Published in final edited form as:

Br J Haematol. 2020 August ; 190(3): 371–384. doi:10.1111/bjh.16539.

Chronic medical conditions and late effects following non-Hodgkin lymphoma in HIV-uninfected and HIV-infected adolescents and young adults: a population-based study

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Summary

Little is known about the incidence of late effects following non-Hodgkin lymphoma (NHL) among adolescent and young adult (AYA, 15–39 years) survivors. Using data from the California Cancer Registry linked to hospital discharge, we estimated the cumulative incidence of late effects at 10 years among AYAs diagnosed with NHL during 1996–2012, who survived ≥2 years. Cox proportional-hazards models were used to investigate the influence of sociodemographic and clinical factors on the occurrence of late effects. Of 4392 HIV-uninfected patients, the highest incident diseases were: endocrine (18·5%), cardiovascular (11·7%), and respiratory (5·0%), followed by secondary primary malignancy (SPM, 2·6%), renal and neurologic (2·2%), liver/pancreatic (2·0%), and avascular necrosis (1·2%). Among the 425 HIV-infected survivors, incidence was higher for all late effects, especially over threefold increased risk of SPM, compared to HIV-uninfected patients (8·1% vs. 2·6%). In multivariable models for HIV-uninfected patients, public or no health insurance (vs. private), residence in lower socioeconomic neighbourhoods (vs. higher), and receipt of a haematopoietic stem cell transplant were associated with a greater risk of most late effects. Our findings of substantial incidence of late effects among NHL AYA survivors

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Author contributions

TK and RA designed the study. TK, QL and RA had full access to all of the data in the study and take responsibility for the accuracy of the data analysis. QI performed the statistical analysis. RA and TK drafted the manuscript. All authors interpreted the results, revised and approved the final manuscript.

Conflict of interests

We declare no conflict of interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

emphasise the need for longterm follow-up and appropriate survivorship care to reduce morbidity and mortality in this vulnerable population.

Keywords

non-Hodgkin lymphoma; late effects; adolescent and young adult; population-based study

In the United States (US), non-Hodgkin lymphoma (NHL) is the fourth and fifth leading cause of cancer deaths among patients aged 20–39 and <20 years, respectively (Siegel *et al.*, 2019). Survival after NHL in adolescents and young adults (AYAs, 15–39 years) has increased in the last decades, from about 60% in the late 1970s to 75% during 2000–2007, except during the early years of the immunodeficiency virus (HIV) epidemic (1980s to early 1990s), when a marked survival decline was observed (Bleyer, 2011). Despite progress, AYA survival improvement has lagged behind that observed among children and older adults with NHL (Keegan *et al.*, 2016a)

The mainstay treatment of NHL is systemic chemotherapy and, in some cases, radiation and/or haematopoietic stem cell transplant (HSCT) (Kahn *et al.*, 2017). The therapeutic management of NHL evolved over the years and is currently guided by histology, immunophenotype and risk stratification, with improved therapy leading to decreased mortality (Hudson *et al.*, 2012). As a result, the number of long-term NHL survivors continues to grow. Due, at least partially, to intensive curative-intent treatment, many survivors have a considerable excess risk of life-threatening conditions (e.g. myocardial infarction and stroke) and other chronic health diseases (Nass *et al.*, 2015). Considering the variety of NHL histological subtypes and the different consequent treatment approaches, clinicians are expected to face a wide range of late effects that can impair the quality of life and reduce AYA survival (Ehrhardt *et al.*, 2019).

Whereas the late effects of childhood NHL are well recognised (Oeffinger *et al.*, 2006; Bhakta *et al.*, 2017; Ehrhardt *et al.*, 2019), little is known about long-term complications among AYA survivors. Importantly, in the era of highly active and effective antiretroviral therapy, the prevalence of HIV-infected patients is increasing (Engels *et al.*, 2008; Shiels *et al.*, 2009) and a rise in acquired immunodeficiency syndrome (AIDS)-unrelated cancers has been observed in these patients (Shiels *et al.*, 2011). HIV-infected patients have a worse cancer prognosis compared to HIV-uninfected patients (Chao *et al.*, 2010; Coghill *et al.*, 2015; Marcus *et al.*, 2015). This current study aimed to estimate the cumulative incidence (CMI) of chronic medical conditions and late effects (hereafter referred to as late effects), potentially secondary to cancer treatment among AYAs with NHL, and investigate the extent to which sociodemographic and clinical factors are associated with the occurrence of these conditions. In addition, we determined differences in the incidence of late effects by HIV status. Our results can help healthcare providers to better understand the needs of AYA NHL survivors and guide the development of best survivorship care plans.

Patients and methods

Patients

Data were obtained from the California Cancer Registry (CCR) linked to hospitalisation data from the California Office of Statewide Health Planning and Development (OSHPD). CCR is the largest state cancer registry in the US, and captures 99% of all cancer diagnoses in California, including second primary malignancy (SPM). OSHPD data include detailed information for every hospitalisation in over 400 non-federal hospitals in California. Eligible patients were those aged 15–39 years when diagnosed with a first primary NHL between 1 January 1996 and 31 December 2012, and who survived ≥2 years after diagnosis, as previously done (Chao *et al.*, 2016; Keegan *et al.*, 2018). Follow-up was through December 2014.

Non-Hodgkin lymphoma morphology was coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) (Fritz *et al.*, 2013) and classified using the AYA Site/WHO Recode 2008 of the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER, https://seer.cancer.gov/ayarecode/aya-who2008.html). NHL subtypes were grouped as follows: diffuse large B cell lymphoma (DLBCL), follicular lymphoma, Burkitt lymphoma, other B cell lymphoma, NK/T cell lymphoma, lymphoblastic lymphoma, and unspecified (Table SI).

Sociodemographic and clinical data

Age and stage at diagnosis, sex, race/ethnicity, neighbourhood socioeconomic status (nSES), and initial treatment (chemotherapy, radiation, chemotherapy *plus* radiation, none/unknown) were obtained from CCR. HSCT was ascertained from CCR and OSHPD. With information on extent of disease from the CCR, we classified patients by the presence of HIV or AIDS (hereafter referred to as HIV-infected) at cancer diagnosis. From OSHPD, we identified a few additional HIV-infected patients ($n = 20$). Stage at diagnosis, based on SEER Summary Stage, was classified as localised (stage I), regional (stage II), or advanced (stage III/IV). We further combined localised and regional stages (stage I/II). Race/ethnicity was categorised in four major groups: non-Hispanic white (white), non-Hispanic black (black), Hispanic, and non-Hispanic Asian/Pacific Islander (Asian/PI). Differences in outcomes by nSES were assessed by using a previously developed multi-component index based on block-level census data (Keegan *et al.*, 2018). This index is divided into quintiles based on the statewide distribution. We further classified nSES into two groups: lower (quintiles 1–3) and higher (quintiles 4–5) as performed previously (Keegan *et al.*, 2016b). Health insurance is defined by CCR as the primary insurance carrier or method of payment at time of patient's diagnosis. We initially grouped insurance into private (military, health maintenance organisations, preferred provider organisations, and managed care not otherwise specified), public (Medicaid and other government-assisted programs), none/uninsured and unknown. Considering the findings of earlier studies which suggest that most uninsured AYAs received Medicaid coverage after their cancer diagnosis, and that uninsured and Medicaid-insured AYA cancer patients had a similar mortality risk, we collapsed these two categories of insurance into public/none (Robbins *et al.*, 2014; Rosenberg *et al.*, 2015).

Late effects

OSHPD and CCR data were linked by using sex and an encrypted social security number. Serial records for each patient were identified using record linkage numbers. Clinical information included up to 24 diagnoses and 20 procedures that were coded to the Ninth Edition of the International Classification of Diseases, Clinical Modification (ICD-9-CM). Late effects were classified as follows: cardiovascular (hypertension, ischaemic heart disease, cardiomyopathy/heart failure, heart transplant, other heart diseases), neurologic (stroke, seizure), endocrine (hypothyroidism, diabetes mellitus, ovarian/testicular dysfunction, nutritional deficiencies, other thyroid/endocrine glands disorder, and metabolic diseases), respiratory (asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, pneumonopathy), renal (hypertensive chronic kidney disease, hemodialysis, kidney transplant), liver and pancreas (chronic liver disease, cirrhosis, liver transplant, chronic pancreatitis), avascular necrosis (AVN), and SPM (Table SII). If a patient had one of these late effects prior to NHL diagnosis, this specific condition was not considered as an outcome in the analyses.

Statistical analysis

Chi-squared tests were used to examine whether patient characteristics differed by HIV status. The CMI and associated 95% confidence intervals (CIs) of developing a medical condition ≥2 years after NHL diagnosis was estimated using non-parametric models, accounting for death as a competing risk (Lin *et al.*, 2012). Gray's K-sample test statistic was used to determine whether the CMI of late effects differed by sociodemographic and clinical factors (Gray, 1988).

We used multivariable Cox proportional hazards regression to examine whether race/ethnicity, nSES, health insurance, and initial treatment were associated with late effects in HIV-uninfected and -infected patients. The proportion hazard assumption was tested by examining log–log survival plots, and confirmed, based on cumulative sums of Martingale residuals. Stage at diagnosis and initial treatment violated the proportional hazard assumption, and these were therefore included as stratifying variables in the models. The models were additionally adjusted for sex, age at diagnosis, NHL subtype, and year of diagnosis. HSCT was treated as a time-dependent variable. Analyses were conducted using SAS version 9.4 software. Ethics approval was obtained by the Institutional Review Board of the University of California, Davis and by the California Committee for the Protection of Human Subjects.

Results

During 1996–2012, we identified 8983 patients aged 15–39 years diagnosed with NHL in California. After exclusion of patients who died within two years after diagnosis (n = 2995), had unknown survival time (n = 94), those with unknown/invalid linkage to OSHPD data (n = 1049), and those with a SPM within 60 days after diagnosis or with an unknown date of SPM (n = 28), we identified 4817 AYA survivors. Of those, 4392 (91·2%) were HIV-uninfected and 425 (8·8%) were HIV-infected patients. The median follow-up time was 9·5

and 9·3 years (range 2·0–19·0) for HIV-uninfected and HIV-infected patients, respectively. Overall, 23·8% HIV-uninfected and 39·8% HIV-infected AYAs had ≥1 late effect(s).

Table I shows the baseline characteristics of the NHL survivors by HIV status. The majority of patients were male, of white race/ethnicity, diagnosed at age 30 or older, lived in lower nSES, and had DLBCL. HIV-infected vs. HIV-uninfected survivors had a higher proportion of late stage disease (III/IV) at diagnosis (47·8% vs. 37·3%) and were about twice as likely to be uninsured/publicly (48·0%) vs. privately (21·4%) insured. HIV-uninfected AYAs were over twofold as likely to receive HSCT than HIV-infected patients (13·3% vs. 5·4%). HIV-uninfected patients had a higher proportion of follicular lymphoma, NK/T cell lymphoid neoplasm and lymphoblastic leukaemia, and a lower proportion of DLBCL and Burkitt lymphoma, than HIV-infected patients. Between 1996–2000 and 2009–2012, we observed a decreased utilisation of HSCT (18·1% and 9·0%, $P < 0·001$) and radiation (33·8% and 21·9%, $P < 0·001$) among HIV-uninfected survivors. No significant differences in HSCT and radiation were observed among HIV-infected patients over time (data not shown in Tables).

Among HIV-uninfected AYAs, the most frequent diseases at 10 years were as follows: endocrine (CMI = 18·5%), cardiovascular (CMI = 11·7%), and respiratory (CMI = 5·0%), followed by SPM (CMI = 2·6%), renal and neurologic (CMI = 2·2%), liver/pancreatic (CMI = 2·0%), and AVN (CMI = 1·2%). The two most common SPMs among HIV-uninfected survivors were breast (19·2%) and skin melanoma cancers (12·3%), whereas among HIV-infected survivors, 54·5% of SPM was anorectal cancer (footnotes of Tables II and III, respectively). HSCT was associated with an increased risk of all late effects among HIV-uninfected survivors (Table II). HIV-infected survivors had a higher CMI of all late effects compared to HIV-uninfected patients (Fig 1).

When compared to other racial/ethnic groups, HIV-uninfected blacks and Hispanics had a higher incidence of cardiovascular, renal, endocrine and neurologic diseases, whereas HIV-infected blacks had a greater incidence of cardiovascular, renal, respiratory and neurologic diseases. HIV-uninfected patients with advanced stage disease (III/IV), who were uninsured/publicly insured, and those who lived in lower SES neighbourhoods, had a greater CMI of most late effects. Conversely, among HIV-infected patients, these factors were not significantly associated with the CMI of late effects (Tables II and III).

In multivariable models, among HIV-uninfected patients, public/no insurance (vs. private) was associated with greater risk of most late effects, except AVN. Likewise, receipt of HSCT was associated with a higher risk of most diseases, including AVN, cardiovascular, respiratory, renal and endocrine diseases. The risk of developing late effects varied by nSES, with AYAs who resided in lower (vs. higher) nSES at a higher risk for developing cardiovascular, respiratory and endocrine diseases. Hispanic and black race/ethnicity (vs. white) were associated with a higher risk of renal disease. Male survivors had a higher risk of renal disease, while females were at increased risk of SPM. Our analysis by NHL subtype revealed that lymphoblastic lymphoma was significantly associated with an increased risk of endocrine disorders and AVN (Table IV). In multivariable models limited to HIV-infected patients, we observed a higher risk of renal disease among non-white patients, without evident associations with other factors (Table V). We did not observe differences in late

effects by calendar year of diagnosis, except for a higher risk of neurologic diseases among HIV-uninfected survivors in the later (vs. earlier) period of diagnosis (Table IV).

Discussion

Advances in the management of NHL with risk-stratified and multimodal treatment have led to a significant survival improvement. However, NHL AYA survivors face a lifelong risk of developing late effects. The therapeutic toxicity after NHL has been demonstrated in several studies of childhood cancer survivors (Oeffinger *et al.*, 2006; Bhakta *et al.*, 2016; Bhakta *et al.*, 2017), but just a few reports were specific for NHL (Haddy *et al.*, 1998; Ehrhardt *et al.*, 2017). To our knowledge, this is the first population-based study to investigate the incidence of late effects among AYAs with NHL, and also to explore the impact of sociodemographic and clinical factors on the occurrence of these conditions among HIV-uninfected and -infected patients. We found that AYAs who survived ≥2 years after NHL diagnosis had a substantial burden of late effects, particularly those with public or no insurance, HIV-infected patients, HSCT recipients, and survivors who lived in lower SES neighbourhoods.

The majority of NHL patients receive chemotherapy, and consequently late effects among AYAs are most likely secondary to the cumulative doses and intensities of the chemotherapeutics, mainly anthracycline and alkylating agents (Ehrhardt *et al.*, 2019). Our findings of a higher incidence of cardiovascular and endocrine diseases are consistent with previous childhood studies (Haddy *et al.*, 1998; Meacham *et al.*, 2010; Bhakta *et al.*, 2016; Bhakta *et al.*, 2017; Ehrhardt *et al.*, 2017). For example, a report from the Childhood Cancer Survivor Study showed that young survivors of childhood cancers were more likely to take medications for hypertension, dyslipidemia, and diabetes than their siblings (Meacham *et al.*, 2010). Additionally, a more recent study at a single US institution showed that the four most prevalent late effects among children/adolescent NHL survivors were being overweight/obesity, increased fasting glucose, high total cholesterol, and hypertension (Ehrhardt *et al.*, 2017). Another report from the St. Jude Lifetime Cohort Study (Bhakta *et al.*, 2017) demonstrated that among patients treated for childhood cancer who survived ≥10 years and were aged ≥18 years, respiratory disease and SPM contributed to the overall cumulative burden and severity of chronic medical conditions, supporting our results.

We observed that the majority of SPMs among both HIV-uninfected and HIV-infected survivors were solid tumours. HIV-uninfected AYAs were more likely to develop breast and melanoma skin cancers, whereas over half of SPMs among HIV-infected survivors were anorectal cancers. A report has shown (Wang *et al.*, 2018) that some childhood cancer survivors carry germline mutations in cancer predisposition genes, which are significantly associated with increased rates of solid tumours in irradiated survivors (breast cancer and sarcomas) and non-irradiated survivors (any SPM, breast cancer, non-melanoma skin cancer, and ≥2 histologically different SPMs), supporting the referral of AYA NHL patients for genetic counselling. Recent studies have suggested that chemotherapy with anthracycline and alkylating agents also increase the risk of SPM (Henderson *et al.*, 2016; Teepen *et al.*, 2017). Interestingly, we found a more pronounced increase of SPM in HIV-infected *versus* HIV-uninfected survivors. Multiple factors may have contributed to the increased

incidence of SPM in HIV-infected survivors, including chronic antigenic stimulation, chronic inflammation, cytokine deregulation, and concomitant infections (Yarchoan & Uldrick, 2018). Additionally, HIV-infected patients are nearly twice as likely to smoke, and find it more difficult to quit smoking, than the general population (Mdodo *et al.*, 2015), further increasing the risk of developing smoking-related cancers, as well as cardiovascular and respiratory diseases. Our findings emphasise the importance of AYA long-term surveillance to prevent (e.g. through sun protection and smoking prevention/cessation) and detect SPM early on (e.g. mammography for breast cancer screening, and physical examination and anoscopy/sigmoidoscopy for anorectal cancers).

Approximately 13% of HIV-uninfected AYAs received HSCT. We found that these patients were at greater risk of presenting with cardiovascular, respiratory, renal, endocrine and AVN than non-HSCT recipients. Although patients who received HSCT usually have a good quality of life, they have a lifelong risk of late health complications, which are more frequently seen than after conventional chemotherapy and/or radiation (Bhatia, 2011; Smith *et al.*, 2013). These findings underline the importance of optimal survivorship care in this population.

Our analysis by NHL subtypes showed that among HIV-uninfected patients those with lymphoblastic lymphoma had the highest CMI of AVN (likely due to a high dose of steroids), whereas follicular lymphoma had a greater CMI of cardiovascular, respiratory and endocrine diseases. Patients with Burkitt lymphoma presented the lowest CMI of endocrine and cardiovascular diseases compared to other histological subtypes. We did not observe significant differences in the CMI of late effects by NHL subtype among HIV-infected survivors. These observations need to be interpreted in light of the differences in NHL subtypes between HIV-infected and HIV-uninfected patients, including a higher incidence of Burkitt lymphoma among HIV-infected, and follicular lymphoma among HIV-uninfected patients. While the former patients may have received more intensive multidrug therapy, the later may have received less intensive treatment or a ‘watch and wait’ approach. Furthermore, potential differences in treatment management over time such as reduction in the use of radiation, introduction of immunotherapy combined with chemotherapy for some types of NHL, and improvements in antiretroviral therapy may have influenced the occurrence of late effects we observed.

Uninsured/publicly insured HIV-uninfected AYAs had a higher risk of developing late effects than privately insured survivors. This finding suggests that they have less access to healthcare as well as suboptimal preventive survivorship care. A US report, which used data from the Behavioral Risk Factor Surveillance System, revealed that AYA cancer survivors may avoid healthcare due to financial barriers, precluding prevention and early detection of late adverse effects (Kirchhoff *et al.*, 2012). The authors appropriately highlighted that although expansion of health insurance coverage for AYAs is important, this may not be sufficient to guarantee optimal care for these patients, unless cost-sharing and high out-of-pocket expenses are removed/reduced.

Similarly, nSES also influenced the occurrence of late effects among HIV-uninfected patients. AYAs who lived in lower SES regions had a higher risk of cardiovascular,

respiratory and endocrine diseases. These findings are consistent with an earlier study on AYAs with Hodgkin lymphoma in California, which found that those living in lower SES neighbourhoods had a higher incidence of respiratory and endocrine diseases (Keegan *et al.*, 2018). These data corroborate our colleagues' interpretation (Kirchhoff *et al.*, 2012; Kent *et al.*, 2013; Keegan *et al.*, 2018) that financial barriers can lead to dramatic consequences for the quality of life and survival of AYAs with cancer, as a result of delaying or foregoing much needed healthcare. Conversely, health insurance and nSES were not associated with the development of late effects among HIV-infected survivors. This may relate to a more advanced stage at diagnosis and/or higher risk NHL among these patients, requiring more intensive cancer therapies.

Adolescent and young adults of Hispanic and black race/ethnicity had an increased risk of renal disease in both HIV-uninfected and HIV-infected patients. Consistent with studies in North America (Lucas *et al.*, 2008; Abraham *et al.*, 2015), black HIV-infected patients had a substantial increased hazard of renal disease compared to HIV-uninfected patients. This may be partially explained by the potential nephrotoxic effects of antiretroviral therapy, HIV-associated nephropathy and HIV-immune complex renal disease (D'Agati & Appel, 1998). In addition, recent studies have demonstrated that *APOL1* renal risk variants have been implicated in the increased risk of end-stage renal disease among black *versus* white HIV-infected survivors (Jotwani *et al.*, 2017).

Strengths of the present study include a large population of AYAs diagnosed with NHL in California who survived ≥2 years after diagnosis, comprising a highly diverse racial/ethnic population. While some previous studies used patient-reported late effects without medical validation, we used data from all types of non-federal hospitals, allowing the generalisability of our findings. Additionally, we were able to investigate the late effects among HIV-infected survivors, a population which continues to grow and which endures a higher morbidity and mortality than HIV-uninfected individuals.

Limitations

Our study has several limitations. Firstly, we used data from patients admitted to hospitals (with a more severe disease) and may have missed information on outpatient and emergency room visits. The incidence of late effects may therefore have been underestimated. Secondly, although cancer registration is mandatory in California, 17·5% of patients who did not link to non-federal hospitalisation records were excluded from this study. This could have influenced the incidence of late effects we found. Thirdly, we lack detailed information on chemotherapy doses and intensities, type and intensity of radiation, conditioning regimens for HSCT, use of immunotherapy (e.g. rituximab), different retroviral drugs and regimens and relapse occurrence. Fourthly, we did not have data on the CD4 T cells count, a measure of the severity of HIV infection. Fifthly and finally, although we used a broad list of chronic conditions, it is not all-inclusive, and we may have missed information such as the psychological effects of treatment which can impair the quality of life of AYA survivors.

Conclusions

Adolescent and young adult NHL survivors had a wide spectrum of late effects, more specifically cardiovascular, respiratory, endocrine and secondary malignancies. We identified subgroups of patients with higher risk of diseases, such as uninsured/publicly insured AYAs, those who lived in lower SES neighbourhoods, HSCT recipients and HIV-infected patients. A deepened understanding of the late adverse effects of NHL treatment can facilitate the development of an effective survivorship plan, focusing on prevention, early detection and treatment of these conditions. Expansion of healthcare coverage and reduction of financial barriers may contribute to better long-term care of AYAs with NHL, ultimately improving the survival and quality of life of this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding/support

This study was supported by the Rich and Weissman Family Lymphoma and Survivorship Fund St. Baldrick's Research Grant. In addition, Dr Abrahão's work was funded by the National Research Service Award (NRSA) for Primary Medical Care, from the Health Resources and Services Administration (HRSA), award T32HP300370401. Dr Wun was supported by UL1 0000860, National Center for Advancing Translational Science (NCATS), National Institute of Health. The collection of cancer incidence data used in this study was supported by the California Department of Public Health, pursuant to California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health.

Role of the funder/sponsor

The funders/sponsors had no role in: the design and conduct of the study; collection, management analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. The ideas and opinions expressed herein are those of the author(s), and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended, nor should be inferred.

References

Abraham AG, Althoff KN, Jing Y, Estrella MM, Kitahata MM, Wester CW, Bosch RJ, Crane H, Eron J, Gill MJ, Horberg MA, Justice AC, Klein M, Mayor AM, Moore RD, Palella FJ, Parikh CR, Silverberg MJ, Golub ET, Jacobson LP, Napravnik S & Lucas GM (2015) End-stage renal disease among HIV-infected adults in North America. Clinical Infectious Diseases, 60, 941–949. [PubMed: 25409471]

Bhakta N, Liu Q, Yeo F, Baassiri M, Ehrhardt MJ, Srivastava DK, Metzger ML, Krasin MJ, Ness KK, Hudson MM, Yasui Y & Robison LL (2016) Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: an analysis from the St Jude Lifetime Cohort Study. The Lancet Oncology, 17, 1325–1334. [PubMed: 27470081]

Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, Chemaitilly W, Ehrhardt MJ, Bass J, Bishop MW, Shelton K, Lu L, Huang S, Li Z, Caron E, Lanctot J, Howell C, Folse T, Joshi V, Green DM, Mulrooney DA, Armstrong GT, Krull KR, Brinkman TM, Khan RB, Srivastava DK, Hudson MM, Yasui Y & Robison LL (2017) The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet, 390, 2569–2582. [PubMed: 28890157]

Bhatia S (2011) Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. Expert Review of Hematology, 4, 437–454; quiz 453–4. [PubMed: 21801135]

Bleyer A (2011) Latest estimates of survival rates of the 24 most common cancers in adolescent and young adult Americans. Journal of Adolescent and Young Adult Oncology, 1, 37–42. [PubMed: 26812567]

Chao C, Xu L, Abrams D, Leyden W, Horberg M, Towner W, Klein D, Tang B & Silverberg M (2010) Survival of non-Hodgkin lymphoma patients with and without HIV infection in the era of combined antiretroviral therapy. AIDS, 24, 1765–1770. [PubMed: 20453630]

Chao C, Xu L, Bhatia S, Cooper R, Brar S, Wong FL & Armenian SH (2016) Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: the Kaiser Permanente AYA Cancer Survivors Study. Journal of Clinical Oncology, 34, 1626–1633. [PubMed: 26951318]

Coghill AE, Shiels MS, Suneja G & Engels EA (2015) Elevated cancer-specific mortality among HIV-infected patients in the United States. Journal of Clinical Oncology, 33, 2376–2383. [PubMed: 26077242]

D'Agati V & Appel GB (1998) Renal pathology of human immunodeficiency virus infection. Seminars in Nephrology, 18, 406–421. [PubMed: 9692353]

Ehrhardt MJ, Sandlund JT, Zhang N, Liu W, Ness KK, Bhakta N, Chemaitilly W, Krull KR, Brinkman TM, Crom DB, Kun L, Kaste SC, Armstrong GT, Green DM, Srivastava K, Robison LL, Hudson MM & Mulrooney DA (2017) Late outcomes of adult survivors of childhood non-Hodgkin lymphoma: a report from the St. Jude Lifetime Cohort Study. Pediatric Blood & Cancer, 64, e26338.

Ehrhardt MJ, Hochberg J, Bjornard KL & Brinkman TM (2019) Long-term survivors of childhood, adolescent and young adult non-Hodgkin lymphoma. British Journal of Haematology, 185, 1099–1110. [PubMed: 30714126]

Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS & Goedert JJ (2008) Cancer risk in people infected with human immunodeficiency virus in the United States. International Journal of Cancer, 123, 187–194. [PubMed: 18435450]

Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin M & Whelan S (2013) International Classification of Diseases for Oncology, 3rd edn. Geneva: World Health Organization.

Gray R (1988) A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of Statistics, 16, 1141–1154.

Haddy TB, Adde MA, McCalla J, Domanski MJ, Datiles M 3rd, Meehan SC, Pikus A, Shad AT, Valdez I, Lopez Vivino L & Magrath IT (1998) Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. Journal of Clinical Oncology, 16, 2070–2079. [PubMed: 9626206]

Henderson TO, Moskowitz CS, Chou JF, Bradbury AR, Neglia JP, Dang CT, Onel K, Novetsky Friedman D, Bhatia S, Strong LC, Stovall M, Kenney LB, Barnea D, Lorenzi E, Hammond S, Leisenring WM, Robison LL, Armstrong GT, Diller LR & Oeffinger KC (2016) Breast cancer risk in childhood cancer survivors without a history of chest radiotherapy: a report from the Childhood Cancer Survivor Study. Journal of Clinical Oncology, 34, 910–918. [PubMed: 26700127]

Hudson MM, Neglia JP, Woods WG, Sandlund JT, Pui CH, Kun LE, Robison LL & Green DM (2012) Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. Pediatric Blood & Cancer, 58, 334–343. [PubMed: 22038641]

Jotwani V, Atta MG & Estrella MM (2017) Kidney disease in HIV: moving beyond HIV-associated nephropathy. Journal of the American Society of Nephrology, 28, 3142–3154. [PubMed: 28784698]

Kahn JM, Ozuah NW, Dunleavy K, Henderson TO, Kelly K & LaCasce A (2017) Adolescent and young adult lymphoma: collaborative efforts toward optimizing care and improving outcomes. Blood Advances, 1, 1945–1958. [PubMed: 29296842]

Keegan TH, Ries LA, Barr RD, Geiger AM, Dahlke DV, Pollock BH & Bleyer WA (2016a) Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. Cancer, 122, 1009–1016. [PubMed: 26848927]

Keegan TH, DeRouen MC, Parsons HM, Clarke CA, Goldberg D, Flowers CR & Glaser SL (2016b) Impact of treatment and insurance on socioeconomic disparities in survival after adolescent and young adult Hodgkin lymphoma: a population-based study. Cancer Epidemiology, Biomarkers & Prevention, 25, 264–273.

Keegan THM, Li Q, Steele A, Alvarez EM, Brunson A, Flowers CR, Glaser SL & Wun T (2018) Sociodemographic disparities in the occurrence of medical conditions among adolescent and young adult Hodgkin lymphoma survivors. Cancer Causes & Control, 29, 551–561. [PubMed: 29654427]

Kent EE, Forsythe LP, Yabroff KR, Weaver KE, de Moor JS, Rodriguez JL & Rowland JH (2013) Are survivors who report cancer-related financial problems more likely to forgo or delay medical care? Cancer, 119, 3710–3717. [PubMed: 23907958]

Kirchhoff AC, Lyles CR, Fluchel M, Wright J & Leisenring W (2012) Limitations in health care access and utilization among long-term survivors of adolescent and young adult cancer. Cancer, 118, 5964–5972. [PubMed: 23007632]

Lin G, So Y & Johnston G (2012) Analyzing Survival Data with Competing Risks Using SAS® Software. SAS Global Forum 2012 Conference. Cary, NC: SAS Institute Inc.

Lucas GM, Lau B, Atta MG, Fine DM, Keruly J & Moore RD (2008) Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. Journal of Infectious Diseases, 197, 1548–1557. [PubMed: 18422458]

Marcus JL, Chao C, Leyden WA, Xu L, Yu J, Horberg MA, Klein D, Towner WJ, Quesenberry CP Jr, Abrams DI. & Silverberg MJ. (2015) Survival among HIV-infected and HIV-uninfected individuals with common non-AIDS-defining cancers. Cancer Epidemiology, Biomarkers & Prevention, 24, 1167–1173.

Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT & Skarbinski J (2015) Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Annals of Internal Medicine, 162, 335–344. [PubMed: 25732274]

Meacham LR, Chow EJ, Ness KK, Kamdar KY, Chen Y, Yasui Y, Oeffinger KC, Sklar CA, Robison LL & Mertens AC (2010) Cardiovascular risk factors in adult survivors of pediatric cancer – a report from the childhood cancer survivor study. Cancer Epidemiology, Biomarkers & Prevention, 19, 170–181.

Nass SJ, Beaupin LK, Demark-Wahnefried W, Fasciano K, Ganz PA, Hayes-Lattin B, Hudson MM, Nevidjon B, Oeffinger KC, Rechis R, Richardson LC, Seibel NL & Smith AW (2015) Identifying and addressing the needs of adolescents and young adults with cancer: summary of an Institute of Medicine workshop. The Oncologist, 20, 186–195. [PubMed: 25568146]

Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W & Robison LL (2006) Chronic health conditions in adult survivors of childhood cancer. New England Journal of Medicine, 355, 1572–1582. [PubMed: 17035650]

Robbins AS, Lerro CC & Barr RD (2014) Insurance status and distant-stage disease at diagnosis among adolescent and young adult patients with cancer aged 15 to 39 years: National Cancer Data Base, 2004 through 2010. Cancer, 120, 1212–1219. [PubMed: 24474656]

Rosenberg AR, Kroon L, Chen L, Li CI & Jones B (2015) Insurance status and risk of cancer mortality among adolescents and young adults. Cancer, 121, 1279–1286. [PubMed: 25492559]

Shiels MS, Cole SR, Kirk GD & Poole C (2009) A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. Journal of Acquired Immune Deficiency Syndromes, 52, 611–622. [PubMed: 19770804]

Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, Bhatia K, Uldrick TS, Yarchoan R, Goedert JJ & Engels EA (2011) Cancer burden in the HIV-infected population in the United States. Journal of the National Cancer Institute, 103, 753–762. [PubMed: 21483021]

Siegel RL, Miller KD & Jemal A (2019) Cancer statistics, 2019. CA: A Cancer Journal for Clinicians, 69, 7–34. [PubMed: 30620402]

Smith SK, Mayer DK, Zimmerman S, Williams CS, Benecha H, Ganz PA, Edwards LJ & Abernethy AP (2013) Quality of life among long-term survivors of non-Hodgkin lymphoma: a follow-up study. Journal of Clinical Oncology, 31, 272–279. [PubMed: 23213093]

Teepen JC, van Leeuwen FE, Tissing WJ, van Dulmen-den Broeder E, van den Heuvel-Eibrink MM, van der Pal HJ, Loonen JJ, Bresters D, Versluys B, Neggers S, Jaspers MWM, Hauptmann M, van der Heiden-van der Loo M., Visser O., Kremer LCM. & Ronckers CM. (2017) Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. Journal of Clinical Oncology, 35, 2288–2298. [PubMed: 28530852]

Wang Z, Wilson CL, Easton J, Thrasher A, Mulder H, Liu Q, Hedges DJ, Wang S, Rusch MC, Edmonson MN, Levy S, Lanctot JQ, Caron E, Shelton K, Currie K, Lear M, Patel A, Rosencrance C, Shao Y, Vadodaria B, Yergeau D, Sapkota Y, Brooke RJ, Moon W, Rampersaud E, Ma X, Chang TC, Rice SV, Pepper C, Zhou X, Chen X, Chen W, Jones A, Boone B, Ehrhardt MJ, Krasin MJ, Howell RM, Phillips NS, Lewis C, Srivastava D, Pui CH, Kesserwan CA, Wu G, Nichols KE, Downing JR, Hudson MM, Yasui Y, Robison LL & Zhang J (2018) Genetic risk for subsequent neoplasms among long-term survivors of childhood cancer. Journal of Clinical Oncology, 36, 2078–2087. [PubMed: 29847298]

Yarchoan R & Uldrick TS (2018) HIV-associated cancers and related diseases. New England Journal of Medicine, 378, 1029–1041. [PubMed: 29539283]

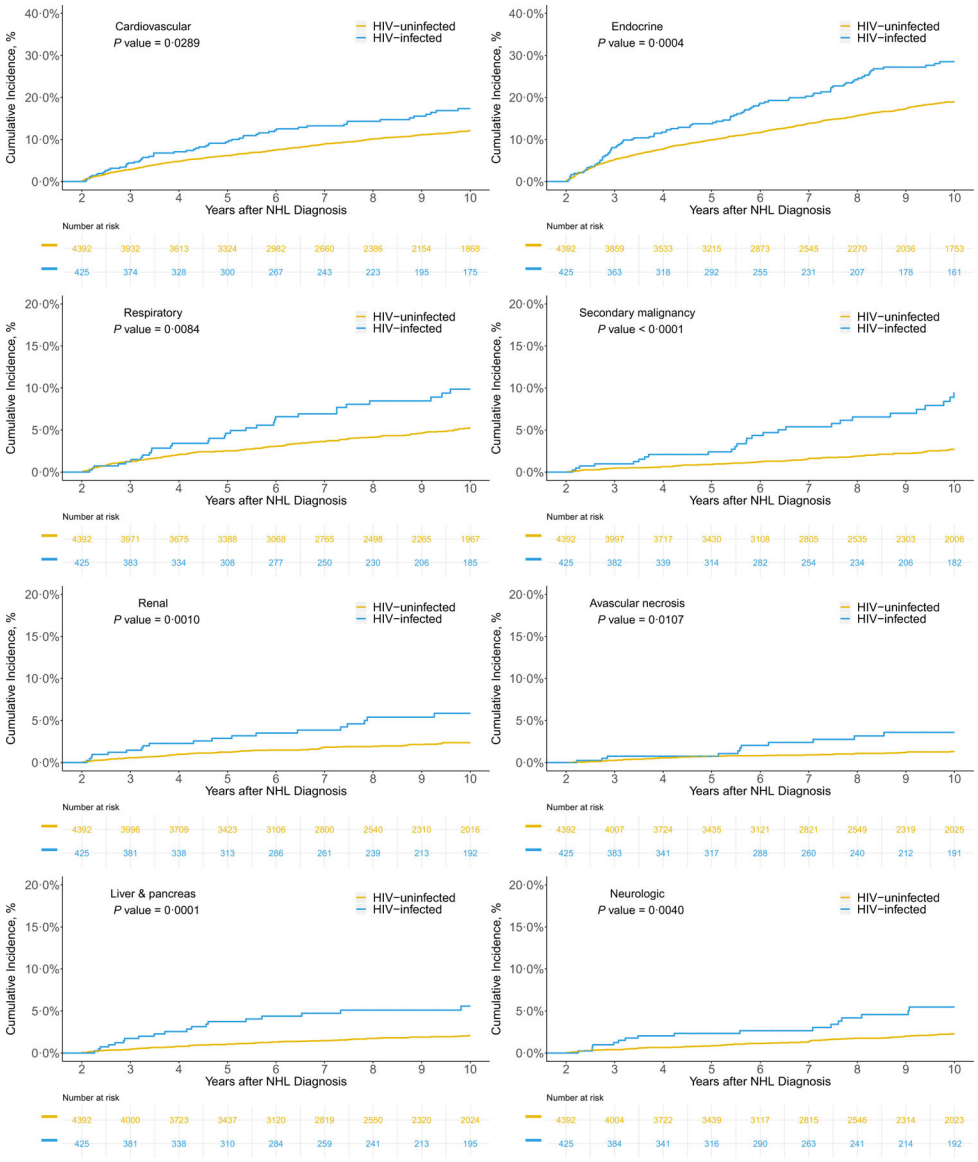

Fig 1.

Cumulative incidence of late effects among 4817 adolescent and young adult survivors of non-Hodgkin lymphoma, by HIV status, California, 1996–2012. The analyses started at 2 years after diagnosis. [Colour figure can be viewed at wileyonlinelibrary.com]

Table I.

Demographic and clinical characteristics of 4817 adolescent and young adult survivors of non-Hodgkin lymphoma, by HIV status, California, 1996–2012.

Baseline characteristics*	HIV-uninfected (*N* = 4392), *N* (%)	HIV-infected (*N* = 425), *N* (%)
Sex		
Female	2027 (46·2)	58 (13·6)
Male	2365 (53·8)	367 (86·4)
Race/ethnicity		
NH White	2285 (52·0)	201 (47·3)
NH Black	315 (7·2)	67 (15·8)
Hispanic	1156 (26·3)	132 (31·1)
NH Asian/PI	546 (12·4)	23 (5·4)
Unknown	90 (2·0)	2 (0·5)
Age at diagnosis, years		
15–19	412 (9·4)	3 (0·7)
20–24	527 (12·0)	23 (5·4)
25–29	721 (16·4)	50 (11·8)
30–34	1065 (24·2)	138 (32·5)
35–39	1667 (38·0)	211 (49·6)
Year of diagnosis		
1996–2000	1252 (28·5)	172 (40·5)
2001–2004	1109 (25·3)	99 (23·3)
2005–2008	1045 (23·8)	80 (18·8)
2009–2012	986 (22·4)	74 (17·4)
NHL histopathology		
B cell lymphoma, total	3283 (74·7)	321 (75·5)
DLBCL	1866 (42·5)	220 (51·8)
Follicular lymphoma	776 (17·7)	13 (3·1)
Burkitt lymphoma/leukaemia	187 (4·3)	81 (19·1)
Other B cell lymphoma	454 (10·3)	7 (1·6)
NK/T cell lymphoma	598 (13·6)	25 (5·9)
Lymphoblastic lymphoma†	180 (4·1)	N/A
Unspecified	331 (7·5)	79 (18·6)
Stage at diagnosis		
I/II – localised/regional	2417 (55·0)	208 (48·9)
III/IV – advanced	1638 (37·3)	203 (47·8)
Unknown	337 (7·7)	14 (3·3)
Health insurance		
Private	3186 (72·5)	197 (46·4)
Public/None	941 (21·4)	204 (48·0)
Unknown	265 (6·0)	24 (5·6)

Baseline characteristics*	HIV-uninfected (*N* = 4392), *N* (%)	HIV-infected (*N* = 425), *N* (%)
Neighbourhood SES		
Low SES (quintiles 1–3)	2270 (51·7)	286 (67·3)
High SES (quintiles 4–5)	2122 (48·3)	139 (32·7)
Initial treatment		
Chemotherapy only	2174 (49·5)	282 (66·4)
Chemotherapy and radiation	990 (22·5)	57 (13·4)
Radiation only	273 (6·2)	18 (4·2)
No/unknown	955 (21·7)	68 (16·0)
Chemotherapy		
Yes	3165 (72·1)	339 (79·8)
No	1150 (26·2)	78 (18·4)
Unknown	77 (1·8)	8 (1·9)
Radiation		
Yes	1274 (29·0)	75 (17·6)
No	3117 (71·0)	350 (82·4)
Unknown	1 (0·0)	N/A
Haematopoietic transplant		
Yes	584 (13·3)	23 (5·4)
No	3808 (86·7)	402 (94·6)
Secondary malignancy		
Solid	134 (3·1)	40 (9·4)
Haematologic	12 (0·3)	4 (0·9)

NHL, non-Hodgkin lymphoma; NH, non-Hispanic; SES, socioeconomic status; HIV, human immunodeficiency virus; NK, natural killer; DLBCL, diffuse large B cell lymphoma; *N*, number; N/A, non-applicable; PI, Pacific Islander.

*Chi-squared *P*-values (probability values) <0·0001 for all categories comparing HIV-infected and uninfected patients.

†Also called acute lymphoblastic leukaemia, it can be T or B cell type.

Table II.

Ten-year cumulative incidence (%) and 95% confidence interval of late effects among 4392 HIV-uninfected adolescent and young adult NHL survivors, California, 1996–2012.

Characteristics	Cardiovascular (*N* = 547)	Respiratory (*N* = 229)	Renal (*N* = 121)	Liver/pancreatic (*N* = 93)	Endocrine (*N* = 811)	Second malignancy‡ (*N* = 146)	Avascular necrosis (*N*= 51)	Neurologic (N = 99)
Overall	11·69 (10·64, 12·80)	5·04 (4·34, 5·82)	2·24 (1·78, 2·78)	1·97 (1·54, 2·48)	18·53 (17·24, 19·86)	2·55 (2·04, 3·14)	1·24 (0·91, 1·65)	2·15 (1·69, 2·69)
Sex								
Female	11·23 (9·74, 12·84)	5·38 (4·32, 6·59)	1·76 (1·20, 2·51)	1·65 (1·12, 2·36)	19·48 (17·55, 21·49)	3·15 (2·34, 4·14)	1·17 (0·73, 1·78)	2·44 (1·75, 3·32)
Male	12·08 (10·63, 13·63)	4·75 (3·84, 5·79)	2·66 (1·99, 3·46)	2·25 (1·63, 3·01)	17·71 (15·99, 19·50)	2·02 (1·43, 2·78)	1·30 (0·85, 1·91)	1·89 (1·33, 2·61)
P-value *	0·637	0·566	0·019	0·179	0·297	0·012	0·624	0·977
Race/ethnicity †								
NH White	11·15 (9·75, 12·65)	4·94 (4·00, 6·01)	1·66 (1·15, 2·31)	1·71 (1·20, 2·38)	18·36 (16·61, 20·19)	2·93 (2·21, 3·81)	0·98 (0·60, 1·53)	1·76 (1·21, 2·47)
NH Black	15·98 (11·75, 20·80)	5·38 (3·05, 8·65)	5·13 (2·85, 8·38)	2·80 (1·23, 5·46)	23·04 (17·99, 28·48)	1·46 (0·39, 3·98)	1·41 (0·47, 3·38)	2·25 (0·93, 4·62)
Hispanic	13·08 (10·88, 15·48)	5·96 (4·48, 7·74)	3·04 (2·02, 4·37)	2·61 (1·69, 3·84)	19·25 (16·64, 22·00)	1·99 (1·18, 3·15)	1·67 (0·96, 2·71)	3·04 (2·01, 4·41)
NH Asian/PI	9·00 (6·56, 11·91)	3·77 (2·26, 5·88)	1·61 (0·71, 3·18)	1·44 (0·54, 3·21)	15·95 (12·66, 19·58)	2·74 (1·43, 4·74)	1·25 (0·52, 2·61)	1·28 (0·53, 2·66)
P-value *	0·053	0·211	0·003	0·474	0·038	0·148	0·693	0·008
Stage at diagnosis †								
I/II – localised, regional	8·81 (7·58, 10·16)	3·70 (2·90, 4·64)	1·77 (1·24, 2·45)	1·44 (0·97, 2·08)	14·28 (12·72, 15·92)	2·07 (1·48, 2·82)	1·04 (0·64, 1·61)	1·80 (1·26, 2·50)
III/IV – advanced	15·95 (13·99, 18·03)	7·04 (5·72, 8·55)	2·96 (2·13, 4·01)	2·65 (1·88, 3·63)	24·87 (22·49, 27·32)	3·36 (2·42, 4·52)	1·75 (1·15, 2·56)	2·47 (1·70, 3·46)
P-value *	<0·0001	0·001	0·005	0·044	<0·0001	0·216	0·026	0·586
Health insurance †								
Private	10·23 (9·07, 11·47)	4·14 (3·41, 4·98)	1·91 (1·42, 2·51)	1·76 (1·29, 2·35)	16·59 (15·14, 18·10)	2·50 (1·92, 3·21)	1·15 (0·78, 1·64)	1·36 (0·95, 1·89)
Public/none	17·50 (14·83, 20·36)	7·54 (5·73, 9·66)	3·79 (2·60, 5·31)	2·91 (1·88, 4·28)	25·59 (22·44, 28·84)	2·74 (1·71, 4·15)	1·47 (0·80, 2·50)	4·59 (3·20, 6·33)
P-value *	<0·0001	<0·0001	<0·0001	0·009	<0·0001	0·666	0·532	<0·0001

Characteristics	Cardiovascular (*N* = 547)	Respiratory (*N* = 229)	Renal (*N* = 121)	Liver/pancreatic (*N* = 93)	Endocrine (*N* = 811)	Second malignancy[‡] (*N* = 146)	Avascular necrosis (*N*= 51)	Neurologic (N = 99)
Neighbourhood SES								
Low SES (quintiles 1–3)	13·86 (12·29, 15·52)	6·13 (5·07, 7·32)	2·38 (1·76, 3·16)	2·50 (1·84, 3·32)	21·81 (19·90, 23·78)	2·37 (1·71, 3·19)	1·18 (0·76, 1·77)	2·89 (2·17, 3·78)
High SES (quintiles 4–5)	9·37 (8·03, 10·84)	3·89 (3·02, 4·92)	2·09 (1·47, 2·88)	1·40 (0·93, 2·04)	15·05 (13·36, 16·83)	2·73 (2·00, 3·64)	1·30 (0·83, 1·94)	1·37 (0·88, 2·03)
P-value[*]	<0·0001	<0·0001	0·016	0·017	<0·0001	0·968	0·953	0·001
Initial treatment[†]								
Chemotherapy only	13·97 (12·34, 15·70)	6·07 (4·96, 7·32)	2·47 (1·80, 3·30)	2·58 (1·91, 3·42)	20·74 (18·80, 22·74)	2·69 (1·97, 3·60)	1·34 (0·87, 1·96)	2·30 (1·65, 3·11)
Chemotherapy &; radiation	10·48 (8·53, 12·65)	4·00 (2·85, 5·44)	1·63 (0·91, 2·72)	1·47 (0·80, 2·50)	17·48 (14·98, 20·14)	2·14 (1·28, 3·35)	1·32 (0·70, 2·29)	2·11 (1·27, 3·31)
Radiation only	5·35 (2·80, 9·10)	5·27 (2·76, 8·97)	0·92 (0·18, 3·04)	0·60 (0·05, 3·03)	13·50 (9·24, 18·56)	3·68 (1·70, 6·88)	¶	1·64 (0·54, 3·90)
P-value[*]	0·011	0·145	0·168	0·007	0·029	0·173	0·34	0·626
Haematopoietic transplant								
Yes	25·66 (22·02, 29·45)	11·31 (8·77, 14·21)	4·13 (2·63, 6·13)	3·67 (2·31, 5·50)	3·56 (2·18, 5·46)	4·50 (2·93, 6·58)	4·07 (2·59, 6·05)	3·56 (2·18, 5·46)
No	9·31 (8·27, 10·41)	3·96 (3·29, 4·73)	1·88 (1·44, 2·41)	1·70 (1·27, 2·23)	1·89 (1·43, 2·44)	2·20 (1·69, 2·81)	0·73 (0·47, 1·08)	1·89 (1·43, 2·44)
P-value[*]	<0·0001	<0·0001	<0·0001	0·014	0·012	<0·0001	<0·0001	0·012
NHL histology								
DLBCL	10·69 (9·16, 12·35)	4·09 (3·15, 5·19)	2·79 (2·04, 3·73)	2·05 (1·41, 2·90)	15·79 (13·96, 17·71)	2·35 (1·63, 3·29)	0·87 (0·48, 1·46)	2·00 (1·36, 2·84)
Follicular lymphoma	13·76 (11·12, 16·68)	7·79 (5·79, 10·17)	2·33 (1·32, 3·81)	1·93 (1·04, 3·29)	24·48 (21·06, 28·05)	3·76 (2·44, 5·51)	0·46 (0·13, 1·29)	2·77 (1·64, 4·39)
Burkitt lymphoma/ leukaemia	6·02 (2·69, 11·26)	4·75 (1·85, 9·75)	¶	0·56 (0·05, 2·86)	8·18 (4·37, 13·50)	1·23 (0·10, 5·98)	0·87 (0·08, 4·34)	1·23 (0·24, 4·04)
Other B cell lymphoma	13·33 (10·05, 17·08)	5·96 (3·82, 8·76)	1·84 (0·82, 3·60)	1·27 (0·48, 2·81)	23·37 (19·11, 27·88)	2·27 (1·05, 4·31)	0·22 (0·02, 1·19)	2·21 (1·03, 4·18)
NK/T cell lymphoma	12·00 (9·25, 15·12)	3·77 (2·29, 5·80)	1·58 (0·74, 3·00)	1·82 (0·89, 3·33)	16·51 (13·26, 20·07)	1·81 (0·84, 3·45)	1·25 (0·51, 2·66)	2·22 (1·12, 3·95)
Lymphoblastic lymphoma[§]	12·50 (7·88, 18·23)	4·69 (2·19, 8·64)	1·75 (0·34, 5·64)	1·79 (0·49, 4·78)	23·70 (17·16, 30·85)	2·66 (0·86, 6·28)	11·04 (6·51, 16·91)	1·17 (0·23, 3·84)
Unspecified	11·83 (8·31, 16·00)	4·95 (2·81, 7·97)	2·07 (0·85, 4·26)	3·58 (1·82, 6·29)	18·45 (14·09, 23·29)	3·03 (1·41, 5·67)	1·44 (0·48, 3·48)	2·23 (0·92, 4·58)

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Characteristics	Cardiovascular (*N* = 547)	Respiratory (*N* = 229)	Renal (*N* = 121)	Liver/pancreatic (*N* = 93)	Endocrine (*N* = 811)	Second malignancy‡ (*N* = 146)	Avascular necrosis (*N*= 51)	Neurologic (N = 99)
P-value *	0·043	0·013	0·305	0·333	<0·0001	0·114	<0·0001	0·489

NHL, non-Hodgkin lymphoma; NH, non-Hispanic; HIV, human immunodeficiency virus; SES, socioeconomic; DLBCL, diffuse large B cell lymphoma; NK, natural killer; PI, Pacific Islander; *N*, number; *P*-value, probability value.

*Gray's K-sample test statistic for the difference in cumulative incidence of late effects by sociodemographic and clinical characteristics.

†Data for patients with unknown race/ethnicity, stage at diagnosis, health insurance status, and no/unknown initial treatment are not shown.

‡91·8% of secondary malignancies were solid tumours, and the most common were breast cancer (*n* = 28, 19·2%) and skin melanoma (*n* = 18, 12·3%).

§Also called acute lymphoblastic leukaemia, it can be T or B cell type.

¶Small number of events prevented estimation of cumulative incidence in this category.

Br J Haematol. Author manuscript; available in PMC 2022 June 30.

Table III.

Ten-year cumulative incidence (%) and 95% confidence interval of late effects among 425 HIV-infected adolescent and young adult NHL survivors, California, 1996–2012.

Characteristics	Cardiovascular (*N* = 78)	Respiratory (*N* = 41)	Renal (*N* = 23)	Liver/pancreatic (*N* = 24)	Endocrine (*N* = 120)	Second malignancy‡ (*N* = 44)	Avascular necrosis (*N* = 12)	Neurologic (*N* = 21)
Overall	15·93 (12·31, 19·96)	8·68 (6·02, 11·94)	5·22 (3·23, 7·88)	5·06 (3·14, 7·64)	26·79 (22·23, 31·55)	8·09 (5·44, 11·40)	3·13 (1·65, 5·37)	4·82 (2·90, 7·46)
Sex								
Female	20·00 (10·09, 32·32)	15·92 (6·72, 28·64)	9·87 (3·51, 20·17)	5·45 (1·40, 13·74)	31·15 (18·25, 44·95)	6·39 (1·63, 15·94)	§	7·13 (2·26, 15·88)
Male	15·27 (11·48, 19·57)	7·64 (5·02, 10·96)	4·47 (2·54, 7·21)	4·96 (2·94, 7·76)	26·09 (21·27, 31·16)	8·36 (5·48, 12·00)	3·58 (1·89, 6·14)	4·42 (2·45, 7·25)
P value *	0·200	0·159	0·055	0·222	0·498	0·492	0·179	0·109
Race/ethnicity †								
NH White	14·48 (9·74, 20·12)	9·58 (5·78, 14·53)	1·68 (0·46, 4·50)	7·06 (3·93, 11·41)	25·01 (18·85, 31·64)	8·03 (4·57, 12·74)	3·27 (1·34, 6·65)	2·13 (0·70, 5·05)
NH Black	29·14 (18·10, 41·08)	22·64 (12·57, 34·52)	15·97 (8·08, 26·24)	1·49 (0·12, 7·15)	42·24 (29·01, 54·88)	4·21 (0·75, 12·87)	2·09 (0·16, 9·77)	9·94 (3·95, 19·23)
Hispanic	11·84 (6·31, 19·24)	0·83 (0·07, 4·14)	6·31 (2·51, 12·60)	4·37 (1·59, 9·36)	23·14 (15·32, 31·93)	9·48 (4·54, 16·63)	4·10 (1·32, 9·44)	6·79 (2·71, 13·46)
NH Asian/PI	13·33 (2·00, 35·43)	§	§	§	19·23 (4·37, 41·97)	10·83 (0·45, 40·02)	§	6·67 (0·38, 26·90)
P-value *	0·047	0·002	<0·0001	0·814	0·142	0·209	0·867	0·029
Stage at diagnosis †								
I/II – localised, regional	14·82 (9·74, 20·92)	6·96 (3·76, 11·47)	3·79 (1·52, 7·73)	4·43 (2·06, 8·19)	27·06 (20·51, 34·02)	6·50 (3·39, 10·99)	1·87 (0·50, 5·05)	5·82 (2·81, 10·40)
III/IV – advanced	18·45 (13·15, 24·47)	9·51 (5·74, 14·42)	7·06 (3·93, 11·40)	5·29 (2·70, 9·16)	25·60 (19·37, 32·27)	8·17 (4·53, 13·16)	4·58 (2·13, 8·44)	4·33 (2·02, 8·01)
P-value *	0·210	0·774	0·492	0·755	0·995	0·557	0·183	0·603
Health insurance †								
Private	15·29 (10·16, 21·39)	6·85 (3·57, 11·57)	5·87 (2·98, 10·15)	4·25 (1·85, 8·21)	24·02 (17·60, 31·01)	9·13 (5·17, 14·47)	3·18 (1·17, 6·91)	3·58 (1·45, 7·28)
Public/none	15·59 (10·53, 21·56)	10·58 (6·48, 15·83)	5·34 (2·58, 9·56)	4·31 (2·01, 7·97)	28·75 (22·04, 35·79)	7·10 (3·69, 12·00)	3·55 (1·45, 7·17)	5·48 (2·65, 9·78)
P-value *	0·604	0·209	0·347	0·146	0·183	0·593	0·624	0·206

Characteristics	Cardiovascular (*N* = 78)	Respiratory (*N* = 41)	Renal (*N* = 23)	Liver/pancreatic (*N* = 24)	Endocrine (*N* = 120)	Second malignancy[‡] (*N* = 44)	Avascular necrosis (*N* = 12)	Neurologic (*N* = 21)
Neighbourhood SES								
Low SES (quintiles 1–3)	16·06 (11·72, 21·00)	9·41 (6·11, 13·54)	5·63 (3·20, 9·03)	5·51 (3·13, 8·86)	26·62 (21·15, 32·38)	7·89 (4·80, 11·96)	3·78 (1·84, 6·81)	5·35 (2·96, 8·74)
High SES (quintiles 4–5)	15·72 (9·65, 23·14)	7·12 (3·29, 12·95)	4·33 (1·58, 9·27)	4·16 (1·54, 8·87)	27·21 (19·22, 35·80)	8·51 (4·12, 14·90)	1·79 (0·34, 5·76)	3·72 (1·19, 8·69)
P value	0·934	0·204	0·212	0·658	0·457	0·973	0·242	0·615
Initial treatment[†]								
Chemotherapy only	16·08 (11·69, 21·10)	10·13 (6·65, 14·46)	5·61 (3·19, 9·00)	5·43 (3·01, 8·87)	25·16 (19·71, 30·95)	6·69 (3·86, 10·57)	4·36 (2·21, 7·62)	3·36 (1·56, 6·27)
Chemotherapy and radiation	17·78 (8·57, 29·71)	5·50 (1·42, 13·85)	2·49 (0·19, 11·43)	1·82 (0·14, 8·59)	31·44 (18·96, 44·69)	8·96 (2·76, 19·76)		5·46 (1·41, 13·75)
Radiation only	13·73 (1·91, 36·92)	6·35 (0·36, 25·98)	§	17·09 (3·93, 38·12)	28·70 (9·83, 51·09)	5·93 (0·35, 24·45)	5·93 (0·35, 24·45)	31·04 (8·79, 56·96)
P-value[*]	0·558	0·621	0·496	0·034	0·762	0·856	0·142	<0·0001
Haematopoietic transplant								
Yes	30·16 (11·21, 51·87)	13·26 (3·18, 30·62)	§	4·55 (0·29, 19·41)	51·79 (25·07, 73·13)	10·71 (1·64, 29·69)	4·76 (0·30, 20·20)	13·70 (3·26, 31·52)
No	15·11 (11·50, 19·19)	8·42 (5·72, 11·77)	5·53 (3·42, 8·33)	5·08 (3·10, 7·75)	25·39 (20·81, 30·20)	7·91 (5·23, 11·30)	3·02 (1·54, 5·31)	4·27 (2·43, 6·91)
P-value[*]	0·271	0·589	0·239	0·787	0·042	0·553	0·674	0·048
NHL histology								
DLBCL	14·71 (10·13, 20·11)	9·28 (5·69, 13·93)	4·98 (2·53, 8·67)	3·94 (1·84, 7·29)	29·15 (22·82, 35·76)	8·12 (4·71, 12·72)	3·77 (1·66, 7·28)	4·05 (1·88, 7·52)
Follicular lymphoma	15·38 (2·22, 39·85)	15·38 (2·22, 39·85)	§	7·69 (0·40, 30·38)	17·09 (2·29, 43·78)	8·46 (0·41, 32·95)	§	§
Burkitt lymphoma/ leukaemia	27·61 (15·32, 41·35)	12·59 (5·14, 23·52)	3·86 (0·68, 11·96)	7·33 (2·06, 17·19)	33·97 (21·35, 47·00)	7·08 (1·65, 18·10)	2·95 (0·54, 9·32)	7·10 (2·18, 16·05)
Other B cell lymphoma	28·57 (2·99, 63·94)	14·29 (0·40, 50·30)	§	14·29 (0·45, 49·61)	28·57 (3·12, 63·60)	14·29 (0·40, 50·30)	§	14·29 (0·40, 50·30)
NK/T cell lymphoid neoplasms	§	§	§	§	4·00 (0·27, 17·36)	10·98 (0·46, 40·43)	§	§
Unspecified	13·36 (6·78, 22·19)	4·24 (1·10, 10·93)	9·48 (4·12, 17·53)	6·62 (2·42, 13·79)	20·72 (12·17, 30·83)	8·42 (3·39, 16·37)	2·77 (0·51, 8·73)	5·62 (1·79, 12·77)
P-value[*]	0·347	0·898	0·575	0·359	0·133	0·889	0·939	0·545

NHL, non-Hodgkin lymphoma; NH, non-Hispanic; HIV, human immunodeficiency virus; SES, socioeconomic; DLBCL, diffuse large B cell lymphoma; NK, natural killer; NH, non-Hispanic PI, Pacific Islander; *N*, number; *P*-value, probability value.

*Gray's K-sample test statistic for the difference in cumulative incidence of late effects by sociodemographic and clinical characteristics.

†Data for patients with unknown race/ethnicity, stage at diagnosis, health insurance status, and no/unknown initial treatment are not shown.

‡91·0% of secondary malignancies were solid tumours, and the most common was anorectal cancer (n = 24, 54·6%).

§Small number of events prevented estimation of cumulative incidence in these categories.

Br J Haematol. Author manuscript; available in PMC 2022 June 30.

Table IV.

Multivariable adjusted* hazard ratios (HR) and associated 95% confidence interval (CI) of late effects among 4392 HIV-uninfected adolescent and young adult survivors of non-Hodgkin lymphoma, California, 1996–2012.

	HR (95% CI)							
Characteristics	**Cardiovascular**	**Respiratory**	**Renal**	**Liver/pancreatic**	**Endocrine**	**Second malignancies**	**Neurologic**	**Avascular necrosis**
Sex								
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	0·98 (0·83, 146)	M0 (0·85, 1·43)	0·63 (0·43, 0·92)	0·79 (0·52, 1·21)	1·08 (0·94, 1·25)	1·52 (1·09, 241)	1·02 (0·69, 1·51)	143 (0·62, 2·06)
Health insurance†								
Private	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Public/none	1·56 (1·28, 1·91)	1·73 (1·27, 2·36)	2·02 (1·34, 3·03)	1·60 (1·01, 2·54)	1·49 (1·26, 1·75)	1·21 (0·81, 1·80)	2·40 (1·54, 3·75)	1·21 (0·63, 2·34)
Race/ethnicity†								
NH White	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
NH Black	1·23 (0·90, 1·68)	1·08 (0·66, 1·76)	1·91 (1·02, 3·57)	1·05 (0·50, 2·23)	1·20 (0·92, 1·56)	0·37 (043, 1·02)	1·23 (0·58, 2·62)	1·50 (0·47, 4·79)
Hispanic	0·95 (0·77, 148)	1·02 (0·74, 1·41)	1·73 (1·11s, 2·71)	1·07 (0·65, 1·75)	0·95 (0·79, 143)	0·87 (0·56, 1·33)	1·56 (0·95, 2·56)	1·64 (0·80, 3·38)
NH Asian/PI	0·86 (0·65, 145)	0·81 (0·50, 1·31)	0·94 (0·48, 1·85)	0·67 (0·30, 1·50)	0·98 (0·78, 1·23)	145 (0·71, 1·86)	1·02 (0·50, 2·07)	1·02 (0·38, 2·71)
Neighbourhood SES								
High SES (quintiles 4–5)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Low SES (quintiles 1–3)	1·41 (146, 1·71)	1·38 (1·03, 1·85)	1·07 (0·70, 1·65)	1·34 (0·84, 2·12)	1·40 (1·20, 1·64)	1·07 (0·76, 1·50)	1·51 (0·96, 2·38)	0·63 (0·35, 146)
NHL histopathology								
B cell lymphoma	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Lymphoblastic lymphoma‡	144 (0·74, 1·77)	0·99 (0·50, 1·98)	0·51 (0·16, 1·62)	0·85 (0·26, 2·78)	1·47 (1·04, 2·07)	1·25 (0·51, 3·05)	0·49 (042, 2·06)	9·54 (4·49, 20·27)
NK/T cell lymphoma	1·27 (0·97, 1·64)	0·74 (0·46, 1·20)	0·89 (0·50, 1·58)	1·07 (0·53, 2·16)	1·02 (0·82, 1·28)	0·80 (0·44, 1·45)	1·01 (0·54, 1·89)	1·78 (0·70, 4·55)
Unspecified	0·92 (0·67, 1·26)	0·92 (0·58, 1·47)	0·87 (0·45, 1·69)	1·70 (0·93, 3·11)	1·06 (0·82, 1·36)	0·78 (0·43, 1·42)	0·77 (0·36, 1·67)	1·56 (0·57, 4·25)
Haematopoietic transplant								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1·57 (1·25, 1·97)	1·87 (1·35, 2·59)	2·32 (1·54, 3·50)	148 (0·65, 247)	1·88 (1·55, 2·28)	1·32 (0·86, 2·01)	1·56 (0·94, 2·59)	4·61 (2·40, 8·87)
Year of diagnosis								
1996–2000	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2001–2004	1·04 (0·84, 1·28)	1·18 (0·86, 1·63)	1·45 (0·95, 2·22)	0·88 (0·53, 1·48)	148 (0·99, 1·40)	0·78 (0·51, 1·20)	0·74 (0·44, 1·24)	0·89 (0·42, 1·88)
2005–2009	0·76 (0·58, 1·00)	0·87 (0·57, 1·32)	0·78 (0·42, 1·44)	0·52 (0·25, 1·08)	0·98 (0·79, 1·22)	0·70 (0·40, 1·22)	1·74 (1·05, 2·87)	1·00 (0·45, 2·24)

	HR (95% CI)							
Characteristics	**Cardiovascular**	**Respiratory**	**Renal**	**Liver/pancreatic**	**Endocrine**	**Second malignancies**	**Neurologic**	**Avascular necrosis**
2010–2014	1·28 (0·94, 1·73)	M0 (0·66, 1·82)	1·17 (0·59, 2·33)	0·52 (0·25, 1·08)	0·98 (0·79, 1·22)	0·89 (0·40, 1·97)	1·03 (0·46, 2·29)	1·61 (0·70, 3·69)

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; NK, natural killer; HIV, human immunodeficiency virus; SES, socioeconomic status; NH, non-Hispanic; PI, Pacific Islander; *N*, number; N/A, not applicable.

*Additionally adjusted for age at diagnosis and stratified by stage at diagnosis and initial treatment. Haematopoietic transplant was a time-dependent variable.

†Data for patients with unknown health insurance status and race/ethnicity are not presented.

‡Lymphoblastic lymphoma is also called acute lymphoblastic leukaemia, it can be T or B cell type.

Table V.

Multivariable adjusted* hazard ratios (HR) and associated 95% confidence interval (CI) of late effects among 425 HIV-infected adolescent and young adult survivors of non-Hodgkin lymphoma, California, 1996–2012.

	HR (95% CI)							
Characteristics	**Cardiovascular**	**Respiratory**	**Renal**	**Liver/pancreatic**	**Endocrine**	**Second malignancies**	**Neurologic**	**Avascular necrosis**
Sex								
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	1·63 (0·89, 2·99)	1·74 (0·74, 4·10)	1·98 (0·69, 5·66)	1·77 (0·71, 4·44)	1·17 (0·68, 2·02)	0·64 (0·21, 1·92)	1·95 (0·63, 6·04)	N/A
Health insurance†								
Private	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Public/none	1·04 (0·66, 1·63)	1·54 (0·75, 3·14)	0·58 (0·24, 1·40)	1·44 (0·58, 3·59)	1·34 (0·91, 1·96)	1·37 (0·74, 2·54)	1·27 (0·42, 3·81)	0·76 (0·28, 2·09)
Race/ethnicity‡								
NH White	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Other	147 (0·73, 1·88)	0·77 (0·41, 1·46)	5·64 (1·88, 16·90)	0·72 (0·31, 1·67)	0·93 (0·63, 1·37)	1·14 (0·58, 2·24)	2·71 (0·86, 8·55)	0·76 (0·23, 2·52)
Neighbourhood SES								
High SES (quintiles 4–5)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Low SES (quintiles 1–3)	0·99 (0·59, 1·67)	1·42 (0·68, 2·94)	1·19 (0·40, 3·56)	1·28 (0·52, 3·16)	1·17 (0·76, 1·80)	0·98 (0·49, 1·96)	1·40 (0·42, 4·63)	3·21 (0·60, 17·08)
NHL histopathology								
DLBCL	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Burkitt lymphoma	1·43 (0·70, 2·92)	0·98 (0·40, 2·43)	0·44 (0·10, 2·05)	2·06 (0·58, 7·23)	1·25 (0·74, 2·11)	M2 (0·43, 2·95)	1·55 (0·35, 6·87)	1·33 (0·25, 7·10)
Other	0·92 (0·54, 1·55)	0·98 (0·47, 2·01)	M0 (0·42, 2·85)	1·84 (0·75, 4·49)	0·55 (0·35, 0·86)	0·87 (0·44, 1·73)	1·61 (0·64, 4·02)	0·77 (0·17, 3·53)
Year of diagnosis								
(continuous)	0·97 (0·90, 1·04)	1·02 (0·94, M0)	0·98 (0·85, M3)	0·93 (0·82, 1·05)	0·95 (0·91, 1·00)	0·85 (0·77, 0·93)	1·10 (0·95, 1·28)	0·87 (0·69, 1·10)

NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; NK, natural killer; HIV, human immunodeficiency virus; SES, socioeconomic status; NH, non-Hispanic; PI, Pacific Islander; *N*, number; N/A, not applicable.

*Simplified model for patients with HIV infection. Due to the relatively small number of patients, race/ethnicity and NHL subtypes were collapsed, and transplant was not included in the model. Additionally adjusted for age at diagnosis and stratified by stage at diagnosis and initial treatment.

†Data for patients with unknown health insurance status and race/ethnicity are not presented.

‡'Other' race/ethnicity refers to Hispanic, NH Black, NH Asian/PI, or other/unknown.