Title: Differences in virological and immunological risk factors for non-Hodgkin and Hodgkin lymphoma

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Abbreviations:

95%CI	95% confidence interval
aHR	adjusted hazard ratio
AIC	Akaike information criterion
AIDS	acquired immune deficiency syndrome
AUC	area under the curve
BMI	body mass index
cART	combination antiretroviral therapy
DLBCL	Diffuse large B cell lymphoma
EBV	Epstein-Barr virus
HIV	human immunodeficiency virus
HIV-VL	HIV-viral-load
HL	Hodgkin lymphoma
HR	hazard ration
NHL	non-Hodgkin lymphoma
PBCNSL	primary brain lymphoma
PLWH	people living with HIV
PYFU	person years of follow-up

Key words: NHL, HL, HIV, immune deficiency viral load

Abstract

Background

Non-Hodgkin (NHL) and Hodgkin lymphomas (HL) are increased in populations with immune dysfunction including people living with HIV, however, there is little evidence for to what degree immunological and virological factors differently affect NHL and HL risk.

Methods

Data from the D:A:D cohort was analysed to identify independent risk factors for NHL and HL using hazard ratios (HR), focusing on current and cumulative area under the curve [AUC] measures of immunological and virological status. Variables with different associations with NHL and HL were identified using marginal cox models. All statistical tests were two sided.

Results

Among 41,420 people followed for 337,020 person-years, 392 developed NHL (incidence rate 1.7/1000 person-years 95%CI: 1.06, 1.30) and 149 HL (0.44/1000 PYFU 95%CI: 0.38, 0.52). Higher risk of both NHL and HL was associated with lower current CD4-cell count, whereas higher current HIV-viral-load (HIV-VL) and higher AUC of HIV-VL was associated with NHL only. Both current and AUC of HIV-VL were factors which had different associations with NHL and HL, where the hazard ratio for NHL was progressively higher than for HL with increasing HIV-VL category. Lower current CD4-cell had a strongly but similar association with both NHL and HL.

Conclusion

CD4 depletion increased risk of both types of lymphomas while current and accumulated HIV-VL was associated with NHL only. This suggests that NHL development is related to both CD4-cell depletion and added immune dysfunction derived from ongoing HIV replication. This latter factor was not associated with HL risk.

Introduction

Use of combination antiretroviral treatment (cART) in the people living with HIV (PLWH) has led to a decline in the incidence of non-Hodgkin lymphoma (with the exception of Burkitt lymphoma [BL]) but not Hodgkin lymphoma (HL)[1-10]. Recent estimates indicate that the incidence of NHL and HL remain elevated in PLWH compared to the general population, with NHL incidence estimated to be around 10-fold higher [11-13] and HL incidence estimated to be around 11-fold higher [9, 12].

In PLWH, the pathogenesis of NHL and HL is thought to be driven by a combination of latent infection with Epstein-Barr virus (EBV) and HIV-associated immune suppression and dysfunction [14-16]. The interaction between HIV-infection, immune suppression and dysfunction and EBV co-infection is thought to differ between NHL and HL, as well as between NHL subtypes [17]. For example, approximately half of BL occur at relatively preserved CD4-cell counts and are not EBV-related [18].

Primary brain lymphomas (PBCNSL) often occur at very low CD4 levels, however, a lack EBV-specific CD4 T-cell function has been shown in PLWH people prior to PBCNSL development irrespective of absolute CD4-cell counts [19]. Almost all HL is EBV-related in PLWH and although HL is associated with low CD4-cell counts [8, 18, 20, 21], it is not as strong as for PBCNSL or diffuse large B-cell lymphomas.

Several prior studies have suggested that the risk factors and strengths of associations differ for NHL and HL in the context of PLWH [22-29]. For example, older age has been linked to NHL, however, several studies have reported no association between HL incidence and age in PLWH [20, 30-34]. Many studies have identified an association between lower current CD4-cell count and both NHL and HL incidence [5, 20, 31, 35-39]. However both current and cumulative HIV-VL have been linked with NHL incidence, independently of CD4 [34, 40], an association not usually reported for HL [37]. The START study demonstrated that immediate cART significantly reduced the risk of infection-related cancer, independently of CD4 and HIV-VL, suggesting that HIV-associated cancer risk is mediated through other mechanisms such as immune activation and reduced immune surveillance, above and beyond the depletion of CD4-cell counts [41].

Although there are many studies investigating incidence of NHL and HL since the introduction of cART and associated risk factors, to our knowledge no studies have directly compared the risk factors. Therefore, we aimed to identify independent risk factors of NHL and HL and to identify factors that differently affect NHL and HL risk in order to develop the understanding of different mechanistic pathways, which may then suggest different preventive approaches for reducing NHL and HL risk.

Methods

The Data Collection on Adverse events of Anti-HIV Drugs Study (D:A:D) is a prospective cohort collaboration established in 1999; the dataset includes more than 49000 HIV-1-positive people in Europe, the USA, and Australia. The D:A:D Study has been described in detail previously [42]. Data for routine clinical care, including demographic factors, HIV treatment, laboratory values, and AIDS-defining events (including NHL[43]) are collected at enrolment and annually thereafter. Non-AIDS defining cancers, such as HL, have been routinely collected and validated since 1 January 2004. Detailed information on all Non-AIDS-defining cancers is collected via designated case report forms, including date of diagnosis, type/location of cancer, stage and histology/cytology report or other applied diagnostic methods, such as imaging and biochemical assays, and are supplemented by submitted source documentation supporting the way of diagnosis. NHL is further characterized by histological type (BL, Diffuse-large-B-cell-lymphomas [DLBCL], PBCNSL and other or unknown). All events are centrally validated at the D:A:D coordinating center by a medical doctor, with a proportion of complicated cases selected to be reviewed by an external oncologist. Events are regularly monitored for accuracy, with random monitoring at participating sites to ensure complete case ascertainment. All participating cohorts followed local national guidelines or regulations regarding patient consent and ethical review. In particular, of the countries represented by the participating cohorts, only Switzerland and Australia require specific ethical approval for D:A:D in addition to that required for their national cohorts (Swiss HIV Cohort Study and the Australian HIV Observational Database), both of which have obtained this approval.

We investigated the association between immunological and virological factors and two main outcomes: (1) first diagnosis of NHL, and (2) first diagnosis of HL during follow-up. Baseline was defined as the latest of date of study entry, first reported CD4-cell count, or 1st January 2004, and people were

followed from baseline until the earliest of NHL or HL diagnosis, last visit plus 6 months, death, or 1st February 2015.

We investigated the associations between nadir and current CD4-cell count, and current and area under the curve(AUC) of HIV-VL and each outcome. The AUC of HIV-VL refers to the area under each individuals viralload curve[44] and was calculated using all HIV-VL measures since entry into D:A:D. Formally, it can be interpreted as the total number of copies/mL of HIV-RNA accumulated over time. For example, an AUC of HIV-VL of 10,000 copies/mL-year is equal to having a HIV-VL of 10,000 copies/mL for 1 year or a HIV-VL of 1,000 copies/mL for 10 years. Due to the high correlation between nadir and current CD4, only one measure was included in the analysis according to the lowest Akaike information criterion(AIC) for both NHL and HL. Current and AUC of HIV-VL were not strongly correlated and therefore both were included in the same model.

Incidence rates of NHL and HL were calculated by calendar year of follow-up. Separate Cox regression models were used to identify factors associated with NHL and HL, focussing on current and nadir CD4, and current and AUC of HIV-VL. Models were adjusted for baseline factors (gender, HIV transmission-mode, ethnicity, calendar year of baseline) and current factors (age, body mass index [BMI], smoking status, hepatitis-B and C coinfection, prior AIDS-defining cancer [excluding NHL], AIDS-defining diagnosis [excluding cancer], hypertension [diastolic blood pressure >90 mmHg, systolic blood pressure > 140 mmHg, receiving antihypertensive medication or ACE inhibitors], cardiovascular disease, diabetes [as validated event or use of anti-diabetic medication], and cumulative time on cART [defined as being on ≥1 protease inhibitor or non-nucleoside reverse transcriptase inhibitor). Immunological and virological risk factors for NHL subtypes were also investigated in those with NHL subtype reported(33.6%).

The Wei, Lin, and Weissfeld method, based on marginal cox models[45] was used to identify factors that differently affected NHL and HL risk. The models were used to jointly calculate and compare adjusted hazard ratios(aHR) for NHL and HL for all current and historical measures of HIV-VL and CD4-cell count(separately), adjusting for variables listed previously. In order to fit a more parsimonious model, variables not associated with either NHL or HL incidence were assumed to have a similar association for both NHL and HL. The remaining variables were allowed to vary according to outcome. The marginal cox models differed to those used to identify independent risk factors with minor differences in adjustments(fixed and outcome specific variables) which give slightly different estimates. The ratio of the adjusted HRs(RHR) was used to identify factors with different risk profiles for NHL and HL, which we have termed "differential factors". Variables for which the 95% confidence-interval(95%CI) for the RHR cross 1 indicates a similar association between the risk factor and both HL and NHL.

All statistical tests were two sided.All statistical analyses were performed using SAS 9.4 (Statistical Analysis Software, Cary NC, USA).

Results

There were 41,420 people included in the analysis contributing 337,020 PYFU with a median follow-up of 9.2 (Interquartile range [IQR]: 6.3,1.1) years per person. A total of 392 people developed NHL (incidence rate [IR] 1.17/1000 PYFU, 95%CI: 1.06,1.30) and 149 developed HL (IR 0.44/1000 PYFU 95%CI: 0.38,0.52) during follow-up.

Baseline characteristics

Baseline characteristics of the study population, as well as those who developed NHL or HL during follow-up are shown in table 1. Overall, 17.4% were aged ≥ 50 years at baseline, 72.9% were of male gender and 43.8% acquired their HIV through sex between men. 49.9% were of white ethnicity and 40.9% had unknown ethnicity. Just over half were on cART(51.8%) at baseline, with a median cART duration of 1.1(IQR: 0.0,4.9) years. The median CD4-cell count was 431(IQR: 280,620) cells/mm^3 and the median HIV-VL was 260(IQR: <50, 20,400) copies/mL.

Crude Incidence rates over time

The crude incidence of NHL and HL by calendar year is shown in figure 1. The crude incidence of NHL declined by 13.3% per year (95%CI: 10.3,16.2%) from an incidence rate of 1.96(95%CI: 1.48,2.58) events/1000 PYFU in 2004 to 0.32(95%CI: 0.17,0.62) in 2014/15. In 2014/15, the incidence of NHL was similar to HL (HL: 0.36 95%CI: 0.19,0.66), however HL incidence was stable over time (change per year: -2.7%, 95%CI: -7.7,2.6%).

Independent risk factors for NHL and HL

Current and nadir CD4-cell counts were considered for inclusion in the main analysis. Both associated with NHL in adjusted analyses, whereas only current CD4 was associated with HL. A 2-fold higher (i.e. doubling of) current CD4 count was associated with a 19% reduced risk of NHL(95%CI: 15, 23%) and a 14% reduced risk of HL(95%CI: 7,21%), whereas a 2-fold higher nadir CD4 count was associated with a 12% reduced risk of NHL(95%CI: 7,17%) but not HL (aHR: 0.96 95%CI: 0.87,1.05). However, current CD4 was the strongest immune marker for both NHL and HL, and so was the only immunological marker included in multivariate models (provided the best statistical fit, measured as by the AIC).

Independent risk factors of NHL and HL from a multivariate model are shown in table 2. For example, a higher rate of NHL was strongly associated with lower current CD4-cell count category (CD4 <100 VS > 599 cells/mm^3 aHR 8.08 95%CI: 5.63, 11.61), higher current HIV-VL (HIV-VL> 1000 VS <50 copies/mL aHR: 1.97 95%CI: 1.50,2.59) and higher AUC of HIV-VL (highest vs lowest quintile aHR: 2.91 95%CI: 1.92,4.41). Higher rates of NHL were also observed in older people and males. A higher rate of HL was also associated with lower current CD4-cell count category, however no association was found for current or AUC of HIV-VL. Current smokers had almost a 2-fold higher rate of HL compared to non-smokers. No association was found for HCV or HBV status with either NHL or HL. Rates of both NHL and HL reduced with longer time on cART.

Differences in risk factors for NHL and HL

Factors that were associated with either NHL or HL in table 2 were jointly modelled to identify factors that were differently associated with NHL and HL (differential factors). Current HIV-VL was a differential factor, as demonstrated by the increase in ratio of the aHRs with higher HIV-VL category (figure 2). For example, the RHRs were 2.52(95%CI: 1.32, 4.81) and 4.57(95%CI: 2.20, 9.50) in those with current HIV-VL 50 – 1000 copies/mL and >1000 copies/mL relative to <50 copies/mL respectively, indicating a progressively stronger association with NHL than for HL with higher current HIV-VL. A similar result was found for the AUC of HIV-VL, which was also a differential factor. Current CD4 was not a differential factor as the 95%CI of the ratio of the aHRs for each CD4-cell count category relative to CD4 200-299 cells/mm^3 contained 1, indicating no evidence that lower CD4-cell count was differently associated with NHL and HL. Age was a differential risk factor as the ratio of the aHRs of people aged >60 relative to those aged 30-39 was more than 3(95%CI: 1.43,6.55), indicating a relative increase in rates of NHL than for HL for people in this older age group. Finally, smoking status was a differential factor, as the ratio of the aHRs for current smokers relative to never smokers was 0.49

(95%CI: 0.28,0.83), indicating a significantly higher relative increase in risk for HL in this group. No other factors investigated were differential factors.

NHL subtypes

Of the 392 NHL, 42 were BL(10.7%), 25 were PBCNSL (6.4%), 65 were DLBCL(16.6%), and 260 were unknown(66.3%). People with known and unknown NHL subtype had similar characteristics at diagnosis. Slightly more people with known subtype reported being on protease inhibitors (known subtype: 46.2% vs unknown subtype: 38.6%, P=0.05), and slightly less had a previous cancer diagnosis (3.1% vs 10.6%, P=0.02). Associations between immunological and virological risk factors for each subtype (in those with a subtype recorded) are shown in table 3. For example, lower risk of PBCNSL was associated with higher current and nadir CD4-cell count (aHR for 2-fold higher: 0.59 95%CI: 0.51, 0.70 and 0.68 95%CI: 0.58,0.80 respectively) and lower AUC of HIV-VL (aHR for 10-fold higher: 2.21 95%CI: 1.22,4.00), but not current HIV-VL. Lower DLBCL NHL risk was associated with higher current and nadir CD4 and lower current and AUC of HIV-VL. Lower BL risk was associated with higher current and AUC of HIV-VL but not immunological markers. Nadir CD4-cell count was not associated with PBCNSL, DLBCL lymphoma or BL after additional adjustment for current CD4-cell count.

Discussion

This study is the first to attempt to identify differences in the underlying pathology of NHL and HL in PLWH by directly comparing the immunological and virological risk factors for each and identifying differences. Higher current and cumulative exposure to HIV-VL were stronger risk factors for NHL than HL. Although current CD4 was a strong predictor of both, there was no evidence of a different association between with NHL and HL. In this study, the crude incidence of NHL declined steadily over time while HL incidence remained stable. The trends over time are not surprising and have been reported before [1-10], however, our study is one of the first to show that incidence of NHL and HL is similar in PLWH in recent years. This highlights a shift away from the cancers with a strong

link with immune deficiency and the need for a better understanding of how generalised immune dysfunction (beyond low CD4-cell counts) can facilitate lymphoma development.

The risk of NHL and HL differed according to current and accumulated HIV-VL, but not current CD4-cell count. Our results indicate a similar pathological requirement of immunodeficiency for both NHL and HL development, however, an important distinction is the involvement of HIV-VL in NHL but not HL development. This indicates that HIV-infection may contribute to lymphomagenesis of NHL through additional immune dysfunction not captured by supressed CD4 [46], possibly though reduced immune surveillance for proteins expressed by cells infected with latent EBV, immune activation, and/or CD8-dysfunction leading to depleted response from EBV-specific CD8 cytotoxic cells [14-16, 19, 47, 48]. Some studies have found that levels of circulating free light chains have predictive value of NHL in PLWH, which supports the involvement of immune activation [49, 50]. In addition, the ratio and percentage of CD8-cells has been shown to be predictive of HL [30] and may also be predictive of EBV-associated NHL [19, 51]. Alternatively, HIV may play a more direct role in lymphomagenesis [46, 52], with HIV-derived p17 secreted within lymphoid tissues, possibly promoting lymphoma development by inducing changes to the microenvironment[52]. Furthermore, the CD4-independent effect of HIV-VL was significant and consistent across the known sub-types studied. This was surprising in the case of BL, which has little association with CD4[53].

Smoking status had a different association with HL and NHL, where risk of HL was elevated in current smokers. Research in the general population has indicated that smoking may play an etiological role in HL, particularly EBV-positive [54, 55]. Almost all HL in PLWH is EBV-related, therefore, smoking presents as one of the few modifiable risk factors for this cancer and emphasises the importance of smoking cessation strategies in PLWH. Age had a different association with NHL and

HL, where people aged over 50 years had a higher relative increase in the rate of NHL than for HL, which is consistent with previous studies[14, 20, 30, 32, 33, 56]. This may reflect increases in immune activation and inflammation associated with aging and further supports the hypothesis that immune dysfunction beyond low CD4 is involved in the pathology[57]. The lack of association between either HCV or HBV status and NHL or HL is in contrast to results from the COHERE study, which found a significant association between both HCV and HBV and NHL risk in treated patients[58], and two meta analyses[59, 60]. Although other studies have failed to show a convincing association [20, 61, 62].

This study has many advantages. The D:A:D study contains follow up on over 40,000 people and allows for the analysis of a relatively large number of prospectively collected and validated NHL and HL events. Furthermore, the D:A:D data contains highly detailed demographic, HIV and health related factors collected over a long follow-up period. However, the limitations need to be considered. There were several known risk factors for NHL and HL that are not collected in D:A:D, for example, autoimmune disorders and family history. Furthermore, NHL subtype is only reported by a subset of cohorts in D:A:D, and as a result it was missing on 66% of people, however, the characteristics of those with and without subtype information were similar. D:A:D does not collect additional markers of immune suppression or dysfunction, or EBV-viral-load. And finally, this is an observational study and it is possible that confounding due to unmeasured or unknown factors remain and the causality of the associations presented here cannot be determined. It should also be kept in mind that NHL is treated as a single entity the main analysis, however, there is considerable heterogeneity in aetiology between NHL subtypes [63]. Several studies from the COHERE collaboration have been referenced, however, these studies are in naïve patients, of which the proportion in D:A:D is very low resulting in minimal overlap between the two studies.

In conclusion, whereas CD4 depletion similarly increased risk of both types of lymphomas, current and accumulated HIV-VL was more predictive of NHL than HL. This suggests that NHL development is related to both CD4-cell depletion and added immune dysfunction derived from ongoing HIV replication. This latter factor was not associated with HL risk. These findings stress the importance of early HIV diagnosis and treatment, and of ensuring sustained viral suppression.

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Acknowledgements

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Tables

Table 1 Baseline characteristics of D:A:D participants included in the analysis

Factors	All persons (N=41,420)	Persons who developed NHL (n=392)	Persons who developed HL (N=149)
	N (%)	**N (%)**	**N (%)**
Age (years)			
<30	5,922 (14.3)	22 (5.6)	16 (10.7)
30 - 39	14,833 (35.8)	118 (30.1)	44 (29.5)
40 - 49	13,449 (32.5)	142 (36.2)	56 (37.6)
50 - 59	5,170 (12.5)	71 (18.1)	23 (15.4)
>=60	2,046 (4.9)	39 (9.9)	10 (6.7)
Gender			
Male	30,214 (72.9)	337 (86.0)	126 (84.6)
Female	11,206 (27.1)	55 (14.0)	23 (15.4)
HIV-transmission mode			
Homosexual	18,124 (43.8)	200 (51.0)	87 (58.4)
IDU	5,926 (14.3)	53 (13.5)	15 (10.1)
Heterosexual	14,800 (35.7)	106 (27.0)	39 (26.2)
Other/Unknown	2,570 (6.2)	33 (8.4)	8 (5.4)
Race			
White	20,658 (49.9)	181 (46.2)	70 (47.0)
Black	2,963 (7.2)	10 (2.6)	6 (4.0)
Other	840 (2.0)	7 (1.8)	3 (2.0)
Unknown	16,959 (40.9)	194 (49.5)	70 (47.0)
smoking status			
Current	16,859 (40.7)	155 (39.5)	70 (47.0)
Ex	7,332 (17.7)	65 (16.6)	31 (20.8)
Never	11,364 (27.4)	98 (25.0)	28 (18.8)
Unknown	5,865 (14.2)	74 (18.9)	20 (13.4)
BMI group			
<18	1,377 (3.3)	13 (3.3)	4 (2.7)
18 - 26	27,709 (66.9)	255 (65.1)	102 (68.5)
27 - 30	5,360 (12.9)	59 (15.1)	15 (10.1)
>30	1,833 (4.4)	16 (4.1)	10 (6.7)
Unknown	5,141 (12.4)	49 (12.5)	18 (12.1)
Previous AIDS defining event	8,801 (21.2)	85 (21.7)	31 (20.8)
Previous AIDS cancer	1,419 (3.4)	26 (6.6)	8 (5.4)
On cART	21,436 (51.8)	161 (41.1)	70 (47.0)
HBV			
Negative	29,355 (70.9)	271 (69.1)	119 (79.9)
Positive/prior	7831 (18.9)	86 (21.9)	19 (12.8)
Unknown	4,234 (10.2)	35 (8.9)	11 (7.4)

HCV					
Negative		28,168 (68.0)		261 (66.6)		117 (78.5)
Positive		7,947 (19.2)		76 (19.4)		19 (12.8)
Unknown		5,305 (12.8)		55 (14.0)		13 (8.7)
Prior CVD		857 (2.1)		5 (1.3)		6 (4.0)
Diabetes*		1,055 (2.5)		12 (3.1)		2 (1.3)
Hypertension†		6,121 (14.8)		68 (17.3)		30 (20.1)
Baseline year					
2004 - 2005		29,715 (71.7)		290 (74.0)		99 (66.4)
2006 - 2007		6,334 (15.3)		65 (16.6)		29 (19.5)
2008 - 2009		5,327 (12.9)		35 (8.9)		21 (14.1)
2010 - 2011		29 (0.1)		1 (0.3)		0 (0.0)
2012 - 2015		15 (0.0)		1 (0.3)		0 (0.0)
HIV-VL ≤ 500 copies/mL		21,546 (52.0)		113 (28.8)		65 (43.6)
Age (years)	41420	40 (34,47)	392	43 (38,51)	149	42 (35,49)
CD4 count (cells/mm³)	41420	431 (280,620)	392	342 (189,534)	149	409 (276,575)
Nadir CD4 count (cells/mm3)	41420	248 (116,403)	392	197 (77,368)	149	259 (130,409)
Time CD4 <200 cells/mm³ (years)	37962	0.0 (0.0,0.4)	353	0.0 (0.0,0.6)	137	0.0 (0.0,0.2)
HIV-VL(cps/mL)	39883	260 (<50,20400)	378	13419 (80,90951)	146	2615 (<50,34000)
Log10 AUC HIV-VL (copies/mL-year)	36840	4.2 (3.0,4.9)	345	4.5 (3.3,5.2)	135	4.3 (2.4,5.0)

NHL: non-Hodgkin lymphoma, HL: Hodgkin lymphoma, BMI: Body mass index, cART: combination antiretroviral treatment, HBV: Hepatitis B, HCV: Hepatitis C, CVD: Cardiovascular disease, HIV-VL: HIV viral load, AUC: area under the curve.

*Diabetes defined as a validated event reported on a case-report form or use of anti-diabetic medication

†Hypertension defined as diastolic blood pressure >90 mm Hg or systolic blood pressure > 140 mm Hg or receiving antihypertensive medication.

Table 2 adjusted Hazard ratios (aHR) and 95% confidence intervals for factors associated with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)

Factors	NHL aHR[†] (95%CI)	P	HL aHR[†] (95%CI)	P
Current CD4 cell count (cells/mm^3) [*]				
<100	8.08 (5.63,11.61)	<.001	4.58 (2.22,9.45)	<.001
100 – 199	3.67 (2.49,5.39)	<.001	6.36 (3.62,11.20)	<.001
200 – 299	2.96 (2.12,4.13)	<.001	3.37 (1.99,5.69)	<.001
300 – 399	2.43 (1.78,3.33)	<.001	1.72 (0.99,2.97)	0.053
400 – 499	1.62 (1.15,2.29)	0.006	2.59 (1.64,4.08)	<.001
>=500	reference		reference	
Current HIV-VL[*]				
<= 50	reference		reference	
51 - 1,000	1.35 (1.00,1.83)	0.051	1.08 (0.69,1.69)	0.724
>1,000	1.97 (1.50,2.59)	<.001	0.67 (0.39,1.17)	0.158
Unknown	0.65 (0.15,2.81)	0.563	3.73 (0.22,62.35)	0.36
AUC of HIV-VL (Quintiles) [*]				
1 - Lowest	reference		reference	
2	1.10 (0.69,1.76)	0.685	0.65 (0.37,1.12)	0.12
3	1.47 (0.94,2.30)	0.088	0.79 (0.47,1.34)	0.379
4	1.81 (1.17,2.80)	0.007	0.65 (0.38,1.14)	0.133
5 - Highest	2.91 (1.92,4.41)	<.001	1.01 (0.61,1.68)	0.965
unknown	1.63 (0.93,2.85)	0.088	0.14 (0.02,1.04)	0.055
age (years) [*]				
<30	0.49 (0.27,0.89)	0.019	0.90 (0.41,1.95)	0.781
30 – 39	reference		reference	
40 – 49	1.53 (1.16,2.01)	0.003	1.25 (0.81,1.93)	0.322
50 – 59	2.02 (1.47,2.78)	<.001	1.37 (0.82,2.28)	0.224
≥60	3.15 (2.17,4.58)	<.001	1.06 (0.53,2.15)	0.865
Female gender	0.55 (0.40,0.76)	<.001	0.73 (0.43,1.25)	0.253
Race				
White	reference		reference	
Other	0.65 (0.39,1.10)	0.109	0.98 (0.47,2.04)	0.948
Unknown	0.99 (0.80,1.24)	0.949	0.95 (0.66,1.35)	0.758
HIV transmission mode				
Homosexual	reference		reference	
IDU	0.91 (0.59,1.40)	0.677	0.72 (0.32,1.59)	0.413
Heterosexual	0.91 (0.70,1.20)	0.523	0.67 (0.42,1.06)	0.084
Unknown	1.35 (0.92,1.98)	0.125	0.78 (0.37,1.66)	0.525
smoking[*]				
Current	0.91 (0.69,1.19)	0.48	1.97 (1.23,3.16)	0.005
Ex	0.89 (0.66,1.21)	0.461	1.54 (0.92,2.58)	0.098
Never	reference		reference	
Unknown	1.35 (0.96,1.89)	0.08	1.25 (0.63,2.47)	0.523
on cART[*] **(Years)**				
Never	1.41 (0.95,2.10)	0.086	1.25 (0.60,2.60)	0.557

0.1 – 2	1.71 (1.23,2.38)	0.001	1.63 (0.97,2.74)	0.064
2.1 – 4	reference		reference	
>4	0.66 (0.47,0.91)	0.01	0.75 (0.45,1.23)	0.256
Previous ADM diagnosis[*]	1.49 (1.02,2.19)	0.041	1.10 (0.55,2.18)	0.792
Previous AIDS diagnosis (excl. ADM)[*]	1.01 (0.79,1.28)	0.967	0.99 (0.67,1.46)	0.956
HBV[*]				
Positive/prior	1.10 (0.85,1.41)	0.479	0.75 (0.47,1.20)	0.232
Negative	reference		reference	
Unknown	0.97 (0.62,1.53)	0.906	0.94 (0.40,2.25)	0.897
HCV[*]				
Positive/prior	1.13 (0.81,1.59)	0.462	0.66 (0.35,1.24)	0.193
Negative	reference		reference	
Unknown	1.20 (0.78,1.84)	0.416	0.33 (0.10,1.10)	0.07
Baseline year				
2004	Reference		Reference	
2005	1.54 (1.1,2.16)	0.012	1.04 (0.53,2.03)	0.921
2006	1.2 (0.85,1.69)	0.301	1.37 (0.78,2.41)	0.279
2007	1.01 (0.65,1.58)	0.957	1.85 (1.02,3.38)	0.044
2008/9	0.92 (0.63,1.33)	0.641	1.69 (1.01,2.83)	0.046

HIV-VL: HIV viral load, AUC: area under the curve, cART: combination antiretroviral treatment, ADM: AIDS defining malignancy, HBV: Hepatitis B, HCV: Hepatitis C,

[*] Time updated variables

[†] Models were adjusted for all other covariates in the table and further adjusted for body mass index (BMI), prior cardiovascular disease (CVD) diagnosis, hypertension, diabetes.

Table 3 adjusted Hazard ratios (HR) and 95% confidence intervals for factors associated with NHL subtypes

	PBCNS (N=25)		DLBCL (N=65)		Burkitt (N=42)	
	aHR* (95%CI)	P	aHR* (95%CI)	P	aHR* (95%CI)	P
$\log_2$ current CD4[†]	0.59 (0.51,0.70)	<0.01	0.75 (0.67,0.85)	<0.01	0.88 (0.74,1.05)	0.15
$\log_2$ nadir CD4[†]	0.68 (0.58,0.80)	<0.01	0.87 (0.77,0.98)	0.02	0.97 (0.82,1.14)	0.68
$\log_{10}$ current HIV-VL[‡]	1.11 (0.80,1.54)	0.54	1.32 (1.08,1.61)	0.01	1.38 (1.08,1.76)	0.01
$\log_{10}$ of AUC of HIV-VL[‡]	2.21 (1.22,4.00)	<0.01	1.60 (1.16,2.21)	<0.01	2.14 (1.35,3.38)	<0.01

PBCNS: Primary brain and central nervous system, DLBCL: Diffuse large B cell lymphoma, HIV-VL: HIV viral load, AUC: area under the curve.

*Models were adjusted age, gender, mode of HIV acquisition, race, current smoking status, cumulative time on cART

[†]Models were additionally adjusted for log10 current HIV-VL and Log10 of area under the curve (AUC) of HIV-VL in addition to variables listed in *

[‡]Models were additionally adjusted for log2 current CD4 in addition to variables listed in *

Figure legends

Figure 1 Crude incidence of NHL and HL by calendar time.

Figure 2 Adjusted ratio of the hazard ratios of NHL (NHL HR) and HL (HL HR) for each considered risk factor, and the ratio of the HR (RHR).

All models were adjusted for age, gender, ethnicity, mode of HIV acquisition, smoking status, body mass index, baseline year, cumulative time on cART, HCV and HBV status, prior AIDS defining malignancies (ADM), prior AIDS events (excluding ADM), prior CVD diagnosis, hypertension, diabetes, current CD4, current HIV-Viral load, AUC of HIV-viral load. Risk factors for which the 95% CI for the Ratio of the hazard ratios of NHL to HL does not cross 1 (and a corresponding p-value<0.05) indicate that there is evidence of a different association of the risk factor with HL and NHL.