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Risk Factors for Hodgkin (HL) and Non-Hodgkin Lymphoma (NHL) in Europe

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BACKGROUND

Non-Hodgkin (NHL) and Hodgkin lymphomas (HL) are common in HIV+ people[1]. Previous research has described significant declines in NHL[2] but not HL[3] after cART, however data on individual risk factors is limited.

OBJECTIVE

Determine the role of demographic, immunological and HIV-related factors on NHL and HL incidence across Europe.

METHODS

EuroSIDA participants with follow-up after 1/1/2001 and without a history of NHL or HL were included. Crude incidence of NHL and HL were calculated and stratified by patient characteristics. Separate Poisson regression models were used to identify risk factors for NHL and HL. Both current and historical measures of HIV Viral-load (HIV-VL) (% of time with HIV-VL <400 copies/ml) and immunosuppression (Nadir CD4, % of time with CD4<200 cells/mm³) were considered.

RESULTS

Baseline characteristics (Table 1)

- A total of 14,820 people were included contributing 97,220 person years of follow-up (PYFU), of which 14,679 (95,804 PYFU) were included in analyses for NHL and 14,785 (96,824PYFU) were included for analyses of HL. **Table 1.**
- The cohort was mainly male (73%), white (87%) with a median age of 39 years at baseline. At baseline, 80% had ever used cART, 59% had a CD4 > 350 cells/mm³ and 54% had a HIV-VL <400 copies/mL.**Table 1.**

Incidence of NHL and HL (Figure 1)

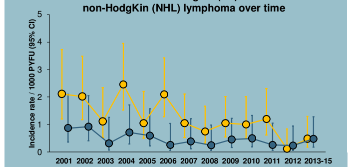
- In total, 117 developed NHL (incidence rate 1.2/1000 PYFU, 95%CI 1.0-1.5) and 45 developed HL (0.5/1000 PYFU, 95%CI 0.3–0.6). Incidence of NHL and HL declined over time. NHL incidence declined by 12 (95%CI: 7–16)% from 2.1 (1.2,3.7) /1000 PYFU in 2001 to 0.5 (0.2,1.3) /1000 PYFU in 2013/14/15 and incidence of HL declined by 9 (1–15)% per year from 0.9 (0.4,2.1)/1000 PYFU to 0.5 (0.2,1.3) /1000 PYFU in unadjusted analyses. **Figure 1.**

Table 1 **Characteristics at baseline[1]**

Factor	Total N (%)	Non-Hodgkin lymphoma N (%)	Hodgkin lymphoma N (%)
Total	14,820 (100)	117 (100)	45 (100)
Median age (years, IQR)	39.1 (33.1,46.3)	41.8 (37.7,50.5)	40.4 (35.0,44.5)
Median Year of baseline (IQR)	2003 (2001,2008)	2001 (2001,2004)	2001 (2001,2003)
Male	10,834 (73.1)	102 (87.2)	36 (80.0)
White	12,954 (87.4)	103 (88.0)	37 (82.2)
HIV transmission mode: Homosexual	6,016 (40.6)	62 (53.0)	24 (53.3)
Prior AIDS (Not NHL)	4,096 (27.6)	35 (29.9)	15 (33.3)
Prior non-AIDS (Not HL)	460 (3.1)	5 (4.3)	3 (6.7)
History of cART use	11,828 (79.8)	89 (76.1)	39 (86.7)
CD4[2]> 350 cells/mm³	8,803 (59.4)	53 (45.3)	26 (54.2)
HIV-Viral Load[2] <400 copies/mL	7,949 (53.6)	44 (35.5)	19 (39.6)

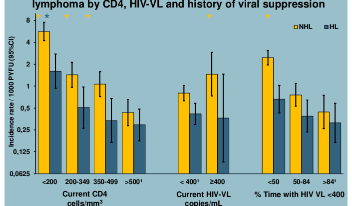
[1]Baseline was the latest of 1 January 2001 or recruitment into EuroSIDA, [2] within 12 months prior to baseline

Figure 1 **Incidence of Hodgkin (HL) and non-HodgKin (NHL) lymphoma over time**



N events	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013-15
NHL	12	13	7	17	7	16	8	6	9	8	9	1	4
HL	5	6	2	5	4	2	3	2	4	4	2	2	4

Figure 2 **Incidence of Hodgkin lymphomas (HL) and non-Hodgkin (NHL) lymphoma by CD4, HIV-VL and history of viral suppression**



*HL P<0.05, *NHL P<0.05, [1]Reference category

Incidence of NHL was higher in those with longer time with CD4<200 cells/mm³, but was not associated with nadir CD4. HL incidence was not associated with either % of time with CD4<200 cells/mm³ or nadir CD4.

Incidence of NHL and HL Continued (Figures 2 and 3)

- Of the 117 NHL, 48 (41%) were immunoblastic, 14 (12%) were Burkitt, 5 (4%) were primary brain, and 46 (43%) were of unknown or other subtype.
- In unadjusted analysis, incidence of NHL increased with lower current CD4 category, HIV-VL≥400 copies/mL, and was higher in those who spent less than half of follow – up with HIV-VL <400 copies/mL. **Figure 2.** Those with a prior AIDS defining malignancy (ADM, excluding NHL) also had higher incidence. **Figure 3.**
- Incidence of HL was higher in those with lower current CD4 category, however this was less marked than for NHL. **Figure 2.**Incidence of HL was not found to be associated with current HIV-VL, % follow-up spent with HIV-VL <400 copies/mL or a prior ADM (excluding NHL). **Figure 2 and Figure 3.**
- Neither NHL or HL incidence was associated with age, cART use, or transmission mode.

Adjusted analysis (Figure 4)

After adjustment for factors displayed and listed in the footnote of **Figure 4**:

- Historical HIV-related variables, such as a prior diagnosis of ADM or less time with controlled HIV RNA, were more strongly associated with NHL incidence than current HIV-VL. **Figure 4.**
- The association between lower CD4 cell count and increased incidence remained for both HL and NHL, however no time trend in either NHL or HL incidence was evident after adjustment. **Figure 4.**
- Older age was associated with higher NHL but not HL incidence. **Figure 4.**

CONCLUSION

NHL development was associated with current immunodeficiency and history of uncontrolled viral replication, suggesting that exposure to uncontrolled viral replication may play a part in NHL development in addition to current immunodeficiency. Conversely, HL incidence was elevated in those with current severe immunodeficiency (CD4<200 cells/mm³), but cumulative exposure to uncontrolled HIV replication was not a risk factor.

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2. Clifford, G. M., et al. (2005). "Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy." J Natl Cancer Inst 97(6): 425-432.
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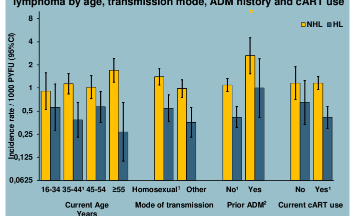
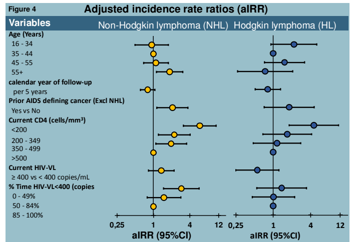
Figure 3 **Incidence of Hodgkin lymphomas (HL) and non-Hodgkin (NHL) lymphoma by age, transmission mode, ADM history and cART use**



*HL P<0.05, *NHL P<0.05, [1]Reference category, [2] AIDS defining malignancy (excluding NHL)

Figure 4 **Adjusted incidence rate ratios (aIRR)**



Model for HL adjusted additionally for gender, region of Europe, prior AIDS defining event (excluding cancer), prior non-AIDS defining event (excluding cancer)prior non-AIDS defining cancer (excluding HL), current treatment (None/ART vs Cart), Anaemia (Males <14, females <12). **Model for NHL** adjusted additionally for gender, region of Europe, smoking status (Never, Ever, Missing), prior AIDS defining event (excluding cancer), prior non-AIDS defining event (excluding cancer) prior non-AIDS defining cancer (excluding HL), current treatment (None/ART vs Cart), Anaemia (Males <14, females <12). Due to small numbers and high correlations, different measures of CD4 were considered separately in multivariate models. Current CD4 was the strongest predictor of both NHL and HL and is presented here.

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