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

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Abstract

Background: Non-Hodgkin lymphoma (NHL) continues to be the most common AIDS defining condition in the era of antiretroviral therapy. Whether chronic hepatitis B and C infection (HBV, HCV) promotes NHL in HIV infection is unclear.

Objective: To investigate whether chronic HBV and HCV is associated with increased incidence of NHL in HIV infection.

Design: Cohort study.

Setting: 18 of 33 cohorts from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE).

Patients: HIV infected patients with information on HBV surface antigen measurements and detectable HCV RNA or positive HCV antibodies if HCV RNA was not available.

Measurements: Time dependent Cox models to assess the risk of NHL in patients remaining naïve and after start of antiretroviral therapy with inverse probability weighing to control for informative censoring.

Results: We included 52,479 antiretroviral therapy-naïve patients (1339 (3.3%) with chronic HBV and 7506 (18.7%) with HCV), of which 40,219 (77%) then went on to start antiretroviral therapy. The median follow up was 13 months for naïve and 50 months for patients on antiretroviral therapy. 252 - naïve and 310 treated patients developed NHL, with incidence rates of 219 and 168 per 100,000 person-years. The hazard ratio of NHL with HBV and HCV was 1.33 (95% CI 0.69, 2.56) and 0.67 (0.40, 1.12) in naïve patients and 1.74 (1.08, 2.82) and 1.73 (1.21, 2.46) in antiretroviral therapy -treated patients, respectively.

Limitations: Many naïve patients initiated antiretroviral therapy limiting the study of the associations of chronic HBV and HCV infection with NHL in this patient group.

Conclusions: In HIV-infected antiretroviral therapy -treated patients chronic co-infection with HBV and HCV is associated with an increased risk of NHL.

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Introduction

In the HIV-negative population, there is growing evidence that chronic hepatitis B virus infection (HBV) and hepatitis C virus infection (HCV) are both associated with non-Hodgkin lymphoma (NHL) (1). Mechanisms underlying this association remain unclear, but chronic immune activation and B-cell proliferation have been postulated as potential mechanisms for both infections (2). HBV DNA has been identified in NHL tumor tissue (3), whereas active in vivo HCV replication in lymphocytes has not been consistently found (2). The role of chronic co-infection with HBV and HCV in promoting NHL in HIV infection is unclear (4).

The incidence rate of NHL in HIV-infected individuals is about 10 times higher compared to HIV-negative populations (5). NHL is strongly related to compromised immune function or recovery and is an important cause of AIDS and death, even in the presence of antiretroviral therapy (ART), accounting for up to one third of all AIDS related events (6-8). Some viruses such as Epstein Barr virus and human herpes virus 8 can transform lymphocytes in normal or immune compromised hosts and promote the development of NHL such as Burkitt’s lymphoma, or primary effusion lymphoma. Growing evidence indicates that some infections increase the risk of NHL through chronic immune stimulation in the immune compromised host (9).

We investigated in a large European multi-cohort study of antiretroviral drug naïve and treated HIV-infected individuals whether chronic HBV and HCV infection is associated with an increased risk of NHL.
Methods

The COHERE Collaboration

We included 18 cohorts with routine data collection for hepatitis B and C co-infection of 33 cohorts from the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) that contributed to the 2013 COHERE in EuroCoord data merger (http://www.cohere.org; study documents). Data collected included information on patient characteristics, ART, CD4 cell count, HIV RNA viral load, co-infection with hepatitis B or C, AIDS events, and causes of death. Institutional review board approval was obtained for each participating cohort.

Patients

Patients were analyzed in two separate periods: (1) when they were ART-naïve; and (2) during ART for those who started ART. We included all HIV-infected adults (≥16 years old) who were ART-naïve on January 1st 2000 or at cohort entry if this was later with at least one measurement for HBV and HCV infection and followed them until the date of NHL diagnosis, start of ART, death or the last follow up visit - whichever came first - through March 27, 2013. Patients initiating ART (defined as any combination of antiretroviral drugs) were followed the same way from the start date of the first ART. We ignored subsequent changes to treatment, including discontinuations. All patients with NHL prior to baseline were excluded. Patient visits and monitoring frequencies were conducted according to the rules of individual cohorts.

Exposure Variables and Outcome

HBV and HCV measurement was not done uniformly but in some cohort at baseline, later during follow-up, or from stored samples. Chronic HBV infection was defined as presence of two positive HBV surface antigen (HBsAg) measurements more than 6 months apart. HCV infection was defined as having a detectable HCV RNA or HCV IgG antibody if HCV RNA was not available.

If there were no negative HBV or HCV measurements prior to the first positive measurement, we assumed the patient had been infected with chronic HBV or HCV since baseline, otherwise the date of the first positive
HBsAg or HCV antibody /HCV RNA measurement was the defined start of infection, with individuals assumed to be negative for chronic hepatitis B or C until this date. Individuals known to be HBV or HCV negative that acquired a new chronic HBV or HCV infection changed their status.

Our primary outcome was time to the diagnosis of NHL based on the 1993 US Centers for Disease Control (CDC) histology criteria (10). We included all subtypes of NHL: Burkitt’s lymphoma (classical or atypical), diffuse large B-cell lymphoma (immunoblastic or centroblastic), primary brain lymphoma, and unspecified type and death due to NHL based on ICD-10 codings. These endpoints were adjudicated individually in each cohort.

**Statistical Analyses**

We approximated a Cox proportional hazards model using a spline-based, parametric survival model, and parameterized the log cumulative hazard using cubic splines of time with 5 internal knots at the 5th, 27.5th, 50th, and 72.5th and 95th percentiles to estimate hazards ratios (HR) and corresponding 95% confidence intervals (CI) for the association between chronic HBV and HCV infection and risk of NHL in naïve and ART treated patients(11). The exposure to chronic HBV or HCV was time updated, and the following a prior chosen baseline covariates were adjusted: age, gender, HIV transmission via intravenous drug use (IDU), CD4 cell count and viral load. In a separate model, we further adjusted for time updated CD4 cell count and HIV viral load.

We used inverse probability of censoring weights to adjust for bias due to informative censoring resulting from differences between patients continuing to provide measurements over time and those who died, started ART or were lost to follow up. A single inverse probability of censoring weight was estimated for each patient to account for censoring due to different reasons. The inverse probability of censoring weights were estimated by pooled logistic regression using covariates hypothesized to strongly influence censoring: age, gender, Caucasian ethnicity, HIV transmission via IDU and cohort at baseline, CD4 cell count and viral load both at baseline and time updated (12;13).
We next obtained smooth estimates of the cumulative incidence curves stratified by HBV status. These estimates for both the HBV positive and HBV negative groups were standardised so that they were adjusted to the overall distribution of the characteristics of the entire study population. We then calculated adjusted differences in cumulative incidences of NHL using our parametric survival model for HBV positive compared to HBV negative individuals at 1, 2, 3, 5, 10 and 12 years. Corresponding 95% CIs were constructed using bootstrapping, randomly resampling with replacement 1000 samples of equal size to the original study population (Monte Carlo algorithm). Analyses were then repeated for HCV status.

We investigated the robustness of our results by sensitivity analyses in particular to address survivor bias. First, we extended the definition of chronic HBV infection to include patients with single HBsAg measurements by combining information from other HBV markers (see Appendix Table 1). Second, if the patient had at least one positive HBsAg or HCV-RNA or HCV antibody measurement, we assumed that the patient had been chronically infected for the whole follow-up period. Third, if the first HBsAg or HCV measurement was positive, we assumed that if the first positive HBsAg or HCV-RNA or HCV antibody measurement was less than 6 months after baseline, the patient had been infected since baseline; if the first measurement was more than 6 months after baseline and the patient was an injecting drug user, the patient had been infected since baseline; in the remaining patients, we reset the baseline to the date of the first measurement. Fourth, to control for immortality bias we reassigned baseline to the date of the first available HBV or HCV measurement if this was later than the baseline used in the main analyses; (45,107 ART naïve and 40,097 ART treated patients were kept in the analyses). Fifth, we removed patients who enrolled into cohort before 2000 (35,236 ART naïve and 27,537 ART treated patients were kept in the analyses). Finally, in ART-naïve patients we constructed different censoring weights according to different censoring reasons, i.e. the start of ART or otherwise.

We used SAS version 9.2 (SAS Institute Inc., Cary, NC) for analyses, PROC GENMOD for regression analysis, and PROC SURVEYSELECT for bootstrapping. We used the stcurve macro in Stata version 14.0 for graphics.

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Results

Patient Characteristics

Of 299,690 patients from 33 cohorts, 208,840 patients from 15 cohorts that did not routinely measure HBV and HCV markers were excluded from the analyses and a further 36,922 patients were excluded for the reasons detailed in Figure 1.

We included 52,479 ART-naïve patients, of which 40,219 (77%) then went on to start ART. The median follow up was 13 (interquartile range [IQR], 2, 41) months for ART naïve and 50 (IQR, 24, 88) months for patients on ART. At the time of inclusion into cohorts there were 1339 (2.6%) patients with chronic HBV infection, 7506 (14.3%) patients with HCV infection (with HCV RNA confirmed in 3807 individuals and missing in the remaining) and 210 (0.4%) patients with dual chronic infection. During follow-up an additional 70 and 52 ART naïve and 50 and 267 ART treated patients acquired a new chronic HBV and HCV infection. Of HBV-coinfected individuals initiating ART, 89% received at least one HBV-active drug including lamivudine, emtricitabine or tenofovir. Of HCV co-infected individuals, 1204 (15%) were treated for HCV and 753 (63%) had a sustained virological response at week 12.

Of all included individuals, 22% were females, and 56% of HCV co-infected individuals were injecting drug users. Median CD4 cell count in HBV, HCV co-infected and not co-infected patients was 320, 380 and 380 cells/mm³ at baseline, and 240, 230 and 250 cells/mm³ at initiation of ART, respectively (Table 1). At the time of NHL diagnosis median CD4 cell counts were not higher in ART treated HBV and HCV co-infected patients than in naïve patients.

Outcomes in ART Naïve Patients and their Association with Chronic HBV and HCV Infections

During 115,049 person-years of follow up in ART-naive individuals, 252 developed NHL. Of those, 47 (18.7%) were Burkitt’s lymphoma, 27 (10.7%) diffuse large B-cell lymphoma, 9 (3.6%) primary brain lymphoma, and 169 (67.1%) were unspecified NHL types. There were 547 deaths with 67 (12.2%) deaths from NHL, and the rest being from other causes. Incidence rates of NHL in ART naïve individuals uninfected with HBV and HCV
were 186 (95% confidence interval [CI], 180, 193) per 100,000 person-years, while incidence rates were 187 (95% CI 152, 229), 134 (95% CI 123, 145) and 149 (95% CI 88, 252) per 100,000 person-years in individuals with chronic HBV, HCV and dual HBV and HCV infection, respectively. Figure 2 upper part provides survival functions for NHL events with or without chronic HBV or HCV in ART naïve individuals.

Table 2 (upper part) shows the results of multivariate models considering the outcomes of NHL in ART-naïve patients. We provide hazard ratios with and without accounting for informative censoring, and with time updated adjustment for current CD4 cell count and HIV-1 RNA. In ART-naïve patients, the adjusted hazard ratios (with censoring weights applied) for NHL with chronic HBV and HCV infections were 1.33 (95% CI 0.69, 2.56) and 0.67 (95% CI 0.40, 1.12), respectively. Hazard ratios for NHL in models with time updated CD4 cell count and HIV viral load were similar to the ones with adjustment for baseline covariates only. Hazard ratios for all baseline covariates included into all models are provided in the web appendix.

The respective adjusted 5-year risk differences in rates of NHL for naïve individuals was for chronic HBV 1.6 (95% CI 0.3, 5.9), and for HCV -1.8 (95% CI -6.9, -0.4) cases per 1000 persons (Table 3).

**Outcomes in ART Treated Patients and their Association with Chronic HBV and HCV Infections**

During 191,257 person years of follow-up, 310 ART-treated individuals developed a NHL. Of those, 59 (19.0%) were Burkitt’s lymphoma, 33 (10.6%) diffuse large B-cell lymphoma, 20 (6.5%) primary brain lymphoma, and 198 (63.9%) were unspecified NHL types. There were 1523 deaths with 107 (7.0%) deaths from NHL, and the rest being from other causes. Incidence rates of NHL in ART treated individuals were 149 (95% CI 143, 155) per 100,000 person years in individuals uninfected with HBV and HCV and 241 (95% CI 198, 293), 200 (95% CI 182, 220) and 294 (95% CI 178, 487) per 100,000 person-years in individuals with chronic HBV, HCV and dual HBV and HCV infection, respectively. Figure 2 (lower part) provides survival functions for NHL events with or without chronic HBV or HCV in ART treated individuals.

Both chronic HBV and HCV infections were associated with an increased risk of NHL, with an adjusted hazard ratio of 1.74 (95% CI, 1.08, 2.82) and 1.73 (95% CI, 1.21, 2.46), respectively (Table 2, lower part). Hazard ratios
for NHL in models with time updated CD4 cell count and HIV viral load were also similar to the ones with adjustment for baseline covariates only.

The respective adjusted 5-year risk differences in rates of NHL for ART treated individuals was for chronic HBV 5.9 (95% CI 1.8, 14.7), and for HCV 5.4 (95% CI 1.6, 14.6) cases per 1000 persons (Table 3).

Sensitivity analyses based on different definitions and exposure time to chronic HBV and HCV infections and in particular when controlling for immortality bias gave in all models for both naïve and ART treated co-infected individuals similar hazard ratios for NHL as in the main models specified above.
Discussion

In this multicohort study we found that ART-treated patients with chronic HBV or HCV infection were at increased risk for NHL and for the combined endpoint of NHL or death compared to HBV or HCV uninfected individuals. Estimates in ART naïve patients were less certain, possibly due to the lower number of events, limited follow-up as patients initiated ART or due to other unmeasured competing factors masking the effect of chronic HBV and HCV infections in this population. Median CD4 cell count at time of NHL diagnosis in both ART naïve and treated HBV and HCV co-infected patients was below 250 cells/mm$^3$ indicating that HBV and HCV co-infected patients with NHL initiate ART late, and/or have insufficient HIV viral control and immune recovery that may be related to multiple reasons. This unfavourable constellation is aggravated by the fact that chronic HBV attenuates immune recovery in individuals treated with ART (14). Whether this is also the case for chronic HCV infection is less clear (15;16).

This study has several limitations. Our analysis is based only on a limited number of cohorts and a fraction of patients from COHERE that provided detailed information on chronic HCV and HBV infection. This precluded a more powerful analysis for co-infected ART naïve patients and may limit the generalizability of our findings. The hazard ratios and cumulative incidence functions indicating a protective effect of chronic HCV infection in ART naïve individuals are indicative for the competing risk of death from any cause which we found in additional analyses (data not shown). Suboptimal screening or data collection for hepatitis co-infections in HIV-infected populations is a problem and has been reported in different settings (17). In the different cohorts, presence of chronic HCV and HBV infection was not uniformly measured at baseline. However, we accounted for these limitations in extensive sensitivity analyses, which all confirmed our findings. Most cohorts did not measure or collect HCV RNA to confirm the chronic HCV infection status. HBsAg and HCV clearance are not routinely measured in all cohorts. HBV DNA in ART treated patients and HCV RNA clearance following treatment are not routinely monitored or might have been underreported. A substantial proportion of ART treated HBV co-infected patients continue to express HBV DNA and some patients might experience relapses (18). HBV reactivation in the presence of ART in severely immunosuppressed patients or HBV resistance to lamivudine might be possible explanations for the observed increased risk of NHL in co-infected...
Continued immune stimulation following antiviral treatment against HBV and HIV in co-infected patients might be another mechanism, given that chronic B cell stimulation by HBsAg continues to persist despite inhibition of viral replication by antiviral therapy and indirect effects mediated by increased pro-inflammatory cytokine expression and secretion in these patients may also contribute to lymphomagenesis (20-22). Only a limited number of cohorts routinely test HCV and HBV negative patients for incident infections or HCV re-infection following successful treatment (23;24). All these deficiencies will introduce misclassification biases, the direction of the bias, however, is in all instances conservative and will underestimate the true association of HCV and HBV co-infection and NHL in ART naïve or treated patients. A large number of NHL types were not classified and therefore all NHL cases had to be coalesced, which precluded an analysis according to NHL subtypes. In addition, ascertainment of NHL was not uniformly reported by all cohorts. As a consequence, our findings might not accurately reflect the prognosis of chronic HCV and HBV co-infection relevant for different types of NHL. Better screening and reporting of chronic HBV and HCV is needed in addition to more detailed data on NHL subtypes.

To our knowledge this is the first large prospective cohort study indicating an association between chronic HBV and HCV infection and NHL in HIV co-infected individuals. Previous studies not confirming such an association were smaller cohort or case control studies (4;25). Incidence rates for NHL in ART treated compared to naïve patients were not remarkably different in both chronic HBV and HCV infection. This might at least partially be attributed to cases of unmasking NHL in the context of immune reconstitution syndrome when patients, as in our study population, initiate ART at low CD4 cell count (26;27). HBV and HCV co-infected patients are more likely to die from other causes, due to injecting drug use or other epidemiological differences impacting on mortality. Therefore, to adjust for bias due to informative censoring we used inverse probability of censoring weights.

Several meta-analyses of observational studies have investigated the association between chronic HBV and HCV infection in HIV uninfected individuals. The pooled odds ratios for chronic HBV infection and NHL in 5 cohort and 17 case control studies were 2.06 (95% CI 1.44–2.95) and 2.27 (CI 1.74–2.94) respectively, but heterogeneity for both estimates was moderate to high (28). The association could be confirmed for studies
conducted in high and low prevalence areas and in a subset of studies for the diffuse large cell lymphoma NHL subtype. In a later published nationwide study from Sweden not included into the meta-analysis individuals with a chronic HBV infection showed an increased standardized incidence ratio of 4.89 (95% CI 3.81-6.18) for NHL (29). Incidence rates for NHL of HBV co-infected individuals from our study indicate that the risk for NHL is – irrespective of antiretroviral therapy – about 10 times higher in the presence of HIV than in HBV mono-infected individuals (30).

In a meta-analysis of 15 case control and two cohort studies in HIV uninfected individuals the pooled odds ratio for chronic HCV infection and NHL were 2.5 (95% CI, 2.1-3.1) and 2.0 (95% CI, 1.8-2.2) respectively, with high heterogeneity between case controls study findings (1). Diffuse large B-cell lymphoma and marginal zone lymphoma are NHL types most frequently associated with HCV. Several pathogenic mechanisms have been suggested for explaining this association (31). Studies showing regression of B-cell NHL following HCV eradication represent a strong argument in favour of a causal relationship between HCV infection and these types of NHL (32). In HIV infection, B-cell type NHL, in particular diffuse large cell subtypes represent the majority of NHL, which is in line with a potential contribution of HCV to the pathogenesis of NHL. Due to the large number of uncharacterized NHL this study, however, lacks the power to detect an association of HCV with specific subtypes. Nonetheless, our findings do suggest that chronic HCV co-infection, along with immune suppression may represent a relevant cause for the increased incidence of NHL observed in persons living with HIV.

In conclusion, ART treated patients with chronic HBV and HCV co-infection are at increased risk of NHL, the currently most frequent occurring AIDS defining condition. Our study was not sufficiently powered to show such an association in ART naïve co-infected patients. Early diagnosis and treatment of HIV in conjunction with routine screening for chronic HBV and HCV infection is indispensable to further lower NHL morbidity and mortality in HIV-infected individuals. Uptake of treatment for chronic HCV infection in co-infected patients in Europe has been low and, due to peg-interferon and ribavirin based regimen related high failure and toxicity rates, mainly limited to patients with higher CD4 cell count (above 350 cells/mm³) and advanced liver fibrosis and high costs of direct acting antiviral drugs (33-36). Our findings provide a strong case that
HCV co-infected patients with poor immune status or restoration (CD4 cell count below 250 cells/mm$^3$) represent a population at high risk of NHL and death and deserve high priority for access to well tolerated interferon-free direct acting antiviral treatment programs similar to patients with advanced liver fibrosis or liver cirrhosis.

References


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

**COHERE** Collaboration of Observational HIV Epidemiological Research Europe, **HBV** hepatitis B virus, **HCV** hepatitis C virus, **NHL** non-Hodgkin lymphoma

Figure 2: Non-Hodgkin lymphoma event-free survival in antiretroviral therapy (ART)-naïve and ART treated HIV infected patients by chronic hepatitis B and hepatitis C status at baseline

**ART** antiretroviral therapy, **HBV** hepatitis B virus, **HCV** hepatitis C virus
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Qing Wang, Andrea de Luca, Colette Smith and Heiner C. Bucher conceived the project, established and coordinated the COHERE working group, designed and executed the analysis, interpreted the findings, and wrote and revised the first and subsequent drafts of the manuscript. Qing Wang did the analysis design and execution and Colette Smith contributed to the data analysis. Colette Smit, Robert Zangerle, Helen Sambatakou, Fabrice Bonnet, Philipp Schommers, Alicia Thornton, Juan Berenguer, Lars Peters, Vincenzo Spagnolo, Adriana Ammassari, Andrea Antinori, Eugenia Quiros Roldan, Cristina Mussini, Jose M Miro, Deborah Konopnicki and Jan Fehr reviewed and commented on the final draft of the manuscript and were involved in the interpretation of findings. Heiner C. Bucher, Lars Peters, Christina Mussini, Adriana Ammassari, Andrea Antinori and Jan Fehr were involved in data collection. Maria A Campbell and Monique Termote were involved in data collection and preparation of the manuscript.