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Association of immunosuppression and HIV viremia with non-Hodgkin lymphoma risk overall and by subtype in persons living with HIV in the United States and Canada: a multi-center cohort study

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Authors' Contributions

RUH-R and RD drafted the manuscript. RUH-R, LQ, HL, RSN, EAE, MJS, and RD contributed to the conception and design of this work. RUH-R, WL, KNA, CJA, NAH, GD, KAG, MJG, SG, MAH, JL, WCM, AMM, LSP, CSR, KS, ACJ, RDM, and MJS participated in the acquisition or management of the data. RUH-R performed the statistical analysis. RUH-R, LQ, HL, EAE, MJS, and RD contributed to the analysis and interpretation of the data. All authors revised the manuscript critically for important intellectual content, and approved the final version of the report.

Declaration of interests

KNA serves on the scientific advisory board of TrioHealth, Inc.. MJG has served as an ad hoc member of Canadian HIV Advisory Boards of Merck, Gilead and ViiV. RDM has previously consulted for Medscape. MJS has received grants from Gilead and, formerly, Merck. The remaining authors have no conflicts of interest to disclose.

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North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS

SUMMARY

Background—Research is needed to better understand relationships between immunosuppression and HIV viremia and risk for non-Hodgkin lymphoma (NHL), a common cancer in persons living with HIV (PLWH). We aimed to identify key CD4 count and HIV RNA level predictors for NHL risk, overall and by subtype.

Methods—We studied 102,131 PLWH during 1996–2014 from 21 cohorts participating in the North American AIDS Cohort Collaboration on Research and Design. To determine key independent predictors for NHL risk, we assessed associations with time-updated recent, past, cumulative, and nadir/peak CD4 and HIV RNA measures using demographics-adjusted, cohort-stratified Cox models, and compared models using the Akaike’s information criterion.

Findings—712 persons developed NHL. The key independent predictors for overall NHL risk were recent CD4 (hazard ratio [HR] for <50 vs. 500 cells per μL 3.2, 95% CI 2.2–4.7) and cumulative (average) HIV RNA during a 3-year window lagged by half a year (HR for 100,000 vs. 500 copies per mL 9.6, 6.5–14.0). These measures were also the key predictors for diffuse large B-cell lymphoma risk (HR for CD4 <50 vs. 500 cells per μL 2.4, 1.4–4.2; HR for HIV RNA 100,000 vs 500 copies per mL 7.5, 4.5–12.7). However, recent CD4 was the sole key predictor for central nervous system NHL (HR for <50 vs. 500 cells per μL 426.3, 58.1–3126.4); and cumulative HIV RNA (proportion of time >500 copies per mL during the 3-year window) was the sole key predictor for Burkitt lymphoma (HR for entire time vs. no time >500 copies per mL 41.1, 9.1–186.6).

Interpretation—Both recent immunosuppression and prolonged HIV viremia play important independent roles in NHL development, with likely subtype heterogeneity. Early, sustained antiretroviral therapy to decrease HIV replication, dampen B-cell activation, and restore overall immune function is crucial for preventing NHL.

INTRODUCTION

The incidence of non-Hodgkin lymphoma (NHL) among persons living with HIV (PLWH) has dramatically declined in developed countries with the introduction of combination antiretroviral therapy (ART), but remains substantially higher than in the general population.

¹⁻³ HIV-induced loss of immunoregulatory control of Epstein-Barr virus (EBV)-infected B-cells and chronic B-cell activation are important lymphomagenesis (here we restrict this term to NHL, excluding Hodgkin lymphoma) mechanisms in PLWH.^{4,5}

The increased NHL risk associated with lower CD4+ T-cell count (CD4) is well-established.^{3,6-23} Furthermore, evidence supports a direct association between plasma HIV-1 RNA level (HIV RNA) and NHL risk independent of CD4,^{8,15-17,19-24} suggesting HIV effects on lymphomagenesis beyond lowering CD4.

NHL is an etiologically heterogeneous cancer group and evidence suggests that the principal reasons for the increased NHL risk in PLWH vary by NHL subtype. Risk for NHL in PLWH is particularly elevated for the three AIDS-defining subtypes – central nervous system NHL (CNS-NHL), diffuse large B-cell lymphoma (DLBCL; the most common subtype), and Burkitt lymphoma (BL).^{1,2} Compared with PLWH without AIDS, those diagnosed with AIDS exhibit a markedly higher risk for CNS-NHL, and, to a lesser degree for DLBCL, but only a slightly higher risk for BL.¹ Moreover, lower CD4 has been found to be more strongly associated with an increased risk for CNS-NHL than for DLBCL,^{8,11,14,18} but is not associated with BL risk.^{11,18,20} Furthermore, after introduction of ART, risks have dramatically decreased for CNS-NHL, and, to a lesser degree for DLBCL, but not for BL.^{1,11} The risk associated with HIV RNA by NHL subtype has been minimally investigated.²⁰

The time courses over which immunosuppression and HIV viremia exert their lymphomagenic effects are unclear. For overall NHL risk, there is growing evidence that recent CD4 is the best CD4 predictor,^{8,9,16,19-21} whereas evidence suggesting that cumulative HIV RNA is the best HIV RNA predictor is limited.¹⁹⁻²¹ Subtype-specific evidence is sparse. A better understanding of these time courses may provide insights into NHL etiology and approaches to NHL prevention in PLWH. For example, if cumulative HIV RNA were the key independent HIV RNA risk predictor, it would indicate that risk may be reduced by promptly curtailing chronic HIV viremia, even in the presence of high CD4, reinforcing current recommendations for prompt ART initiation upon HIV diagnosis and lifelong ART adherence to maintain viral suppression.²⁵ In this study, we aimed to determine key independent predictors for NHL risk, overall and by subtype, through comprehensive evaluation of time-updated recent, past, cumulative, and nadir/peak CD4 and HIV RNA measures among PLWH in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

METHODS

Study design

We studied PLWH (> 18 years) from 21 USA and Canadian cohorts participating in the NA-ACCORD (January 1, 1996-December 31, 2014; <https://statepiaps7.jhsph.edu/naaccord/>). Cohorts submitted demographic and clinical data using standardized collection methods, including validated cancer data derived from either cancer registry linkage or manual review of medical records and pathology reports.²⁶ Institutional Review Board approval was obtained for each participating cohort.

Definitions and measures

We classified incident NHL cases into five subtypes: CNS-NHL, DLBCL, BL, other specified NHL (e.g., follicular lymphoma), and NHL not otherwise specified (NHL-NOS; Appendix p 4). Follow-up started at the latest of the following dates: 1) January 1, 1996, 2) NA-ACCORD entry (first of two HIV primary care visits no more than 12 months apart), 3) cohort-specific start for reporting cancer diagnoses, 4) 18th birthday, or 5) 360 days before the later of the first CD4 or HIV RNA measurement. Follow-up ended at the earliest of the following dates: 1) cohort-specific end for reporting cancer diagnoses, 2) death, 3) NHL diagnosis, or 4) 540 days after the earlier of the last CD4 or HIV RNA measurement. We excluded persons with <2 CD4 or <2 HIV RNA measurements or with follow-up <180 days.

To construct time-updated CD4 and HIV RNA measures, we estimated CD4 and HIV RNA values at 30-day intervals, using observed laboratory measurements, as previously described.²⁷ We examined CD4 and HIV RNA lagged by 180 days (~6 months; defined as “recent”) and then by longer lags (from 540 to 2340 days, by 360 day [~1 year] increments). We lagged all measures by at least 180 days to reduce the possibility of reverse causality.

We also constructed lagged cumulative (CD4 or HIV RNA average and proportion of time CD4 <200 cells per μL or HIV RNA >500 copies per mL) and nadir/peak (CD4 nadir and HIV RNA peak) measures during pre-specified moving time windows. The duration of the “early” (more distant past) and “late” (more recent past) windows was 1080 days (~3 years). The early window was lagged by 1260 days (i.e., covered ~6.5 to ~3.5 years in the past), and the late window was lagged by 180 days (i.e., covered ~3.5 years to ~6 months in the past). The “overall” (early and late combined) window (2160 days duration; ~6 years) covered 2340 to 180 days (~6.5 years to ~6 months) in the past.

Analyses of these various measures were restricted to persons with follow-up duration greater than the examined lag or window start (e.g., measures lagged by 1260 days and the late window [starting at 1260 days in the past] can only be assessed among persons with follow-up >1260 days). Thus, the analyzed sample size decreased with increasing lag or amount of time in the past of the window start. Since more than two-thirds of NHL cases were diagnosed before 2340 days of follow-up, we did not examine measures that required excluding persons with follow-up >2340 days.

Statistical analysis

We assessed associations between CD4 and HIV RNA measures and NHL risk using cohort-stratified Cox regression with follow-up time as the time scale (counting process syntax; 30-day intervals). We modeled CD4 and HIV RNA measures as categorical variables and performed likelihood ratio tests to calculate global p-values for their associations with NHL risk, and as continuous variables to test for trends (p-trend). We adjusted for sex, race/ethnicity, and baseline age and calendar period (see categorizations in Table 1).

We compared models using the Akaike’s information criterion (AIC),²⁸ which accounts for both model fit and parsimony (Appendix p 1). A smaller AIC indicates a better model; a difference in AIC of >10 between models is considered meaningful.²⁸ To make valid AIC

comparisons, models being compared must use the same set of participants (e.g., those with follow-up >2340 days for comparisons across all the examined measures).

Our first goal was to identify a final model with the most robust independent CD4 and/or HIV RNA predictors for overall NHL risk. To select CD4 measures for further testing, we compared separate models including each CD4 measure individually. Then, to choose the best CD4 measure(s), we compared models that included the measures selected for further testing, two at a time in the same model. We did the same for HIV RNA measures. To develop our final model, we compared models including combinations of the best CD4 and/or HIV RNA measures in the same model.

Our second goal was to evaluate whether CD4 and HIV RNA predictors varied across NHL subtypes. First, using the same approach as for overall NHL, we conducted subtype-specific analyses to identify a final model for CNS-NHL, DLBCL, and BL, respectively. Second, we fit a demographics-adjusted, subtype-and-cohort-stratified Cox model to estimate associations between subtype-specific risk and the key predictors identified for overall NHL risk and test for heterogeneity of these associations (p-heterogeneity; Appendix p 1).

We did not adjust for HIV risk group or smoking in the primary analyses due to a large number of unknowns. In separate sensitivity analyses, we adjusted our final overall NHL model for HIV risk group, smoking, and cumulative ART use (Appendix p 1).

We used SAS version 9.4 (SAS Institute Inc., Cary, NC) to perform analyses, and a two-sided p-value of 0.05 to determine statistical significance.

Role of the funding source

The study's sponsors had no involvement in: study design; collection, analysis, and interpretation of data; report writing; and the decision to submit the paper for publication. RUH-R had full access to all data in the study and had final responsibility for the decision to submit this work for publication.

RESULTS

A total of 102,131 persons (Table 1) from the 122,840 PLWH included in the 21 NA-ACCORD cohorts were eligible for this study. We excluded 14,415 persons with <2 CD4 or <2 HIV RNA measurements and 6,294 persons with no follow-up time according to our definitions. Most eligible persons were male (85%), of white (44%) or black race (40%), and started follow-up during 1996–2003 (57%). At baseline, most of the persons were aged 40 years (57%) and ART-naïve (67%), with CD4 200 cells per μL (69%) and HIV RNA >500 copies per mL (70%). Persons diagnosed with NHL (N=712) included a larger proportion of males (90%), persons of white race (54%), and persons who started follow-up during 1996–1999 (56% vs. 32%). At baseline, they were more likely to be aged 40 years (65%), ART-naïve (75%), and have HIV RNA >500 copies per mL (84%), and less likely to have CD4 200 cells per μL (54%). The subtype distribution of NHL cases (Appendix p 5) was CNS-NHL, 67 (9.4%; incidence per 100,000 person-years: 9.6); DLBCL, 358 (50.3%; 51.3); BL,

83 (11.7%; 11.9); other specified NHL, 94 (13.2%; 13.5); and NHL-NOS, 110 (15.4%; 15.8).

In separate models, overall NHL risk was significantly associated with each CD4 and HIV RNA recent, lagged, cumulative, and nadir/peak measure (Appendix pp 7–9). To make valid comparisons across these models, we first examined AICs among persons with follow-up >2340 days (N=45,108; NHL cases=217). For both CD4 and HIV RNA, these comparisons showed that the best models (i.e., lowest AICs) and strongest associations (i.e., highest hazard ratios [HR]) were concentrated among lagged, cumulative, and nadir/peak measures 1260 days in the past (Appendix pp 2 and 7–9). Therefore, we next decided to compare models of measures 1260 days in the past among the larger set of persons with follow-up >1260 days (N=68,585; NHL cases=403). Comparison of models with CD4 measures showed recent CD4 (i.e., lagged by 180 days) to be the best CD4 measure; comparison of models with HIV RNA measures showed late HIV RNA average (i.e., 1260 to 180 days [~3.5 years to ~6 months] in the past) and HIV RNA lagged by 540 days (~1.5 years) to be the best HIV RNA measures (Appendix pp 2 and 10).

We then derived a final model by comparing models with combinations of these three measures (Table 2). We found that adding recent CD4 (the best individual CD4 measure; AIC=6625) to a model with late HIV RNA average (the best individual HIV RNA measure; AIC=6522) resulted in a meaningful improvement in model fit (AIC=6488). Further addition of HIV RNA lagged by 540 days (the second-best individual HIV RNA measure) resulted in no further improvement (AIC=6486). Thus, our final model included recent CD4 and late HIV RNA average. Increased risk for overall NHL was significantly associated with lower recent CD4 (HR for <50 vs. 500 cells per μL 3.2, 95% confidence interval [95% CI] 2.2–4.7) and higher late HIV RNA average (HR for 100,000 vs. 500 copies per mL 9.6, 95% CI 6.5–14.0).

In sensitivity analyses (Appendix p 11), adjusting the final model for HIV risk group, smoking, or cumulative ART use did not meaningfully change the HRs for recent CD4 and late HIV RNA average. Adjustment for cumulative ART use did not meaningfully improve the model fit.

In separate subtype-specific analyses, using the same approach we used for overall NHL, we derived a final model for DLBCL, CNS-NHL, and BL, respectively (Table 3). Both recent CD4 (HR for <50 vs. 500 cells per μL 2.4, 95% CI 1.4–4.2) and late HIV RNA average (HR for 100,000 vs. 500 copies per mL 7.5, 95% CI 4.5–12.7) remained as the key predictors for DLBCL; recent CD4 was the sole key predictor for CNS-NHL (HR for <50 vs. 500 cells per μL 426.3, 95% CI 58.1–3126.4); and late proportion of time HIV RNA >500 copies per mL was the sole key predictor for BL (HR for entire time vs. no time >500 copies per mL 41.1, 95% CI 9.1–186.6). Of the 67 CNS-NHL cases in this analysis, 57 (85%) were diagnosed with recent CD4 <200 cells per μL , whereas only one was diagnosed with recent CD4 500 cells per μL . Of the 37 BL cases in this analysis, 30 (81%) were diagnosed with proportion of time HIV RNA >500 copies per mL >50%, whereas only two were diagnosed with proportion of time HIV RNA >500 copies per mL of 0%.

Then, we estimated NHL-subtype-specific HRs for the key predictors for overall NHL risk and tested for heterogeneity (Table 4). According to global p-values and p-trends, we found significant associations between lower recent CD4 and increased risks for CNS-NHL (HR for <50 vs. 500 cells per μL 9.6, 95% CI 10.2–917.6) and DLBCL (2.4, 1.4–4.3), but not for other subtypes. The association between recent CD4 and risk was significantly stronger for CNS-NHL than for DLBCL or other subtypes (pairwise p-heterogeneity<0.0001 for CNS-NHL vs. each of the other subtypes; global p-heterogeneity<0.0001). Furthermore, we note that one can infer from Tables 2, 3, and 4 that recent CD4 <200 copies per mL (the conventional marker for significant immunosuppression) is a risk factor for overall NHL, CNS-NHL, and DLBCL, but not for BL.

We also found significant associations between higher late HIV RNA average and increased risks for each NHL subtype: CNS-NHL (HR for 100,000 vs. 500 copies per mL 9.7, 95% CI 1.5–61.1), DLBCL (7.7, 4.6–13.0), BL (48.1, 10.7–216.6), other specified NHL (5.9, 2.3–14.8) and NHL-NOS (11.7, 4.3–32.3). The association between late HIV RNA average and risk was significantly stronger for BL than for DLBCL (pairwise p-heterogeneity=0.025) and other specified NHL (pairwise p-heterogeneity=0.0039), but not than for CNS-NHL (pairwise p-heterogeneity=0.36) or NHL-NOS (pairwise p-heterogeneity=0.15; global p-heterogeneity=0.16).

DISCUSSION

Among PLWH in the USA and Canada, we observed recent, past, cumulative, and nadir/peak measures of immunosuppression and HIV viremia to be strongly associated with overall NHL risk, with the strongest associations concentrated on measures ~3.5 years to ~6 months in the past. Recent CD4 (i.e., lagged by ~6 months) and cumulative HIV RNA (i.e., average from ~3.5 years to ~6 months in the past, a time period we term “late”) were the most robust independent predictors for overall NHL risk. Moreover, the associations of recent CD4 and cumulative HIV RNA with NHL risk differed across NHL subtypes.

A strong association between lower recent CD4 and increased overall NHL risk is well-established.^{8,9,15–17,19–23} Similar to our study, recent CD4 was the best CD4 predictor in other studies that compared CD4 measures.^{8,9,16,19–21} However, few other studies performed a comprehensive evaluation of CD4 measures. Our finding that recent CD4 was a better predictor than past, cumulative, or nadir CD4 solidifies the evidence that recent CD4 is the best CD4 predictor of NHL risk, and indicates that immunosuppression acts late in lymphomagenesis in PLWH.

Like in our study, cumulative HIV RNA was the best HIV RNA predictor of NHL risk in two^{20,21} of three previous studies^{19–21} that simultaneously evaluated cumulative and recent HIV RNA, whereas recent HIV RNA was the best predictor in one study.¹⁹ In these and other studies, the direct association of cumulative and other HIV RNA measures with overall NHL risk was independent of recent CD4.^{8,15–17,19–24} Our clear demonstration of a cumulative HIV RNA effect independent of CD4 adds to the evidence of a role for prolonged HIV viremia in lymphomagenesis through mechanisms apart from lowering CD4. Furthermore, our results suggest that cumulative HIV viremia plays a role in

lymphomagenesis during the period from ~3.5 years to ~6 months prior to NHL diagnosis. Thus, using windows of different recency allowed us to detect the novel finding that late HIV RNA average (from ~3.5 years to ~6 months in the past) was a better predictor than early HIV RNA average (from ~6.5 to ~3.5 years in the past). Late HIV RNA average was also a better predictor than overall HIV RNA average, consistent with a previous study in which NHL risk was more strongly associated with cumulative HIV RNA during the past 3 years than during the entire follow-up period.²⁰

Importantly, our findings add to the evidence for NHL-subtype etiological heterogeneity.^{4,5,8,11,14,20,29} As with overall NHL, we found recent CD4 and cumulative HIV RNA from ~3.5 years to ~6 months in the past to be the key predictors for DLBCL. This result was expected, as DLBCL represented half of the NHL cases. However, recent CD4 was the sole key predictor for CNS-NHL and cumulative HIV RNA (from ~3.5 years to ~6 months in the past) was the sole key predictor for BL. Furthermore, recent CD4 was a much stronger predictor for CNS-NHL than for other subtypes, and cumulative HIV RNA was a much stronger predictor for BL than for other subtypes. These findings are consistent with previous studies that have suggested that recent CD4 is more strongly associated with CNS-NHL,^{8,11,14,18,20} and cumulative HIV RNA is more strongly associated with BL,²⁰ than with other subtypes.

EBV is found in 100% of HIV-related CNS-NHL,⁴ suggesting a necessary role for EBV in CNS-NHL development in PLWH. Thus, low CD4 may be the predominant predictor for increased CNS-NHL risk because immunosuppression results in loss of immune control of latent EBV-infection in B-cells, leading to EBV-induced malignant transformation. Conversely, 60–70% of HIV-related BL are EBV-negative, and EBV-infected BL cells express only one latent EBV protein (EBNA1).²⁹ It is possible that immunosuppression is less important for EBV-negative BL, and that immune surveillance is not a meaningful control mechanism for EBV-positive BL, due to low EBV-related neoantigen expression, explaining why CD4 is not a key predictor for BL risk. Finally, EBV is found in 20–60% of HIV-related DLBCL (depending on morphology), many of which express several latent EBV proteins besides EBNA1.²⁹ It is possible that immune surveillance plays a greater role in suppressing EBV-positive DLBCL than BL development, explaining the modest association between low CD4 and increased DLBCL risk. Ultimately, molecular classification of DLBCL subtypes may be required to understand underlying mechanisms in this heterogeneous subtype.

HIV-induced chronic B-cell activation, with resultant somatic hypermutation and class switch recombination, is also thought to contribute to lymphomagenesis, although other effects of HIV (e.g., lymphomagenic HIV-encoded proteins) may also play a role.^{4,5} High cumulative HIV RNA may be the predominant predictor of increased BL risk because its development is dependent on these mechanisms.

Our study's limitations include lack of information on EBV infection, possible selection bias resulting from exclusion criteria, and incompleteness of HIV risk group and smoking data. Nevertheless, adjusting for HIV risk group or smoking in sensitivity analyses revealed that our final model was highly robust. Furthermore, our study had relatively low statistical

power for examination of CNS-NHL and BL predictors, and insufficient statistical power to investigate predictors for each subtype classified as other specified NHL. Although we have no information about participants moving from one cohort to another, such movement was highly unlikely given the wide geographic range of the cohorts. Finally, our study included a low percentage of females and Hispanics and only USA and Canada populations, thus limiting generalizability.

Our study's strengths include large sample size and number of events; coverage of almost two decades during the ART era; inclusion of persons with varied characteristics and from diverse North American locations; validated NHL diagnoses; and a comprehensive evaluation of CD4 and HIV RNA measures, capturing exposures as far back as ~6.5 years in the past. Our approach of examining cumulative and nadir/peak measures during moving windows of fixed duration may be superior to examining these measures during total follow-up time, which varies by person.

Although risk for NHL has sharply declined with effective ART, risk is still elevated compared to the general population,¹ most likely due to late ART initiation and chronic immune activation and dysfunction that persists in spite of treatment.³ Our finding that cumulative HIV RNA is a key NHL predictor reinforces the importance of early diagnosis of HIV infection followed by prompt ART initiation, before prolonged HIV viremia has exerted its lymphomagenic effects. Full implementation of the current recommendation of immediate ART initiation upon diagnosis, only in effect since 2016,²⁵ is likely to result in further declines in NHL incidence, as would early HIV diagnosis through widespread adoption of the U.S. Preventive Services Task Force HIV screening recommendations,³⁰ followed by prompt linkage to care.

In conclusion, we found recent CD4 and cumulative HIV RNA (average during ~3.5 years to ~6 months in the past) to be key independent, strong predictors for overall NHL risk, which reflects a multifactorial etiology for NHL, involving effects of immunosuppression at a late lymphomagenesis phase and effects of HIV viremia, independent of lowering CD4, during a ~3-year phase preceding the immunosuppression effects. Our results also add to the growing evidence that the relationships between immunosuppression and HIV viremia and NHL risk vary across NHL subtypes, with recent immunosuppression very strongly associated with CNS-NHL and cumulative HIV viremia very strongly associated with BL. Our results and the sharp decline in overall NHL incidence after the advent of ART² indicate that early, sustained ART to decrease HIV replication, dampen B-cell activation, and restore overall immune function is crucial for preventing NHL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for citations published up to Dec 31, 2017 with MeSH terms “Lymphoma, Non-Hodgkin”, “HIV Infections”, and “CD4 Lymphocyte Count” or “Viral Load”, reviewed personal collections of publications, and examined reference lists of reviewed publications to identify publications that reported associations between CD4+ T-cell count (CD4) and HIV-1 RNA level (HIV RNA) measures and non-Hodgkin lymphoma (NHL) risk among persons living with HIV. Evidence indicated a well-established inverse association between CD4 and NHL risk and a direct association between HIV RNA and NHL risk independent of CD4. Evidence also indicated that relationships between CD4 and risk may vary by NHL subtype, but less is known about relationships between HIV RNA and risk by NHL subtype. Moreover, there were few comprehensive comparisons of different CD4 or HIV RNA measures (recent, past, cumulative, or nadir/peak), which capture different time courses over which immunosuppression or HIV viremia might exert their lymphomagenic effects.

Added value of this study

This study, which used data from the North American AIDS Cohort Collaboration on Research and Design, is the largest effort to comprehensively evaluate recent, past, cumulative, and nadir/peak CD4 and HIV RNA measures to determine the key predictors for NHL risk, overall and by subtype. By fitting models with one or more CD4 and/or HIV RNA measure and comparing models based on the Akaike’s information criterion, we observed that recent CD4 (i.e., lagged by 6 months) and cumulative HIV RNA during a 3-year window lagged by 6 months were the key independent predictors for overall NHL and diffuse large B-cell lymphoma (DLBCL); that recent CD4 was the sole key predictor for central nervous system NHL (CNS-NHL); and that cumulative HIV RNA was the sole key predictor for Burkitt lymphoma (BL).

Implications of all the available evidence

Immunosuppression plays a major role in NHL development among persons living with HIV, acting late in the development of this malignancy. There is also evidence that prolonged HIV viremia is an independent risk factor for NHL development, acting over several years during an earlier developmental phase than immunosuppression. The roles of recent immunosuppression and cumulative HIV viremia varied by NHL subtype – both were major contributors to DLBCL, recent immunosuppression was the major contributor to CNS-NHL, and cumulative HIV viremia was the major contributor to BL. We hypothesize that loss of control of Epstein-Barr virus infection resulting from HIV-related immunosuppression plays a major role in the development of HIV-related CNS-NHL and DLBCL, but a lesser role in HIV-related BL. Moreover, we hypothesize that chronic B-cell activation (with resultant somatic hypermutation and class switch recombination) or lymphomagenic effects of HIV-encoded proteins resulting from prolonged HIV viremia plays a prominent role in HIV-related DLBCL and BL development. Early, sustained antiretroviral therapy is crucial for NHL prevention.

Table 1.

Baseline characteristics of study sample, NA-ACCORD, 1996–2014.

Characteristic	All (N=102,131) N (%)	NHL cases (N=712) N (%)
Sex		
Male	86,479 (84.7)	640 (89.9)
Female	15,652 (15.3)	72 (10.1)
Race/ethnicity		
Black	41,123 (40.3)	236 (33.2)
White	44,437 (43.5)	385 (54.1)
Hispanic	6,888 (6.7)	41 (5.8)
Other	4,070 (4.0)	26 (3.7)
Unknown imputed	5,613 (5.5)	24 (3.4)
Age, years		
18–29	13,069 (12.8)	54 (7.6)
30–39	30,711 (30.1)	199 (28.0)
40–49	35,682 (34.9)	283 (39.8)
50	22,669 (22.2)	176 (24.7)
Calendar period		
1996–1999	32,230 (31.6)	400 (56.2)
2000–2003	25,794 (25.3)	174 (24.4)
2004–2007	19,710 (19.3)	90 (12.6)
2008–2011	18,194 (17.8)	44 (6.2)
2012–2014	6,203 (6.1)	4 (0.6)
Combination ART naive		
No	33,792 (33.1)	180 (25.3)
Yes	68,339 (66.9)	532 (74.7)
CD4 count, cells per μ L		
<50	11,111 (10.9)	106 (14.9)
50–<100	6,773 (6.6)	80 (11.2)
100–<200	13,446 (13.2)	143 (20.1)
200–<350	22,109 (21.6)	152 (21.3)
350–<500	19,996 (19.6)	115 (16.2)
500	28,696 (28.1)	116 (16.3)
HIV RNA level, copies per mL		
500	30,869 (30.2)	117 (16.4)
>500–<10,000	20,653 (20.2)	128 (18.0)
10,000–<100,000	30,194 (29.6)	259 (36.4)
100,000	20,415 (20.0)	208 (29.2)
HIV risk group		
Injection drug use	12,630 (12.4)	87 (12.2)
Men who have sex with men	32,461 (31.8)	206 (28.9)
Heterosexual	16,023 (15.7)	74 (10.4)

Characteristic	All (N=102,131) N (%)	NHL cases (N=712) N (%)
Other	2,058 (2.0)	16 (2.3)
Unknown imputed ^a	5,582 (5.5)	35 (4.9)
Unknown not imputed ^a	33,374 (32.7)	294 (41.3)
Smoking status		
Ever	54,670 (53.5)	435 (61.1)
Never	19,355 (19.0)	121 (17.0)
Unknown imputed ^a	15,610 (15.3)	60 (8.4)
Unknown not imputed ^a	12,496 (12.2)	96 (13.5)

ART=antiretroviral therapy. NHL=non-Hodgkin lymphoma.

^aWe imputed HIV risk group and smoking status for persons with unknown values, except for cohorts with a high proportion of unknowns, or, for smoking, with all the knowns being smokers.

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Table 2. Best CD4 count and HIV RNA level predictors and final model for overall NHL risk, NA-ACCORD, 1996–2014.

Best predictors	Separate models ^a		Combined models ^b				
	NHL cases	HR (95% CI)	NHL cases	Model 1 HR (95% CI)	Model 2 (Final model) HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Recent CD4 count (i.e., CD4 count 180 d lag), cells per μL							
<50	114	11.1 (8.6–14.4)	60		3.2 (2.2–4.7)	4.1 (2.8–6.0)	2.9 (2.0–4.3)
50–<100	66	5.8 (4.3–7.9)	41		2.5 (1.7–3.8)	3.2 (2.1–4.7)	2.3 (1.6–3.5)
100–<200	117	3.5 (2.7–4.5)	59		1.5 (1.1–2.2)	1.9 (1.3–2.7)	1.5 (1.0–2.1)
200–<350	150	2.1 (1.7–2.7)	78		1.2 (0.9–1.6)	1.4 (1.0–1.9)	1.2 (0.8–1.6)
350–<500	128	1.7 (1.3–2.1)	70		1.1 (0.8–1.6)	1.2 (0.9–1.7)	1.1 (0.8–1.5)
500	137	1.0 (ref)	95		1.0 (ref)	1.0 (ref)	1.0 (ref)
Global p-value ^c		<0.0001			<0.0001	<0.0001	<0.0001
Per 50 cells per μ L		0.86 (0.85–0.88)			0.95 (0.93–0.97)	0.93 (0.91–0.96)	0.95 (0.93–0.98)
P-trend		<0.0001			<0.0001	<0.0001	0.0001
AIC ^c		6625					
Late HIV RNA level average, copies per mL^d							
500	81	1.0 (ref)	81	1.0 (ref)	1.0 (ref)		1.0 (ref)
>500–<10,000	81	2.2 (1.6–3.0)	81	1.9 (1.3–2.8)	2.1 (1.5–2.8)		1.9 (1.3–2.7)
10,000–<100,000	153	5.4 (4.1–7.2)	153	3.9 (2.7–5.6)	4.2 (3.1–5.7)		3.4 (2.3–5.0)
100,000	88	16.6 (12.0–22.9)	88	8.8 (5.5–14.2)	9.6 (6.5–14.0)		6.2 (3.7–10.2)
Global p-value ^c		<0.0001		0.0001	<0.0001		<0.0001
Per log10 copies per mL		2.36 (2.14–2.60)		1.96 (1.69–2.27)	2.09 (1.87–2.34)		1.80 (1.54–2.10)
P-trend		<0.0001		<0.0001	<0.0001		<0.0001
AIC ^c		6522					
HIV RNA level 540 d lag, copies per mL							
500	199	1.0 (ref)	142	1.0 (ref)		1.0 (ref)	1.0 (ref)
>500–<10,000	109	2.0 (1.6–2.5)	73	1.3 (0.9–1.8)		1.8 (1.4–2.5)	1.2 (0.8–1.7)
10,000–<100,000	167	4.0 (3.2–4.9)	106	1.6 (1.1–2.2)		2.9 (2.2–3.9)	1.4 (1.0–2.0)

Best predictors	Separate models ^d		Combined models ^b				
	NHL cases	HR (95% CI)	NHL cases	Model 1 HR (95% CI)	Model 2 (Final model) HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
100,000	122	9.1 (7.2–11.6)	82	2.3 (1.5–3.5)		5.7 (4.1–8.0)	1.9 (1.2–2.9)
Global p-value ^c		<0.0001		0.0017		<0.0001	0.044
Per log ₁₀ copies per mL		1.91 (1.78–2.04)		1.24 (1.10–1.49)		1.75 (1.59–1.92)	1.20 (1.06–1.36)
P-trend		<0.0001		0.0007		<0.0001	0.0040
AIC ^c		6582		6513	6488	6530	6486
Combined models' AIC^c							

AIC=Akaike's information criterion. HR=hazard ratio. 95% CI=95% confidence interval. NHL=non-Hodgkin lymphoma.

^aEach measure was individually included in a cohort-stratified Cox model adjusted for sex, race/ethnicity, and baseline age and calendar period. The N and number of NHL cases used for the model of each measure was: CD4 180 d lag (N= 102,131; number of NHL cases= 712), HIV RNA 540 d lag (N= 93,917; number of NHL cases= 597), and late HIV RNA average (N= 68,585; number of NHL cases= 403).

^bFrom cohort-stratified Cox model with combinations of key predictors as covariates and adjusted for sex, race/ethnicity, and baseline age and calendar period among persons with follow-up > 1260 days (N= 68,585; number of NHL cases= 403).

^cGlobal p-value and AIC from models among persons with follow-up > 1260 days (N= 68,585; number of NHL cases= 403).

^dHIV RNA average during the late moving window (i.e., from 1260 to 180 days in the past).

Table 3.

Final models with key CD4 count and HIV RNA level predictors for CNS-NHL, DLBCL, and BL risk, NA-ACCORD, 1996–2014.

Non-Hodgkin lymphoma (NHL) subtype/Key predictors	NHL cases	HR (95% CI) ^a
Central nervous system NHL (CNS-NHL)		
Recent CD4 count (i.e., 180 d lag), cells per μL		
<50	44	426.3 (58.1–3126.4)
50–<100	7	71.9 (8.8–588.1)
100–<200	6	21.0 (2.5–175.3)
200–<350	4	6.8 (0.8–60.6)
350–<500	5	8.2 (1.0–70.6)
500	1	1.0 (ref)
Global p-value		<0.0001
Per 50 cells per μ L		0.50 (0.44–0.58)
P-trend		<0.0001
Diffuse large B-cell lymphoma (DLBCL)		
Recent CD4 count (i.e., 180 d lag), cells per μL		
<50	23	2.4 (1.4–4.2)
50–<100	25	2.9 (1.7–5.0)
100–<200	34	1.7 (1.1–2.7)
200–<350	42	1.2 (0.8–1.8)
350–<500	37	1.1 (0.7–1.7)
500	52	1.0 (ref)
Global p-value		0.0012
Per 50 cells per μ L		0.95 (0.92–0.98)
P-trend		0.0039
Late HIV RNA level average, copies per mL^b		
500	46	1.0 (ref)
>500–<10,000	43	1.8 (1.2–2.8)
10,000–<100,000	84	3.9 (2.5–5.8)
100,000	40	7.5 (4.5–12.7)
Global p-value		<0.0001
Per log ₁₀ copies per mL		1.94 (1.67–2.25)
P-trend		<0.0001
Burkitt lymphoma (BL)		
Late proportion of time HIV RNA >500 copies per mL^c		
0.00	2	1.0 (ref)
>0.00–0.25	0	--
>0.25–0.50	5	15.0 (2.9–78.4)
>0.50–0.75	4	13.8 (2.5–77.2)
>0.75–<1.00	10	36.0 (7.6–170.1)

Non-Hodgkin lymphoma (NHL) subtype/Key predictors	NHL cases	HR (95% CI) ^a
1-00	16	41.1 (9.1–186.6)
Global p-value		<0.0001
Per 20% of time HIV RNA >500 copies per mL		2.01 (1.62–2.49)
P-trend		<0.0001

HR=hazard ratio, 95% CI=95% confidence interval.

^aFrom subtype-specific cohort-stratified Cox model with key predictor(s) as covariates and adjusted for sex, race/ethnicity, and baseline age and calendar period. CNS-NHL model among all persons (N= 102,131; number of CNS-NHL cases= 67). DLBCL and BL models among persons with follow-up >1260 days (N= 68,585; number of DLBCL cases= 213; number of BL cases= 37).

^bHIV RNA average during the late moving window (i.e., from 1260 to 180 days in the past).

^cProportion of time HIV RNA >500 copies per mL during the late moving window (i.e., from 1260 to 180 days in the past).

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Table 4.

Association of key CD4 count and HIV RNA level predictors for overall NHL risk by NHL subtypes, NA-ACCORD, 1996–2014.

Key predictors for overall NHL risk	Non-Hodgkin lymphoma (NHL) subtypes										
	Central nervous system NHL (CNS-NHL)	Diffuse large B-cell lymphoma (DLBCL)	Burkitt lymphoma (BL)	Other specified NHL	NHL not otherwise specified (NHL-NOS)	Cases	HR (95% CI) ^a	Cases	HR (95% CI) ^a	Cases	HR (95% CI) ^a
Recent CD4 count (i.e., 180 d lag), cells per μL^b											
<50	25	23	2	1	9	96.6 (10.2–917.6)	2.4 (1.4–4.3)	0.5 (0.1–2.6)	0.3 (0.04–2.7)	3.5 (1.2–9.6)	
50–<100	1	25	1	6	8	5.2 (0.3–96.2)	2.9 (1.7–5.0)	0.3 (0.04–2.5)	2.4 (0.8–6.6)	3.7 (1.4–10.1)	
100–<200	1	34	6	11	7	2.2 (0.1–39.6)	1.7 (1.1–2.7)	0.8 (0.3–2.3)	1.8 (0.8–4.1)	1.4 (0.5–3.8)	
200–<350	1	42	11	8	16	1.3 (0.1–22.2)	1.2 (0.8–1.8)	1.0 (0.4–2.3)	0.7 (0.3–1.7)	1.9 (0.9–4.2)	
350–<500	4	37	5	15	9	6.0 (0.6–54.0)	1.1 (0.7–1.7)	0.5 (0.2–1.5)	1.4 (0.7–2.8)	1.2 (0.5–2.9)	
500	1	52	12	19	11	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Global p-value						<0.0001	0.0011	0.61	0.098	0.082	
Per 50 cells per μL						0.65 (0.54–0.79)	0.95 (0.92–0.98)	1.04 (0.97–1.11)	0.97 (0.91–1.02)	0.95 (0.89–1.01)	
P-trend						<0.0001	0.0035	0.29	0.25	0.088	
Late HIV RNA level average, copies per mL^{c,d}											
500	2	46	3	22	8	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	
>500–<10,000	2	43	9	11	16	1.3 (0.2–9.7)	1.9 (1.2–2.9)	8.3 (2.2–31.6)	1.1 (0.5–2.3)	3.2 (1.3–7.6)	
10,000–<100,000	11	84	19	18	21	3.2 (0.6–18.9)	3.9 (2.6–5.9)	23.8 (6.7–85.2)	2.2 (1.1–4.5)	4.4 (1.8–10.8)	
100,000	18	40	6	9	15	9.7 (1.5–61.1)	7.7 (4.6–13.0)	48.1 (10.7–216.6)	5.9 (2.3–14.8)	11.7 (4.3–32.3)	
Global p-value						0.0059	<0.0001	<0.0001	0.0026	<0.0001	
Per log10 copies per mL						3.64 (1.95–6.79)	1.95 (1.68–2.26)	3.33 (2.28–4.86)	1.51 (1.16–1.97)	2.12 (1.58–2.83)	
P-trend						<0.0001	<0.0001	<0.0001	0.0020	<0.0001	

NHL=non-Hodgkin lymphoma.

^aFrom competing risks, event-and-cohort-stratified, Cox model adjusted for sex, race/ethnicity, and baseline age and calendar period among persons with follow-up >1260 days. N= 68,585 times 5 (augmented dataset for analyzing five events [i.e., NHL subtypes]); number of NHL cases= 403 (33, 213, 37, 60, and 60 cases for CNS-NHL, DLBCL, BL, other specified NHL, and NHL-NOS, respectively).

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^b Global p-heterogeneity for measure modeled as categorical and continuous was <0.0001 and <0.0001, respectively. P-heterogeneity for measure modeled as categorical and continuous for pairwise comparisons as follows: CNS-NHL vs. DLBCL (<0.0001 and <0.0001, for categorical and continuous, respectively), CNS-NHL vs. BL (<0.0001 and <0.0001), CNS-NHL vs. other specified NHL (<0.0001 and <0.0001), and CNS-NHL vs. NHL-NOS (<0.0001 and <0.0001), DLBCL vs. BL (0.091 and 0.032), DLBCL vs. other specified NHL (0.18 and 0.65), DLBCL vs. NHL-NOS (0.80 and 0.85), BL vs. other specified NHL (0.12 and 0.13), BL vs. NHL-NOS (0.14 and 0.053), and other specified NHL vs. NHL-NOS (0.060 and 0.61).

^c Global p-heterogeneity for measure modeled as categorical and continuous was 0.16 and 0.0028, respectively. P-heterogeneity for measure modeled as categorical and continuous for pairwise comparisons as follows: CNS-NHL vs. DLBCL (0.78 and 0.042, for categorical and continuous, respectively), CNS-NHL vs. BL (0.36 and 0.81), CNS-NHL vs. other specified NHL (0.97 and 0.0056), and CNS-NHL vs. NHL-NOS (0.83 and 0.11), DLBCL vs. BL (0.025 and 0.0074), DLBCL vs. other specified NHL (0.48 and 0.098), DLBCL vs. NHL-NOS (0.62 and 0.62), BL vs. other specified NHL (0.0039 and 0.0005), BL vs. NHL-NOS (0.15 and 0.060), and other specified NHL vs. NHL-NOS (0.31 and 0.091).

^d HIV RNA average during the late moving window (i.e., from 1260 to 180 days in the past).