.J.O. analyzed the data; A.J.O. and J.J.C. interpreted the results and wrote the article.

Source of funding: A.J.O. is currently supported by the American Society of Hematology Research Scholar Award, and the American Cancer Society Research Scholar Award (grant number RSG-15-211-01-CPHPS).

Presented in abstract form at the 2015 American Society of Hematology Meeting on Hematologic Malignancies, Chicago, Illinois, 18 September 2015.

Conflicts of interest

There are no conflicts of interest.

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