Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Leuk Lymphoma. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

Leuk Lymphoma. 2023 January ; 64(1): 151–160. doi:10.1080/10428194.2022.2133539.

Impact of Multi-Agent Systemic Therapy on All-Cause and Disease-Specific Survival for People Living with HIV Who Are Diagnosed with Non-Hodgkin Lymphoma: Population-based Analyses from the State of Georgia

Joseph Lipscomb, PhD[1,2], **Jeffrey M. Switchenko, PhD**[3,2], **Christopher R. Flowers, MD, MS**[4], **Theresa W. Gillespie, PhD**[5,6,2], **Pascale M. Wortley, MD, MPH**[7], **A. Rana Bayakly, MPH**[7], **Lyn Almon, MSPH**[8], **Kevin C. Ward, PhD**[8,9]

[1]Department of Health Policy and Management, Rollins School of Public Health, Emory University, Atlanta GA

[2]Winship Cancer Institute of Emory University

[3]Department of Biostatistics & Bioinformatics, Rollins School of Public Health

[4]Department of Lymphoma/Myeloma, Division of Cancer Medicine, MD Anderson Cancer Center, Houston TX

[5]Department of Surgical Oncology, Emory University School of Medicine

[6]Department of Hematology & Medical Oncology, Emory University School of Medicine

[7]Georgia Department of Public Health, Atlanta GA

[8]Georgia Center for Cancer Statistics, Rollins School of Public Health

[9]Department of Epidemiology, Rollins School of Public Health

Abstract

For people living with HIV (PLWH) who are subsequently diagnosed with non-Hodgkin lymphoma (NHL), we investigate the impact of standard-of-care (SoC) cancer treatment on all-cause, NHL-specific, and HIV-specific survival outcomes. The focus is on a registry-derived, population-based sample of HIV+ adults diagnosed with NHL within 2004-2012 in the state of Georgia. SoC treatment is defined as receipt of multi-agent systemic therapy (MAST). In multivariable survival analyses, SoC cancer treatment is significantly associated with better all-cause and NHL-specific survival, but not better HIV-specific survival across 2004-2017. Having a CD4 count <200 near the time of cancer diagnosis and Ann Arbor stage III/IV disease are associated with worse all-cause and HIV-specific survival; the effects on NHL survival trend negative but are not significant. Future work should expand the geographic base and cancers examined, deepen the level of clinical detail brought to bear, and incorporate the perspectives and recommendations of patients and providers.

Keywords

non-Hodgson lymphoma; HIV/AIDS; standard-of-care therapy; survival analysis; competing risks; outcomes research

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Introduction

For people living with HIV (PLWH) who are subsequently diagnosed with cancer, two important questions take center stage: In the presence of HIV/AIDS, what is the appropriate course of oncologic therapy? If undertaken, will such standard-of-care (SoC) treatment have a significant positive influence on survival?

These questions become ever more compelling, and clinically challenging, when the malignancy is an AIDS-associated cancer such as non-Hodgkin lymphoma (NHL). With NHL there is the potentially important role of HIV not only in the emergence of the cancer but its rate of progression and aggressiveness [1, 2, 3]. If the individual's HIV/AIDS is not well-controlled via antiretroviral therapy (ART), the decision may be to delay cancer treatment or reduce dose intensity [4, 5]. Cancer therapy-induced increases in immunosuppression can increase the risk of (non-cancer) AIDS-related complications, with attendant implications for morbidity and mortality [2, 4, 6]. Hence, for PLWH diagnosed with NHL, survival outcomes reflect how successfully these two major competing risks are therapeutically managed.

Recent analyses from the state of Georgia, focusing on a population-based sample of PLWH diagnosed with NHL within 2004-2012, identified several factors associated with receipt of SoC cancer treatment. This was defined as multi-agent systemic therapy (MAST), consisting of combinations of chemotherapy and monoclonal antibody agents [7]. Predictors of receipt of MAST included being diagnosed with advanced-stage (Ann Arbor stage III or IV) disease, having private health insurance, the mode of HIV transmission involving MSM, and – most notably – having a CD4 count ≥ 200 cells/mm^3.

Not explored in those analyses was whether receipt of SoC cancer treatment would lead to better survival outcomes. This paper addresses that question. Returning to the core sample of HIV-NHL patients (N=184) analyzed previously [7], we investigate the impact of MAST on survival outcomes, including all-cause, NHL-specific, and HIV-specific across 2004-2017.

There have been surprisingly few patient-level analyses of the impact of cancer therapy on survival for patients who are PLWH. In a Texas Cancer Registry-based analysis comparing lung cancer survival outcomes among HIV+ and HIV− patients, Suneja et al [8] found that receipt of cancer therapy "slightly attenuated" the negative effect of HIV on lung cancer-specific survival; for the HIV+ patients, data on their CD4 count or viral load around the time of cancer treatment were not available.

Of particular relevance, Han et al. [9] used the American College of Surgeons' National Cancer Database (NCDB) for multivariable analyses examining all-cause survival for lymphoma patients diagnosed during 2004-2011 who were PLWH compared with those who were not. Given data constraints, the treatment variable essentially indicated whether the patient received chemotherapy and, if so, within 2 weeks of cancer diagnosis. In addition, the NCDB has no information available on CD4 count or viral load. Overall, the multivariable Cox regression analyses found that having an HIV diagnosis was associated with poorer survival for all lymphoma subtypes examined (including those relevant to our

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

analyses below). But it was not the study's intent to investigate the direct impact of cancer treatment on survival for the subset of patients who were HIV+. In a separate analysis also using the NCDB to compare HIV+ and HIV− individuals diagnosed with lymphoma over 2004-2015, Jayakrishnan et al [10] found that HIV+ patients receiving "systemic therapy" (or else hematopoietic stem cell transplantation) had better all-cause survival than those receiving neither.

Our survival analyses expand upon these studies by using a treatment variable (MAST) that arguably is consistent with SoC NHL therapy for PLWH; a broader set of covariates, including CD4 count and viral load level near the time of NHL diagnosis; and a statistical modeling strategy acknowledging competing mortality risks.

Materials and methods

The derivation of all predictor variables has been presented in detail previously [7] and will be described briefly below.

Data sources and linkages

Building on matching techniques employed by the National Cancer Institute's HIV/AIDS Cancer Match Study [11], the Georgia Department of Public Health linked data from the Georgia Cancer Registry (GCR) and the Georgia HIV/AIDS Surveillance Registry (GHASR) to identify all adults (age ≥18) diagnosed with any cancer within 2004-2012 who had a diagnosis of HIV and/or AIDS on record prior to or during any portion of this period. Linkages were performed using a combination of deterministic and "fuzzy" matching [12], including manual review when needed.

From the GCR, we derived the following sociodemographic variables: age at NHL diagnosis, sex (male/female), race-ethnicity (Black/All Other), insurance status at NHL diagnosis (private/government/not insured), and residential status (Metro/Urban/Rural). NHL-related clinical and treatment variables from the GCR included: NHL subtype, as indicated by histological classification; primary/presenting disease site (nodal/extranodal); the presence of B symptoms (Yes/No); Ann Arbor disease stage (dichotomized as I/II and III/IV); year of NHL diagnosis (dichotomized as 2004-2008 and 2009-2012); whether NHL was diagnosed or treated at a facility approved by the American College of Surgeons Commission on Cancer (CoC); whether NHL treatment was MAST (see below); and the patient's survival status from date of NHL diagnosis through calendar year 2017 (see below).

While the GHASR has no patient-level information on receipt of ART, we capitalized on the availability of CD4 counts (cells/mm^3) and viral load readings (copies/mL) on PLWH, with most (but not all) individuals having multiple readings on each test and prior to their NHL diagnosis. Hence, CD4 count and viral load serve as critical markers for the patient's HIV status. CD4 count was specified as a two-level categorical variable, with severe immunosuppression defined as CD4 < 200 cells/mm^3. Viral load was transformed into a two-level variable, with viral load ≥ 400 copies/mL indicating significantly active HIV.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

From an 8-category Transmission Category variable (see [7], Table 1), we constructed a two-category variable indicating whether HIV transmission was Male sexual contact with other male (MSM) *or* MSM and injection drug use, or else by some other transmission route that also included pathways for female infection. With 44% of study patients being in these two MSM categories, we created the summary variable: MSM and All Other.

Finally, we linked these (linked) cancer-HIV files to the Georgia Hospital Discharge Database (GHDD), for individuals with at least one hospitalization prior to or following their NHL diagnosis, to construct a modified Charlson-Deyo comorbidity index score and also obtain additional information, where needed, on the patient's insurance status [7].

Patient HIV status

For patients with CD4 readings, the median time between the date of NHL diagnosis and the most recent test score prior to NHL was 1.5 months, with 75% of scores within 6.5 months of diagnosis. For viral load readings, the corresponding figures were 1.2 months and 4.8 months. Consequently, in our analyses we used the patient's *final pre-NHL* CD4 and viral load scores, and characterized them as being "near the time of cancer diagnosis."

Non-Hodgkin lymphoma cases: inclusion/exclusion criteria

Included were all PLWH age≥18 whose first primary cancer diagnosis occurred within 2004-2012 and was one of the following NHL subtypes (ICD-O-3 histology code): DLBCL (9680), Burkitt lymphoma (9687), plasmablastic lymphoma (9735), and peripheral T-cell lymphoma (9702, 9714, 9827). The first 3 subtypes are regarded as AIDS-defining, while peripheral T-cell is not [3]; but treatment for all four was chemotherapy-oriented during 2004-2012, thus aligning with MAST as SoC treatment (see below and also Table 1, note e). Finally, none of these included NHL patients was diagnosed with a second primary cancer across 2004-2012.

Excluded were those with a missing diagnosis date for either HIV or NHL. If the HIV diagnosis date was after the AIDS diagnosis date, the former was set equal to the latter. For all patients in these analyses, the resulting HIV/AIDS diagnosis date preceded the NHL diagnosis date.

Multi-agent systemic therapy for NHL

In line with treatment recommendations from the National Comprehensive Cancer Network (NCCN) for NHL patients across 2004-2012 [13] and also the categorization of treatment choices as codified in the GCR, we classified each patient as follows:

SoC: Multi-agent chemotherapy was initiated, and rituximab may also have been part of the regimen (although such monoclonal antibody agents were not distinguished separately in cancer registry coding during 2004-2012). Radiation therapy may also have been administered but was regarded as neither necessary nor sufficient alone for treatment to be SoC.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Not-SoC: Patient received only single-agent or else no chemotherapy; or chemotherapy was not recommended or administered because of risk factors; or chemotherapy was recommended but refused by patient/family/guardian.

A patient's treatment status was regarded as indeterminate, and he/she excluded from analyses, if chemotherapy was administered but the type and number of agents were not documented; the patient died before recommended therapy could begin; chemotherapy was recommended but not known if administered; or it was unknown whether chemotherapy was recommended or administered.

Assigning cause of death

From the National Death Index [14] and state vital records, the GCR provided cause-of-death information for patients known not to have survived through 2017. We categorized deaths as follows (ICD-10 codes): NHL-specific (C82-C85 *and* B21), HIV-specific (B20, B22-B24), and all other. Thus, NHL-specific deaths included not only patients so coded (C82-C85) but also those with HIV disease "resulting in malignant neoplasms" (B21) [14]. Importantly, this categorization recognizes that PLWH and contending with cancer may nonetheless die from other HIV-related causes [15].

Statistical analyses

Modeling approaches.—For all-cause survival analysis, we adopt the traditional Cox proportional hazards (PH) regression model. For disease-specific survival, we adopt two complementary approaches:

- the cause-specific Cox model, with the hazard function for disease k (e.g., NHL) representing the instantaneous rate of occurrence of death at time t attributable to cause k for study-enrolled patients known to be alive at t, and
- the Fine-Gray subdistribution model [16–18], with the hazard function for disease k (e.g., NHL) representing the rate of occurrence of death at time t attributable to k for patients who have not yet experienced *event k* by t. That is, they may be alive *or* have died from a competing risk (e.g., HIV) prior to t.

The importance of recognizing that cancer and HIV are competing mortality risks has been emphasized [20, 21]. Austin et al. [17] recommend pursuing both approaches to gain, "…a more complete understanding not only of the effects of prognostic factors, but also of the absolute risks of the different outcomes in the study sample" [17, p608].

Addressing "immortal person-time" bias.—The time between NHL diagnosis and the initiation of MAST can be characterized as "immortal person-time" [22, 23]. A patient receiving treatment must necessarily live long enough post-diagnosis for its initiation. In response, we adopt the "landmark" approach [24, 25], designating a time point post-diagnosis – in our base-case analyses, 30 days – such that patients not surviving to this time point are removed from the analyses. For all who remain, their intervention status (SoC or Not-SoC) at the landmark defines their intervention status thereafter; those Not-SoC at the landmark who eventually become SoC are censored at the date SoC is initiated.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In principle, the landmark is selected so that patients have adequate opportunity to receive the prescribed interventions. In practice here, this cannot be ensured since some (e.g., those who are immunocompromised) may initiate therapy beyond the selected landmark. In response, we embrace a "conditional" landmark strategy [26], setting it alternatively at 30 days, 50 days, and 70 days post-diagnosis.

Analysis strategy

Descriptive statistics for categorical variables are reported as frequencies and percentages (Table 1). For the all-cause survival analyses (Table 2) and our disease-specific survival analysis – NHL (Table 3) and HIV (Table 4) – we employed univariate analyses to identify potentially important predictors of survival, then multivariable modeling using a parsimonious subset of predictors. The influence of each predictor is reported as a hazard ratio (HR), with statistical significance evaluated with $p = 0.05$ as a benchmark. To assess the proportional hazards (PH) assumption for multivariable models, we plotted weighted Schoenfeld residuals as a function of log survival time, with a zero slope for a predictor variable indicating its influence on survival did not vary significantly with time (thus consistent with PH).

All data are de-identified, and analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). The study was approved by the Institutional Review Boards at Emory University and the Georgia Department of Public Health.

Results

From a total of 2,486 individuals identified in the GCR-GHASR data linkage, there were 328 PLWH in Georgia with a non-Hodgkin lymphoma diagnosis meeting study inclusion/exclusion criteria [7]. Among these, 202 (61.6%) were SoC, 99 (30.2%) were Not-SoC, and 27 (8.2%) were indeterminate.

The analytical sample for all survival analyses consisted of the 184 patients who were either SoC or Not-SoC *and* had no missing values for predictor variables regarded as central to our multivariable investigations. These predictors included CD4 count and viral load, which were missing for 59 and 113 individuals, respectively. Among the remaining 184 patients, 119 (64.7%) were SoC, and 65 (35.3%) were Not-SoC.

Table 1 shows the distributions of variable values for these 184 in total (final column) and for each of four subgroups of patients pertinent to the execution of our conditional landmark survival analyses. Hence, for the base-case (30-day) landmark analyses, we excluded patients who died prior to 30 days post NHL diagnosis; designated those who became SoC by day 30 as "SoC"; and designated those who were Not-SoC throughout the study period *and* those who were not SoC by day 30 (but later became SoC) as "Not-SoC."

One-third of the 184 had a NHL-specific death within 2004-2017, with another 22% dying from a (non-NHL) HIV-specific cause, and 13% from some other cause (Table 1). Among patients who were SoC by 30 days or else would eventually became SoC, the percent dying from NHL was about 26% and 23%, respectively, while the percent dying from a

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(non-cancer) HIV cause was about 23% and 26%. For those Not-SoC throughout, 50% had an NHL-specific death and 10%, an HIV-specific death.

Overall, 62.5% had a CD4 count <200 near the time of cancer diagnosis. There was an inverse relationship between CD4<200 and subsequent receipt of SoC therapy: among patients initiating SoC within 30 days of NHL diagnosis or initiating SoC beyond 30 days of diagnosis, 46% and 51%, respectively, had CD4<200; but among those never receiving SoC, 83% had CD4<200.

All-cause survival

SoC therapy for NHL was strongly associated with better all-cause survival, in both univariate (HR=0.46, p=0.002) and multivariable (HR=0.37, p<0.001) Cox regression models (Table 2). In the multivariable model, significant predictors of all-cause survival in addition to SoC therapy were CD4 count ≥ 200 (HR=0.47, p=0.010); Non-DLBCL NHL subtype (HR=2.26, p=0.006); and Ann Arbor stage III/IV (HR=2.35, p=0.003).

NHL-specific survival

In multivariable analyses, SoC therapy was strongly related to better NHL-specific survival in both the Cox model (HR=0.34, p=0.003) and the Fine-Gray model (HR=0.40, p=0.006) (Table 3). HR estimates for CD4 count and Ann Arbor stage were in the expected direction (<1 for CD4≥200, and >1 for stage III/IV) but not statistically significant in either Cox or Fine-Gray.

HIV-specific survival

When these same three predictor variables were deployed in similarly specified Cox and Fine-Gray multivariable models investigating HIV-specific survival, a notably different pattern of results emerged (Table 4). Now, the hazard ratio for SoC therapy was consistently >1 (though never significant). Having a CD4 count ≥200 was strongly associated with better HIV-specific survival, with HR=0.35 (p=0.024) in the Cox model and HR=0.39 (p=0.049) in Fine-Gray. Ann Arbor stage III/IV was strongly associated with poorer HIV-specific survival, with HR=4.65 (p=0.015) in Cox and HR=3.80 (p=0.020) in Fine-Gray.

Across these base-case all-cause, NHL-specific, and HIV-specific multivariable models, we did not find significant violations of the PH assumption, based on visualizations of the reweighted Schoenfeld residuals plotted against log survival time (plots available upon request).

Sensitivity analyses: Re-setting the landmark time point

To examine the robustness of base-case results, we re-estimated all models in Tables 2–4 with the landmark reset to 50 days post NHL diagnosis and then to 70 days post diagnosis. Almost without exception, the patterns of influence of predictor variables on all-cause, NHL-specific, and HIV-specific survival were sustained in these sensitivity analyses (see Appendix for a detailed comparison across landmark times).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Discussion

For PLWH diagnosed with non-Hodgkin lymphoma in the state of Georgia across 2004-2012 and followed through 2017, receipt of multi-agent systemic therapy was significantly associated with better all-cause and NHL-specific survival outcomes, compared with cancer treatment regarded as Not-SoC. A CD4 count ≥200 near the time of NHL treatment was strongly associated with better all-cause survival and better HIV-specific survival, but was not a significant predictor of NHL-specific survival. While not surprising findings, they have not (to our knowledge) been previously derived on the basis of patient-level multivariable survival analyses, including any that formally recognize NHL and HIV as competing risks.

Overall, there is a high degree of concordance in the results from the Cox and Fine-Gray disease-specific survival models, as evidenced in Tables 3 and 4.

As detailed in the Appendix, the patterns of influence of key predictor variables on survival are reassuringly robust to the choice of landmark here: 30 days, 50 days, or 70 days from the patient's NHL diagnosis date.

Defining an NHL (and HIV) cause of death

For these competing risk survival analyses, we regarded all patients whose registry-encoded ICD-10 cause of death was B21 ("human immunodeficiency virus (HIV) resulting in malignant neoplasms" [14]) as having died as a consequence of their non-Hodgkin lymphoma. In sensitivity analyses, we examined the impact on NHL-specific and HIV-specific survival results *if* B21 deaths are regarded, instead, as HIV-specific.

We re-estimated the 30-day landmark multivariable disease-specific survival models accordingly. The results (available from the authors) were generally at odds with all of the disease-specific findings reported in Tables 3 and 4. *With B21 deaths re-assigned to HIV, receipt of SoC therapy for NHL now appears to have a greater impact on reducing the risk of death from HIV than from NHL.* For example, in the multivariable NHL-specific Cox model, the HR for SoC was 0.87 (p=0.820), while in the HIV-specific Cox model, the HR for SoC was 0.39 (p=0.008). In general, there was a consistent pattern of counterintuitive results that we believe supports the decision to regard B21 deaths as NHL-specific.

Taking stock and identifying next steps

Across all model variants, a central conclusion is that PLWH diagnosed with NHL have significantly better all-cause and NHL-specific survival outcomes if they receive multi-agent systemic therapy.

There is a second, and not initially anticipated, trend running through these analyses that merits further examination: a tendency for SoC therapy to be associated with *worse* HIV-specific survival, with all HR's >1, though never significant here. How might this be? Note in Table 4 the elevated and statistically strong HR's associated with a stage III/IV NHL diagnosis. From [7], we saw that advanced-stage NHL patients were more likely to receive MAST (HR=2.92, p=0.011). We hypothesize that this (highly-toxic) MAST could be

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

wielding a dual influence – acting both to combat the NHL but also weakening the patient's immune system in its fight against potentially fatal HIV-related complications. Now, it might be anticipated that NHL patients on ART would benefit sufficiently from the reconstitution of T cells, and possibly also B cells with anti-CD20 therapy, to counter the pernicious effects of SoC therapy. However, our data show that of the 30 patients with an HIV-related death occurring subsequent to initiation of SoC therapy, 22 (73%) died *within the first 12 months* of initiation; there was no significant difference in rates by CD4 count category: 15 of 21 (71%) for CD4<200, and 7 of 9 (78%) for CD4≥200, with p=0.359. Thus, it is plausible that most such deaths occurred before whatever HIV therapies were being received could wield their protective effects.

This web of interrelationships – involving the patient's HIV status, cancer stage at diagnosis, therapy received not only for cancer but also HIV/AIDS – is scientifically interesting, clinically important, and inherently complex. Future work should proceed on at least three fronts:

Expanding such linked registry-based analyses to include multiple U.S. states and cancer disease sites.—An ideal vehicle for supporting such multi-state treatment-outcome analyses is the groundbreaking NCI-based HIV/AIDS Cancer Match Study (NACM) [11].

Adding clinical detail to the analyses.—To accomplish this, bring together clinical and outcomes researchers, state cancer and HIV/AIDS registries, *and* healthcare delivery systems that treat a substantial number of PLWH diagnosed with cancer.

Learning from the patient, and the provider.—Extend the scope of such research partnerships to include surveys of, and personal interviews with PLWH who have been diagnosed with cancer, as well as their health care providers. The aim would be to identify factors influencing decisions about diagnosis, treatment, and surveillance of the patient's HIV *and* cancer – in ways not fully captured in registries, insurance claims, or even medical records.

This approach is consistent with the National Cancer Institute's paradigm of "multilevel" research [28] that examines patient-, provider-, and health system factors that influence care delivery across the cancer continuum. For PLWH diagnosed with cancer, the journey across that continuum is especially challenging. This is all the more reason to enhance the data resources that can deepen our understanding of the pathways taken, or that should have been.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by NIH grant P30AI050409, with additional funding from the Winship Cancer Institute of Emory University. The collection of cancer incidence data in Georgia was supported by contract HHSN261201800003I, Task Order HHSN26100001 from the National Cancer Institute and cooperative agreement

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

5NU58DP003875-04 from the Centers for Disease Control and Prevention. The research reported in this paper was supported in part by the Biostatistics and Bioinformatics Shared Resource of the Winship Cancer Institute and the National Cancer Institute under award number P30CA138292. The contents are solely the responsibilities of the authors and do not necessarily represent the official views of the NCI, the CDC, or the GA Department of Public Health. The paper has benefitted significantly from the comments and recommendations from two anonymous reviewers. The authors report no conflict of interest. Corresponding author is Joseph Lipscomb (jlipsco@emory.edu).

References

[1]. Coghill AE, Strickler HD. Survival deficit for HIV-infected lymphoma patients in the National Cancer Database (editorial). Cancer Epidemiol Biomarkers Prev. 2017; 26(3):289–290. [PubMed: 28254955]

[2]. Coghill AE, Engels EA. Are cancers outcomes worse in the presence of HIV infection? (Hypothesis/Commentary). Cancer Epidemiol Biomarkers Prev. 2015; 24(8):1165–1166. [PubMed: 26240170]

[3]. Gibson TM, Morton LM, Shiels MS, et al. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS. 2014; 28(15):2313–2318. [PubMed: 25111081]

[4]. Gopal S, Martin KE, Richards KL, et al. Clinical presentation, treatment, and outcomes among 65 patients with HIV-associated lymphoma treated at the University of North Carolina, 2000-2010. AIDS Res Hum Retroviruses. 2012; 28(8):798–805. [PubMed: 22011066]

[5]. Sparano JA, Hu X, Wiernik PH, et al. Opportunistic infection and immunologic function in patients with human immunodeficiency virus-associated non-Hodgkin's lymphoma with chemotherapy. J Natl Cancer Inst. 1997; 89:301–307. [PubMed: 9048834]

[6]. Re A, Cattaneo C, Rossi G. Hiv and lymphoma: from epidemiology to clinical management. Mediterr J Hematol Infect Dis. 2019; 11(1): e2019004, DOI: 10.4084/MJHID.2019.004. [PubMed: 30671210]

[7]. Lipscomb J, Switchenko JM, Flowers CR, et al. Biologic, clinical, and sociodemographic predictors of multi-agent system therapy for non-Hodgkin lymphoma in people living with HIV: a population-based investigation in the state of Georgia. Leukemia & Lymphoma. 2020; 61(4):896–904. [PubMed: 31852329]

[8]. Suneja G, Shiels MS, Melville SK, et al. Disparities in the treatment and outcomes of lung cancer among HIV-infected individuals. AIDS. 2013; 27(3):459–468. [PubMed: 23079809]

[9]. Han X, Jemal A, Hulland E, et al. HIV infection and survival of lymphoma patients in the era of highly active antiretroviral therapy. Cancer Epidemiol Biomarkers Prev. 2016; 26(3):303–311. [PubMed: 27756777]

[10]. Jayakrishnan TT, Bakalov V, Samhouri Y, et al. Outcomes of treatment for HIV-infected lymphoma patients: a National Cancer Database (NCDB) analysis. Clinical Lymphoma, Myeloma & Leukemia. 2020; 20(11):e864–e870.

[11]. National Cancer Institute, Division of Epidemiology and Genetics. HIV/AIDS Cancer Match Study. [cited 2021 June 25]. Available at https://hivmatch.cancer.gov/.

[12]. Fogarasi J (SAS Institute). Fuzzy Matching with SAS: Data Analysts' Tool to Cleaner Data. [cited 2021 July 7]. Available from: https://www.sas.com/content/dam/SAS/en_ca/User%20Group%20Presentations/TASS/fogarasi_fuzzy_matching.pdf.

[13]. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-Hodgkin's Lymphomas. Version 2.2015. [cited 2021 July 8]. Available from https://www2.tri-kobe.org/nccn/guideline/hematologic/nhl/english/foll.pdf.

[14]. Centers for Disease Control and Prevention, National Center for Health Statistics. National Death Index. [cited 2021 July 9]. Available from: https://www.cdc.gov/nchs/ndi/index.htm.

[15]. World Health Organization. (2004). ICD-10: international statistical classification of diseases and related health problems: tenth revision, 2nd ed. World Health Organization.

[16]. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94:496–509.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[17]. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016; 133:601–609. [PubMed: 26858290]

[18]. Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression model. Clin Cancer Res. 2012; 18(8):2301–2308. [PubMed: 22282466]

[19]. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009; 170:244–256. [PubMed: 19494242]

[20]. Dal Maso L, Serraino D. All-cause and cancer-specific mortality among HIV-infected and HIV-uninfected patients with cancer. J Clin Oncol 2016; 34:388–390. [PubMed: 26598757]

[21]. Coghill AE, Shiels MS, Suneja G, Engels EA. Reply to L. Dal Maso et al. J Clin Oncol 2016: 34:390–391. [PubMed: 26598741]

[22]. Lash TL, Cole SR. Immortal person-time in studies of cancer outcomes. J Clin Oncol. 2009; 27(23):e-55–e56. [PubMed: 19597013]

[23]. Park HS, Gross CP, Makarov DV, Yu JB. Immortal time bias: a frequently unrecognized threat to validity in the evaluation of post-operative radiotherapy. Int J Radiation Oncol Biol Phys. 2012; 83(5):1365–1373.

[24]. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013; 31:2963–2969. [PubMed: 23835712]

[25]. Dafni U Landmark analysis at the 25-year landmark point. Cardiovasc Qual Outcomes. 2011; 4:363–371.

[26]. Cortese G, Gerds TA, Anderson PK. Comparing predictions among competing risks models with time-dependent covariates. Statist Med. 2013; 32(18):3089–3101.

[27]. Harrell FE Jr. Regression modeling strategies, with application to linear models, logistic regression, and survival analysis. New York: Springer Series in Statistics, Springer-Verlag; 2015: p. 61.

[28]. Taplan SH, Price RA, Edwards HM, Foster MK, Breslau ES, Chollette V, et al. Introduction: understanding and influencing multilevel factors across the cancer continuum. J Natl Cancer Inst Monogr 2012; (44):2–10. [PubMed: 22623590]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Characteristics of PLWH diagnosed with non-Hodgkin lymphoma in Georgia, 2004-2012, by SoC status as assigned in accordance with designated landmark (set at 30 days post cancer diagnosis)

Variable	Level	SoC (<=30 days) (N=84)	SoC (>30 days) (N=35)	Non-SoC (N=30)	Died prior to 30 days (N=35)	Total (N=184) [a]
Sex	Male	69 (82.14)	28 (80)	27 (90)	30 (85.71)	154 (83.7)
	Female	15 (17.86)	7 (20)	3 (10)	5 (14.29)	30 (16.3)
Race [b]	Black or African American	50 (59.52)	25 (71.43)	23 (76.67)	21 (60)	119 (64.7)
	Other	34 (40.48)	10 (28.57)	7 (23.33)	14 (40)	65 (35.3)
Insurance status [c]	Government	41 (48.81)	17 (48.57)	17 (56.67)	19 (54.29)	94 (51.1)
	Private or Other	28 (33.33)	11 (31.43)	6 (20)	7 (20)	52 (28.3)
	Not insured	15 (17.86)	7 (20)	7 (23.33)	9 (25.71)	38 (20.7)
Urban-rural status [d]	Metro	76 (90.48)	34 (97.14)	28 (93.33)	30 (85.71)	168 (91.3)
	Non-metro	8 (9.52)	1 (2.86)	2 (6.67)	5 (14.29)	16 (8.7)
NHL subtype [e]	Non-DLBCL	37 (44.05)	9 (25.71)	5 (16.67)	12 (34.29)	63 (34.2)
	DLBCL	47 (55.95)	26 (74.29)	25 (83.33)	23 (65.71)	121 (65.8)
Ann Arbor stage	III/IV	60 (71.43)	23 (65.71)	11 (36.67)	23 (65.71)	117 (63.6)
	I/II	24 (28.57)	12 (34.29)	19 (63.33)	12 (34.29)	67 (36.4)
Nodal type [f]	Extranodal	23 (27.38)	12 (34.29)	17 (56.67)	14 (40)	66 (35.9)
	Nodal	61 (72.62)	23 (65.71)	13 (43.33)	21 (60)	118 (64.1)
B symptoms	Yes	41 (52.56)	19 (57.58)	12 (48)	17 (60.71)	89 (54.3)
	No	37 (47.44)	14 (42.42)	13 (52)	11 (39.29)	75 (45.7)
Charlson-Deyo comorbidity score	1+	12 (30)	12 (54.55)	4 (17.39)	17 (48.57)	45 (37.5)
	0	28 (70)	10 (45.45)	19 (82.61)	18 (51.43)	75 (62.5)
Age at diagnosis		42.5 (25 – 69)	44 (18 – 63)	45 (25 – 66)	44 (24 – 62)	44 (18 – 69)
Year of diagnosis	2009-12	50 (59.52)	25 (71.43)	15 (50)	20 (57.14)	110 (59.8)
	2004-08	34 (40.48)	10 (28.57)	15 (50)	15 (42.86)	74 (40.2)
Diagnosis facility	CoC	67 (79.76)	31 (88.57)	24 (80)	27 (77.14)	149 (81.0)
	Non-CoC	17 (20.24)	4 (11.43)	6 (20)	8 (22.86)	35 (19.0)
Diagnosed or treated at CoC facility	Yes	70 (83.33)	33 (94.29)	24 (80)	27 (77.14)	154 (83.7)
	No	14 (16.67)	2 (5.71)	6 (20)	8 (22.86)	30 (16.3)

Leuk Lymphoma. Author manuscript; available in PMC 2024 January 01.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Variable	Level	SoC (<=30 days) (N=84)	SoC (>30 days) (N=35)	Non-SoC (N=30)	Died prior to 30 days (N=35)	Total (N=184) [a]
CD4 count	≥200	45 (53.57)	17 (48.57)	5 (16.67)	2 (5.71)	69 (37.5)
	<200	39 (46.43)	18 (51.43)	25 (83.33)	33 (94.29)	115 (62.5)
Viral load	<400	20 (23.81)	8 (22.86)	3 (10)	4 (11.43)	35 (19.0)
	≥400	64 (76.19)	27 (77.14)	27 (90)	31 (88.57)	149 (81.0)
Transmission mode	Male-MSM	51 (60.71)	16 (45.71)	10 (33.33)	11 (31.43)	88 (47.8)
	Male-non-MSM/Female	33 (39.29)	19 (54.29)	20 (66.67)	24 (68.57)	96 (52.2)
Survival status [g]	Alive	39 (46.43)	13 (37.14)	6 (20)	0 (0)	58 (31.5)
	NHL-specific death	22 (26.19)	8 (22.86)	15 (50)	16 (45.71)	61 (33.2)
	HIV-specific death	19 (22.62)	9 (25.71)	3 (10)	10 (28.57)	41 (22.3)
	Other cause of death	4 (4.76)	5 (14.29)	6 (20)	9 (25.71)	24 (13.0)

[a] All 184 patients had a date of diagnosis for HIV/AIDS that was prior to the date of diagnosis for NHL.

[b] Regarding the two-level categorization (Black and Other) adopted here, there are two points to note. First, because Hispanics comprise under 5% of the total NHL sample, Whites include both non-Hispanic and Hispanic whites, and likewise for the category Black. Second, because of very small cell sizes for the cancer registry-defined categories American Indian/Alaska Native (AI/AN) and Asian, we followed standard registry reporting practice in consolidating those categories with one or more larger categories – here, they are combined with Whites. In fact, the total number of AI/AN and Asian individuals in the sample is < 5.

[c] In light of sample size limitations, we worked from the GCR's 16-category Primary Payer variable to create this 3-category summary variable, wherein Private insurance also includes "private, not otherwise specified"; Government includes coverage by any of these public sector sources listed; and Uninsured includes self-pay as well as "uninsured, not otherwise specified."

[d] Based on the Rural-Urban Continuum Code (RUCC) classification system, the county of residence for each NHL patient at the time of cancer diagnosis was either Metro (meaning the county lay within a defined Metropolitan Statistical Area whose total population was at least 250,000) or Non-Metro. The RUCC classification of Georgia's 159 counties in 2013, based on data from the 2010 Census, showed that 74 counties were Metro (and collectively containing a high percentage of the state's total population) and 85 were Non-Metro; for more about the RUCC system, see [7]. It is not surprising, therefore, that over 90% of these patients resided in counties classified as Metro at the time of their NHL diagnosis.

[e] The 63 Non-DLBCL patients include those with Burkitt lymphoma (N=41), plasmablastic lymphoma (N=11), and peripheral T-cell lymphoma (N=11).

[f] Among these 66 extra-nodal cases, there were 15 primary CNS lymphomas; of these, 13 were DLBCL, 1 was T-cell lymphoma, and 1 was Burkitt lymphoma.

[g] For the Total sample here (N=184), the assigned causes of death within each broad category can be summarized as follows:

NHL-specific: C83 (N=3), C84 (N=1), and C85 (N=21), all of which are NHL; and B21, HIV-related disease resulting in malignant neoplasms (N=36).

HIV-specific: B20, HIV-related infectious and parasitic diseases (N=11); B22, HIV-related other specified diseases (N=22); B23, HIV-related other specified conditions (N=5); and B24, unspecified HIV disease (N=3).

Within the category Other cause of death (N=24), there were the following additional cancer-related CODs, each with N=1: C64, kidney/renal related; C95, other and unspecified leukemia; D21, benign neoplasm; and D43, neoplasm of uncertain or unknown behavior. Non-cancer-related deaths were from a variety of causes, with N≤2 for each COD.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Cox proportional hazards model analyses of the association of Standard-of-Care (SoC) therapy and other factors on *all-cause* survival for PLWH diagnosed with NHL (assuming 30-day landmark)

			Univariate		Multivariable [b]	
Variable	**Level**	**N [a]**	**HR (95% CI)**	**p-value [c]**	**HR (95% CI)**	**p-value [c]**
SoC therapy	Yes	84	0.46 (0.28-0.76)	**0.002**	0.37 (0.20-0.67)	**<.001**
	No	65	Ref	-	Ref	-
Sex	Male	124	0.71 (0.39-1.30)	0.264		
	Female	25	Ref	-		
Race	Black or African American	98	1.85 (1.08-3.17)	**0.025**	1.48 (0.81-2.70)	0.207
	Other	51	Ref	-	Ref	-
Insurance status	Governmental	75	1.26 (0.67-2.37)	0.464	1.43 (0.74-2.79)	0.289
	Private or Other	45	0.76 (0.37-1.57)	0.458	1.14 (0.53-2.44)	0.732
	Not insured	29	Ref	-	Ref	-
Urban-rural status	Non-metro	11	1.06 (0.46-2.45)	0.890		
	Metro	138	Ref	-		
NHL subtype	Non-DLBCL	51	1.17 (0.71-1.90)	0.542	2.26 (1.26-4.06)	**0.006**
	DLBCL	98	Ref	-	Ref	-
Ann Arbor stage	III/IV	94	1.64 (0.98-2.74)	0.061	2.35 (1.33-4.14)	**0.003**
	I/II	55	Ref	-	Ref	-
Nodal type	Extranodal	52	1.12 (0.68-1.84)	0.659		
	Nodal	97	Ref	-		
B symptoms	Yes	72	0.70 (0.42-1.16)	0.164		
	No	64	Ref	-		
Charlson-Deyo comorbidity index	1+	28	0.74 (0.42-1.31)	0.301		
	0	57	Ref	-		
Age at diagnosis		149	1.01 (0.98-1.04)	0.507		
Year of diagnosis	2009-12	90	0.85 (0.53-1.38)	0.512		
	2004-08	59	Ref	-		
Diagnosis facility	CoC	122	1.10 (0.60-2.01)	0.758		

Leuk Lymphoma. Author manuscript; available in PMC 2024 January 01.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

			Univariate		Multivariable [b]	
Variable	**Level**	**N** [a]	**HR (95% CI)**	**p-value** [c]	**HR (95% CI)**	**p-value** [c]
	Non-CoC	27	Ref	-		
Diagnosed or treated at CoC facility	Yes	127	1.10 (0.58-2.10)	0.771		
	No	22	Ref	-		
CD4 count	≥200	67	0.43 (0.26-0.71)	**0.001**	0.47 (0.26-0.84)	**0.010**
	<200	82	Ref	-	Ref	-
Viral load	<400	31	0.40 (0.19-0.83)	**0.015**	0.62 (0.28-1.38)	0.243
	≥400	118	Ref	-	Ref	-
Transmission mode	Male-MSM	77	0.57 (0.36-0.92)	**0.022**	0.65 (0.40-1.07)	0.089
	Male-non-MSM/Female	72	Ref	-	Ref	-

[a] Sample size throughout drops from 184 to 149, with the exclusion now of the 35 patients who died prior to the 30-day landmark (see Table 1).

[b] To guard against overfitting our multivariable survival models, we were guided by a variant of what we term “Harrell’s Rule” [27]: the number of included predictor variables should not much exceed m/10, where m = number of events (deaths) in the model. From Table 1, it can be calculated that for these 149 patients, there were 91 deaths (45 NHL-specific, 31 HIV-specific, and 15 Other Cause) occurring on or after the 30-day landmark. This suggests a multivariable survival model with no more than about 9 predictors. Here, we include 8 predictors, with one (Insurance status) having 3 levels, which amounts roughly to having 9 binary predictors in all.

[c] **Bold** indicates the hazard ratio (HR) is statistically significant at p<0.05 level.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3.

Association of SoC therapy for NHL with *NHL-specific* survival, adjusting for CD4 count and Ann Arbor stage, for PLWH: Cox cause-specific and Fine-Gray sub-distribution modeling results (assuming 30-day landmark)

			Univariate		Multivariable [a]	
Variable	**Level**	**N**	**HR (95% CI)**	**p-value [b]**	**HR (95% CI)**	**p-value [b]**
Cox model						
SoC therapy	Yes	84	0.37 (0.19-0.73)	**0.004**	0.34 (0.16-0.70)	**0.003**
	No	65	Ref	-	Ref	-
CD4 count	≥200	67	0.55 (0.28-1.07)	0.079	0.65 (0.33-1.30)	0.225
	<200	82	Ref	-	Ref	-
Ann Arbor stage	III/IV	94	1.43 (0.72-2.85)	0.311	1.93 (0.94-3.96)	0.074
	I/II	55	Ref	-	Ref	-
Fine-Gray model						
SoC therapy	Yes	84	0.44 (0.23-0.85)	**0.015**	0.40 (0.21-0.77)	**0.006**
	No	65	Ref	-	Ref	-
CD4 count	≥200	67	0.69 (0.36-1.32)	0.265	0.85 (0.44-1.65)	0.633
	<200	82	Ref	-	Ref	-
Ann Arbor stage	III/IV	94	1.27 (0.63-2.54)	0.505	1.63 (0.81-3.30)	0.174
	I/II	55	Ref	-	Ref	-

[a] In line with "Harrell's Rule" [27] (see note b in Table 2), the number of included predictors should not much exceed 45/10 ≈ 4, where 45 is the number of NHL-specific deaths in the sample used for model estimation (thus, including only deaths occurring on or beyond the 30-day landmark). With that proviso in mind, and with SoC therapy, CD4 count, and Ann Arbor stage being consistently strong predictors in alternative multivariable specifications examined, we elected to include these three in our base-case multivariable disease-specific models. The corresponding univariate estimates for each variable are included for comparison purposes.

[b] **Bold** indicates the hazard ratio (HR) is statistically significant at p<0.05.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4.

Association of SoC therapy for NHL with *HIV-specific* survival, adjusting for CD4 count and Ann Arbor stage, for PLWH: Cox cause-specific and Fine-Gray sub-distribution modeling results (assuming 30-day landmark)

			Univariate		Multivariable [a]	
Variable	**Level**	**N**	**HR (95% CI)**	**p-value [b]**	**HR (95% CI)**	**p-value [b]**
Cox model						
SoC therapy	Yes	84	1.35 (0.40-4.58)	0.631	1.13 (0.32-3.98)	0.852
	No	65	Ref	-	Ref	-
CD4 count	≥200	67	0.36 (0.15-0.90)	**0.028**	0.35 (0.14-0.87)	**0.024**
	<200	82	Ref	-	Ref	-
Ann Arbor stage	III/IV	94	4.65 (1.37-15.75)	**0.013**	4.65 (1.34-16.12)	**0.015**
	I/II	55	Ref	-	Ref	-
Fine-Gray model						
SoC therapy	Yes	84	2.48 (0.76-8.11)	0.134	2.51 (0.72-8.76)	0.149
	No	65	Ref	-	Ref	-
CD4 count	≥200	67	0.53 (0.22-1.27)	0.153	0.39 (0.15-1.00)	**0.049**
	<200	82	Ref	-	Ref	-
Ann Arbor stage	III/IV	94	4.29 (1.29-14.25)	**0.017**	3.80 (1.24-11.67)	**0.020**
	I/II	55	Ref	-	Ref	-

[a] In line with "Harrell's Rule" [27] (see note b in Table 2), the number of included predictors should not much exceed 31/10 ≈ 3, where 31 is the number of HIV-specific deaths in the sample used for model estimation (thus, including only deaths occurring on or beyond the 30-day landmark). With that proviso in mind, and with SoC therapy, CD4 count, and Ann Arbor stage being consistently strong predictors in alternative multivariable specifications examined, we elected to include these three in our multivariable base-case disease-specific models. The corresponding univariate estimates for each variable are included for comparison purposes.

[b] **Bold** indicates the hazard ratio (HR) is statistically significant at p<0.05.