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Collaboration of Observational HIV Epidemiological Research Europe

Coordination: Copenhagen HIV Programme (CHIP) & Institut de Santé Publique,d'Epidémiologie et de Développement (ISPED)

Abstract Number 720

Chronic Hepatitis B and C Infection and Risk for Non-Hodgkin Lymphoma in HIV Infected Patients

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Background:

- There is growing evidence that chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is associated with an increased risk of non-Hodgkin lymphoma (NHL) in the HIV-negative population.
- NHL continues to be one of the most common AIDS defining events even in the presence of antiretroviral therapy (ART). It is unclear whether chronic infection with HBV and HCV promotes NHL in HIV infection.

Methods:

- Using data from COHERE, a pan-European cohort collaboration, ART-naïve individuals with no prior NHL diagnoses were followed from the latest of 1st January 2000 or entry into study cohort until NHL diagnosis, death, loss to follow up or 1st January 2013.
- Time periods during which patients were ART-naïve and ART-experienced were analysed separately due to time-dependent confounding.
- The association between time-updated chronic HBV (2 positive HBsAg measurements >6 months apart) and HCV (detectable HCV RNA or positive HCV Ab if HCV RNA unavailable) infection and NHL was assessed using Cox models with adjustment for age, gender, IV-drug use, HIV RNA, CD4 cell count at baseline, study cohort, and time up-dated CD4 cell count and HIV viral load.
- Inverse probability of censoring weights were used to adjust for informative censoring due to death, starting ART or loss to follow up

Results:

- We included 52,479 ART-naïve patients, 1339 (3.3%) patients with HBV and 7506 (18.7%) patients with HCV; median follow up was 13 months while ART-naïve, of whom 40,219 went on to start ART (1255 (3.1%) with HBV and 5481 (13.6%) with HCV); median additional follow up was 50 months.
- Of patients with chronic HBV, 89% received an HBV-active ART; of patients with HCV, 15% were treated for HCV.
- During 306,306 person-years of follow up 252 ART-naïve and 310 ART-treated individuals developed NHL. Of those, 106 (19%) were Burkitt's lymphoma, 60 (11%) diffuse large B-cell lymphoma, 29 (5%) primary brain lymphoma, and 367 (65%) were unspecified NHL types. In total 2070 patients died, of which 174 (8.4%) died following NHL, and the rest from other causes.
- Incidence rates of NHL in the entire population of ART naïve subjects were 219 per 100,000 person-years and 321, 154 and 153 per 100,000 in patients with chronic HBV, HCV and dual HBV and HCV infection.
- The respective figures for ART treated patients were 246 per 100,000 person years in the entire population and 204, 300 and 168 per 100,000 persons years in patients with chronic HBV, HCV and dual HBV and HCV infection.
- In ART-naïve patients, no association was found between chronic HBV (HR=1.29; 95% CI 0.67, 2.48) and HCV infection (HR=0.66; 0.40, 1.10) with NHL (models using censoring weights)
- In ART-treated patients, those with chronic HBV (HR=1.64; 1.01, 2.64) and HCV (HR=1.59; 1.11, 2.17) were at increased risk of NHL (models using censoring weights).
- NHL occurred at low CD4 counts, particularly in HBV+ patients.

Conclusion:

- Chronic infection with HBV and HCV is associated with an increased risk of NHL in HIV-infected patients on ART.
- The higher risk for NHL represents an additional reason for improving prevention, diagnosis and management of viral hepatitis infections and early access to interferon free agents for HCV treatment in particular for HIV-infected patients with poor immune recovery.

Figure 1 : Patient flow for the selection of the study population

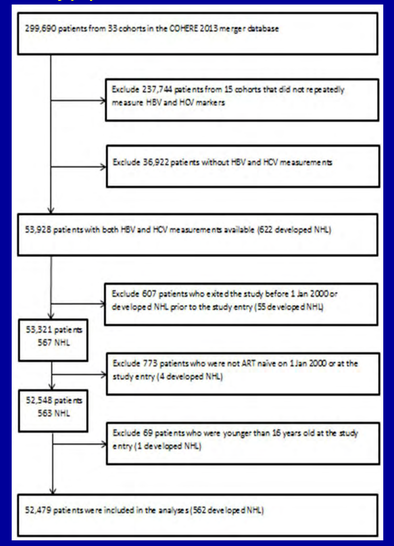

Table 1: Patient characteristics at baseline and during follow up

Characteristics	Patients with chronic HBV	Patients with HCV	Total
At time of study entry:	**n=1339**	**n=7506**	**n=52,479**
Female gender, %	19	24	22
Caucasian ethnicity, %	27	40	37
HIV transmission via IDU, %	12	56	10
Median age, years	36	36	35
Median HIV RNA, $\log_{10}$ copies/ml	4.7	4.5	4.6
Median CD4 cell count, cells/mm^3	320	380	380
At time of starting ART:	**n=1255**	**n=5481**	**n=40,219**
Median HIV RNA, $\log_{10}$ copies/ml	4.9	4.8	4.9
Median CD4 cell count, cells/mm^3	240	230	247
At time of NHL diagnosis (ART-naïve patients):	**n=10**	**n=36**	**n=252**
Median HIV RNA, $\log_{10}$ copies/ml	5.1	4.6	4.8
Median CD4 cell count, cells/mm^3	115	246	206
At time of NHL diagnosis (ART-treated patients):	**n=18**	**n=54**	**n=310**
Median HIV RNA, $\log_{10}$ copies/ml	2.8	2.5	1.8
Median CD4 cell count, cells/mm^3	136	231	236

Table 2: Adjusted hazard ratios (HR) for HBV in ART-naïve patients

	Adjusted HR (95% CI)		
Outcome	Cox model stratified by cohort NHL	Cox model with censoring weights NHL	Cox model with censoring weights NHL or death
Chronic HBV infection	0.98 (0.44, 2.22)	1.29 (0.67, 2.48)	1.40 (0.89, 2.36)
Female gender	0.64 (0.43, 0.94)	0.68 (0.47, 0.97)	1.11 (0.90, 1.36)
Mode of transmission via IDU	0.67 (0.42, 1.06)	0.70 (0.45, 1.11)	2.47 (2.03, 3.01)
Age per 10 years increase	1.43 (1.25, 1.63)	1.42 (1.26, 1.60)	1.67 (1.53, 1.81)
Baseline HIV RNA per 1 $\log_{10}$ copies/ml increase	1.31 (1.05, 1.64)	1.35 (1.06, 1.74)	1.47 (1.26, 1.73)
Baseline CD4 cell count per 100 cells/mm^3 increase	1.12 (1.03, 1.22)	1.08 (1.04, 1.13)	1.10 (1.06, 1.14)
Time-updated HIV RNA per 1 $\log_{10}$ copies/ml increase	0.81 (0.66, 1.00)	0.76 (0.59, 0.96)	0.77 (0.66, 0.90)
Time-updated CD4 cell count per 100 cells/mm^3 increase	0.58 (0.52, 0.65)	0.60 (0.55, 0.66)	0.71 (0.66, 0.76)

Table 3: Adjusted hazard ratios (HR) for HBV in ART-treated patients

	Adjusted HR (95% CI)		
Outcome	Cox model stratified by cohort NHL	Cox model with censoring weights NHL	Cox model with censoring weights NHL or death
Chronic HBV infection	1.64 (1.02, 2.64)	1.64 (1.01, 2.64)	1.23 (0.87, 1.53)
Female gender	0.48 (0.34, 0.68)	0.50 (0.36, 0.72)	0.80 (0.71, 0.91)
Mode of transmission via IDU	0.86 (0.57, 1.32)	0.82 (0.54, 1.26)	2.39 (2.11, 2.70)
Age per 10 years increase	1.37 (1.24, 1.52)	1.38 (1.25, 1.52)	1.70 (1.62, 1.77)
Baseline HIV RNA per 1 $\log_{10}$ copies/ml increase	1.29 (1.11, 1.49)	1.32 (1.13, 1.56)	1.11 (1.04, 1.18)
Baseline CD4 cell count per 100 cells/mm^3 increase	1.17 (1.08, 1.27)	1.17 (1.08, 1.31)	1.13 (1.09, 1.17)
Time-updated HIV RNA per 1 $\log_{10}$ copies/ml increase	1.16 (1.05, 1.28)	1.08 (0.97, 1.21)	1.24 (1.19, 1.30)
Time-updated CD4 cell count per 100 cells/mm^3 increase	0.71 (0.65, 0.77)	0.71 (0.61, 0.82)	0.67 (0.63, 0.70)

Table 4: Adjusted hazard ratios (HR) for HCV in ART-naïve patients

	Adjusted HR (95% CI)		
Outcome	Cox model stratified by cohort NHL	Cox model with censoring weights NHL	Cox model with censoring weights NHL or death
HCV infection	0.87 (0.53, 1.44)	0.66 (0.40, 1.10)	1.30 (0.96, 1.77)
Female gender	0.64 (0.43, 0.94)	0.67 (0.47, 0.96)	1.11 (0.90, 1.36)
Mode of transmission via IDU	0.73 (0.41, 1.31)	0.96 (0.54, 1.71)	2.04 (1.47, 2.81)
Age per 10 years increase	1.43 (1.25, 1.62)	1.42 (1.26, 1.59)	1.67 (1.54, 1.81)
Baseline HIV RNA per 1 $\log_{10}$ copies/ml increase	1.31 (1.05, 1.64)	1.35 (1.05, 1.73)	1.48 (1.26, 1.74)
Baseline CD4 cell count per 100 cells/mm^3 increase	1.12 (1.03, 1.22)	1.09 (1.04, 1.13)	1.10 (1.06, 1.14)
Time-updated HIV RNA per 1 $\log_{10}$ copies/ml increase	0.81 (0.66, 1.00)	0.76 (0.59, 0.96)	0.77 (0.66, 0.90)
Time-updated CD4 cell count per 100 cells/mm^3 increase	0.58 (0.52, 0.65)	0.60 (0.55, 0.66)	0.71 (0.67, 0.76)

Table 5: Adjusted hazard ratios (HR) for HCV in ART-treated patients

	Adjusted HR (95% CI)		
Outcome	Cox model stratified by cohort NHL	Cox model with censoring weights NHL	Cox model with censoring weights NHL or death
HCV infection	1.61 (1.13, 2.30)	1.59 (1.11, 2.27)	1.36 (1.14, 1.61)
Female gender	0.48 (0.34, 0.68)	0.50 (0.35, 0.71)	0.80 (0.71, 0.91)
Mode of transmission via IDU	0.61 (0.37, 1.01)	0.58 (0.35, 0.96)	1.72 (1.46, 2.03)
Age per 10 years increase	1.37 (1.24, 1.52)	1.38 (1.25, 1.52)	1.70 (1.63, 1.77)
Baseline HIV RNA per 1 $\log_{10}$ copies/ml increase	1.29 (1.11, 1.50)	1.33 (1.13, 1.56)	1.11 (1.05, 1.18)
Baseline CD4 cell count per 100 cells/mm^3 increase	1.17 (1.08, 1.27)	0.78 (0.71, 0.85)	1.13 (1.08, 1.17)
Time-updated HIV RNA per 1 $\log_{10}$ copies/ml increase	1.16 (1.05, 1.27)	1.17 (1.05, 1.31)	1.24 (1.19, 1.30)
Time-updated CD4 cell count per 100 cells/mm^3 increase	0.71 (0.66, 0.77)	1.08 (0.97, 1.20)	0.67 (0.64, 0.71)

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Sources of funding: The COHERE study group has received unrestricted funding from: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, the Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. A list of the funders of the participating cohorts can be found on the Regional Coordinating Centre websites at http://www.cphiv.dk/COHERE/tabid/295/Default.aspx and http://etudes.isped.u-bordeaux2.fr/cohere . This project was funded by a grant from Krebsliga Switzerland.

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