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 /HCB 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.

Role of the Funding Source

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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/mm^3 at baseline, and 240, 230 and 250 cells/mm^3 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-naïve 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 naive 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

patients (19). 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/mm^3) 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

(1) Dal ML, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2006 November;15(11):2078-85.

(2) Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol 2013 July;59(1):169-77.

(3) Wang F, Yuan S, Teng KY, Garcia-Prieto C, Luo HY, Zeng MS et al. High hepatitis B virus infection in B-cell lymphoma tissue and its potential clinical relevance. Eur J Cancer Prev 2012 May;21(3):261-7.

(4) Bonnet F, Balestre E, Thiebaut R, Morlat P, Pellegrin JL, Neau D et al. Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France. Clin Infect Dis 2006 February 1;42(3):411-7.

(5) Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS 2014 September 24;28(15):2313-8.

(6) Serraino D, De PA, Zucchetto A, Pennazza S, Bruzzone S, Spina M et al. The impact of Kaposi sarcoma and non-Hodgkin lymphoma on mortality of people with AIDS in the highly active antiretroviral therapies era. Cancer Epidemiol 2010 June;34(3):257-61.

(7) Lewden C, May T, Rosenthal E, Burty C, Bonnet F, Costagliola D et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic). J Acquir Immune Defic Syndr 2008 August 15;48(5):590-8.

(8) Bohlius J, Schmidlin K, Costagliola D, Fatkenheuer G, May M, Caro-Murillo AM et al. Incidence and risk factors of HIV-related non-Hodgkin's lymphoma in the era of combination antiretroviral therapy: a European multicohort study. Antivir Ther 2009;14(8):1065-74.

(9) Viswanatha DS, Dogan A. Hepatitis C virus and lymphoma. J Clin Pathol 2007 December;60(12):1378-83.

(10) Centers for Disease Control and Prevention. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. MMWR 992;41(51):961-2.

(11) Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002 August 15;21(15):2175-97.

(12) Matsuyama Y, Yamaguchi T. Estimation of the marginal survival time in the presence of dependent competing risks using inverse probability of censoring weighted (IPCW) methods. Pharm Stat 2008 July;7(3):202-14.

(13) Howe CJ, Cole SR, Chmiel JS, Munoz A. Limitation of inverse probability-of-censoring weights in estimating survival in the presence of strong selection bias. Am J Epidemiol 2011 March 1;173(5):569-77.

(14) Wandeler G, Gsponer T, Bihl F, Bernasconi E, Cavassini M, Kovari H et al. Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. J Infect Dis 2013 November 1;208(9):1454-8.

(15) Peters L, Mocroft A, Soriano V, Rockstroh JK, Losso M, Valerio L et al. Hepatitis C virus coinfection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. J Acquir Immune Defic Syndr 2009 April 15;50(5):457-63.

(16) De LA, Bugarini R, Lepri AC, Puoti M, Girardi E, Antinori A et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. Arch Intern Med 2002 October 14;162(18):2125-32.

(17) Hoover KW, Butler M, Workowski KA, Follansbee S, Gratzer B, Hare CB et al. Low rates of hepatitis screening and vaccination of HIV-infected MSM in HIV clinics. Sex Transm Dis 2012 May;39(5):349-53.

(18) Soriano V, Mocroft A, Peters L, Rockstroh J, Antunes F, Kirkby N et al. Predictors of hepatitis B virus genotype and viraemia in HIV-infected patients with chronic hepatitis B in Europe. J Antimicrob Chemother 2010 March;65(3):548-55.

(19) Soriano V, Labarga P, de MC, Pena JM, Fernandez-Montero JV, Benitez L et al. Emerging challenges in managing hepatitis B in HIV patients. Curr HIV /AIDS Rep 2015 September;12(3):344-52.

(20) Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. Blood 2011 February 10;117(6):1792-8.

(21) Crane M, Avihingsanon A, Rajasuriar R, Velayudham P, Iser D, Solomon A et al. Lipopolysaccharide, immune activation, and liver abnormalities in HIV/hepatitis B virus (HBV)-coinfected individuals receiving HBV-active combination antiretroviral therapy. J Infect Dis 2014 September 1;210(5):745-51.

(22) Vendrame E, Hussain SK, Breen EC, Magpantay LI, Widney DP, Jacobson LP et al. Serum levels of cytokines and biomarkers for inflammation and immune activation, and HIV-associated non-Hodgkin B-cell lymphoma risk. Cancer Epidemiol Biomarkers Prev 2014 February;23(2):343-9.

(23) Wandeler G, Gsponer T, Bregenzer A, Gunthard HF, Clerc O, Calmy A et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis 2012 November 15;55(10):1408-16.

(24) Kouyos RD, Rauch A, Braun DL, Yang WL, Boni J, Yerly S et al. Higher Risk of Incident Hepatitis C Virus Coinfection Among Men Who Have Sex With Men, in Whom the HIV Genetic Bottleneck at Transmission Was Wide. J Infect Dis 2014 November 15;210(10):1555-61.

(25) d'Arminio MA, Cozzi-Lepri A, Castagna A, Antinori A, De Luca A, Mussini C et al. Risk of developing specific AIDS-defining illnesses in patients coinfected with HIV and hepatitis C virus with or without liver cirrhosis. Clin Infect Dis 2009 August 15;49(4):612-22.

(26) HIV Causal Collaboration. Opportunistic infections and AIDS malignancies early after initiating combination antiretroviral therapy in high-income countries. AIDS 2014 October 23;28(16):2461-73.

(27) Gopal S, Patel MR, Achenbach CJ, Yanik EL, Cole SR, Napravnik S et al. Lymphoma immune reconstitution inflammatory syndrome in the center for AIDS research network of integrated clinical systems cohort. Clin Infect Dis 2014 July 15;59(2):279-86.

(28) Dalia S, Chavez J, Castillo JJ, Sokol L. Hepatitis B infection increases the risk of non-Hodgkin lymphoma: a meta-analysis of observational studies. Leuk Res 2013 September;37(9):1107-15.

(29) Sundquist K, Sundquist J, Ji J. Risk of hepatocellular carcinoma and cancers at other sites among patients diagnosed with chronic hepatitis B virus infection in Sweden. J Med Virol 2014 January;86(1):18-22.

(30) Engels EA, Cho ER, Jee SH. Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study. Lancet Oncol 2010 September;11(9):827-34.

(31) Forghieri F, Luppi M, Barozzi P, Maffei R, Potenza L, Narni F et al. Pathogenetic mechanisms of hepatitis C virus-induced B-cell lymphomagenesis. Clin Dev Immunol 2012;2012:807351.

(32) Mazzaro C, De R, V, Spina M, Dal ML, Festini G, Comar C et al. Pegylated-interferon plus ribavirin for HCV-positive indolent non-Hodgkin lymphomas. Br J Haematol 2009 April;145(2):255-7.

(33) Grint D, Peters L, Schwarze-Zander C, Beniowski M, Pradier C, Battegay M et al. Temporal changes and regional differences in treatment uptake of hepatitis C therapy in EuroSIDA. HIV Med 2013 November;14(10):614-23.

(34) Mira JA, Garcia-Rey S, Rivero A, de lS-G, I, Lopez-Cortes LF, Giron-Gonzalez JA et al. Response to pegylated interferon plus ribavirin among HIV/hepatitis C virus-coinfected patients with compensated liver cirrhosis. Clin Infect Dis 2012 December;55(12):1719-26.

(35) Zinkernagel AS, von W, V, Ledergerber B, Rickenbach M, Furrer H, Battegay M et al. Eligibility for and outcome of hepatitis C treatment of HIV-coinfected individuals in clinical practice: the Swiss HIV cohort study. Antivir Ther 2006;11(2):131-42.

(36) Bhagani S. Current treatment for chronic hepatitis C virus/HIV-infected individuals: the role of pegylated interferon-alpha and ribavirin. Curr Opin HIV AIDS 2011 November;6(6):483-90.

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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.