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

A Cohort Study

Qing Wang, PhD; Andrea De Luca, MD; Colette Smith, PhD; Robert Zangerle, MD; Helen Sambatakou, MD; Fabrice Bonnet, MD, PhD; Colette Smit, MD, PhD; Philipp Schommers, MD; Alicia Thornton, PhD; Juan Berenguer, MD, PhD; Lars Peters, MD; Vincenzo Spagnuolo, MD; Adriana Ammassari, MD; Andrea Antinori, MD; Eugenia Quiros Roldan, MD, PhD; Cristina Mussini, MD; Jose M. Miro, MD, PhD; Deborah Konopnicki, MD, PhD; Jan Fehr, MD; Maria A. Campbell, MMA; Monique Termote, MSc; and Heiner C. Bucher, MD, MPH; on behalf of The Hepatitis Coinfection and Non Hodgkin Lymphoma project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord*

Background: Non-Hodgkin lymphoma (NHL) is the most common AIDS-defining condition in the era of antiretroviral therapy (ART). Whether chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection promote NHL in HIV-infected patients is unclear.

Objective: To investigate whether chronic HBV and HCV infection are associated with increased incidence of NHL in HIV-infected patients.

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 a positive HCV antibody test result if HCV RNA measurements were not available.

Measurements: Time-dependent Cox models to assess risk for NHL in treatment-naive patients and those initiating ART, with inverse probability weighting to control for informative censoring.

Results: A total of 52 479 treatment-naive patients (1339 [2.6%] with chronic HBV infection and 7506 [14.3%] with HCV infection) were included, of whom 40 219 (77%) later started ART. The median follow-up was 13 months for treatment-naive patients and 50 months for those receiving ART. A total of 252 treatment-naive patients and 310 treated patients developed NHL, with incidence rates of 219 and 168 cases per 100 000 person-years, respectively. The hazard ratios for NHL with HBV and HCV infection were 1.33 (95% CI, 0.69 to 2.56) and 0.67 (CI, 0.40 to 1.12), respectively, in treatment-naive patients and 1.74 (CI, 1.08 to 2.82) and 1.73 (CI, 1.21 to 2.46), respectively, in treated patients.

Limitation: Many treatment-naive patients later initiated ART, which limited the study of the associations of chronic HBV and HCV infection with NHL in this patient group.

Conclusion: In HIV-infected patients receiving ART, chronic co-infection with HBV and HCV is associated with an increased risk for NHL.

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For author affiliations, see end of text.

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* Members of the COHERE Steering Committee are listed in the **Appendix** (available at www.annals.org).

In the HIV-negative population, growing evidence suggests that chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are both associated with non-Hodgkin lymphoma (NHL) (1). The mechanisms underlying this association remain unclear, but chronic immune activation and B-cell proliferation have been postulated as potential mechanisms for both infections (2). Hepatitis B virus 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 persons is about 10 times higher than in HIV-negative populations (5). Non-Hodgkin lymphoma is strongly related to compromised immune function or recovery and is an important cause of AIDS and death (even with the use 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 herpesvirus 8, can transform lymphocytes in healthy or immunocompromised hosts and promote certain types of NHL, such as Burkitt lymphoma or primary effusion lymphoma. Growing evidence indicates that some infections increase the risk for NHL through chronic immune stimulation in the immunocompromised host (9).

We performed a large European multicohort study of ART-naive and treated HIV-infected persons to investigate whether chronic HBV and HCV infection are associated with an increased risk for NHL.

METHODS

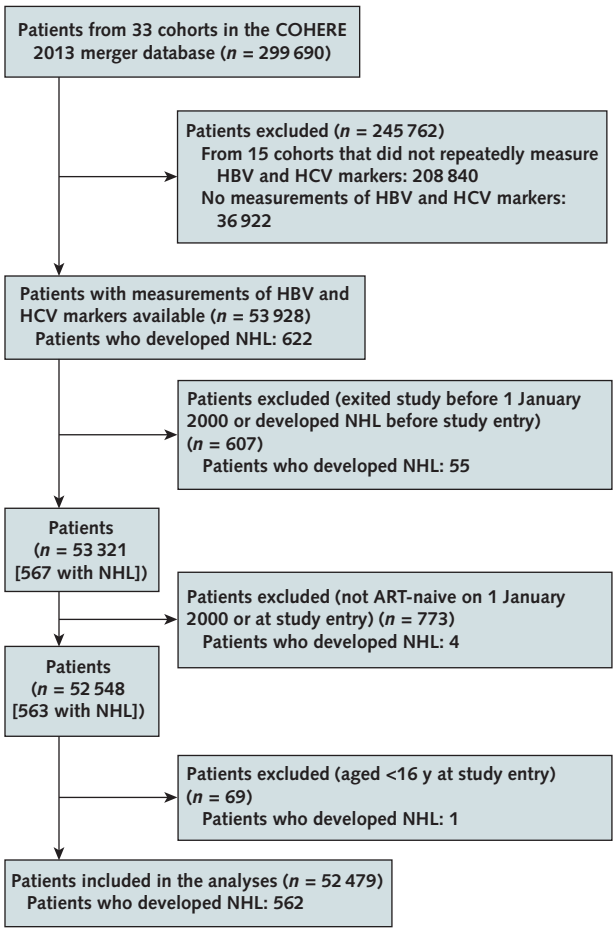
The COHERE Collaboration

We included 18 cohorts with routine collection of data on HBV and HCV co-infection out of 33 cohorts from the Collaboration of Observational HIV Epidemio-

See also:

Editorial comment 1

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



ART = antiretroviral therapy; COHERE = Collaboration of Observational HIV Epidemiological Research Europe; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.

logical Research Europe (COHERE) that contributed to the 2013 COHERE in EuroCoord data merger (see the study documents at www.cohere.org). Data collected included information on patient characteristics, ART, CD4 cell count, HIV RNA viral load, co-infection with HBV or HCV, AIDS events, and causes of death. Institutional review board approval was obtained for each participating cohort.

Patients

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

Exposure Variables and Outcome

Markers of HBV and HCV were measured at baseline in some cohorts, during follow-up in others, and from stored samples in others. Chronic HBV infection was defined as 2 positive HBV surface antigen (HBsAg) measurements more than 6 months apart. Hepatitis C virus infection was defined as detectable HCV RNA, or detectable HCV IgG antibody if HCV RNA measurements were not available.

If there were no negative HBV or HCV measurements before the first positive measurement, we assumed that the patient had been infected with chronic HBV or HCV since baseline. Otherwise, the date of the first positive HBsAg, HCV antibody, or HCV RNA measurement was defined as the start of infection, with persons assumed to be negative for HBV or HCV until this date. Those known to be negative for HBV or HCV who acquired a new infection changed their status.

Our primary outcome was time to diagnosis of NHL, based on the 1993 Centers for Disease Control and Prevention histologic criteria (10). We included all NHL subtypes (Burkitt lymphoma [classic or atypical], diffuse large B-cell lymphoma [immunoblastic or centroblastic], primary brain lymphoma, and unspecified types) and death due to NHL based on codes from the International Classification of Diseases, 10th Revision. These end points were adjudicated individually in each cohort.

Statistical Analysis

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 fifth, 27.5th, 50th, 72.5th, and 95th percentiles to estimate hazard ratios and corresponding 95% CIs for the association between chronic HBV and HCV infection and risk for NHL in treatment-naive and ART-treated patients (11). The exposure to chronic HBV or HCV infection was time-updated, and we adjusted for the following baseline covariates, chosen a priori: age, sex, HIV transmission via intravenous drug use, CD4 cell count, and HIV viral load. In a separate model, we further adjusted for time-updated CD4 cell count and HIV viral load.

We used inverse probability censoring weighting to adjust for bias due to informative censoring resulting from differences between patients who continued to provide measurements over time and those who died, started ART, or were lost to follow-up. A single inverse probability censoring weight was estimated for each patient to account for censoring due to different reasons. The weights were estimated by pooled logistic regression using the following covariates hypothesized

to strongly influence censoring: age, sex, white race, HIV transmission via intravenous drug use and cohort (at baseline), and 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 standardized so that they were adjusted to the overall distribution of the characteristics of the entire study population. We then calculated adjusted differences in cumulative incidence of NHL using our parametric survival model for HBV-positive versus HBV-negative persons at 1, 2, 3, 5, 10, and 12 years. Corresponding 95% CIs were calculated using bootstrapping, with random resampling with replacement from 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 in sensitivity analyses, in particular to address survivor bias. First, we expanded the definition of chronic HBV infection to include patients with single HBsAg measurements by combining information from other HBV markers (Appendix Table 1, available at www.annals.org). Second, if the patient had at least 1 positive HBsAg, HCV RNA, or HCV antibody measurement, we assumed that they had been chronically infected for the entire follow-up. Third, if the first HBsAg or HCV measurement was positive, we assumed that the patient had been infected since baseline if the first positive measurement was taken less than 6 months after baseline or if it was taken more than 6 months after baseline and the patient was an injection drug user. 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-naive patients and 40 097 ART-treated patients were kept in the analyses). Fifth, we removed patients who were enrolled in the cohort before 2000 (35 236 ART-naive patients and 27 537 ART-treated patients were kept in the analyses). Finally, in ART-naive patients, we constructed different censoring weights according to different censoring reasons (for example, initiation of ART).

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

Role of the Funding Source

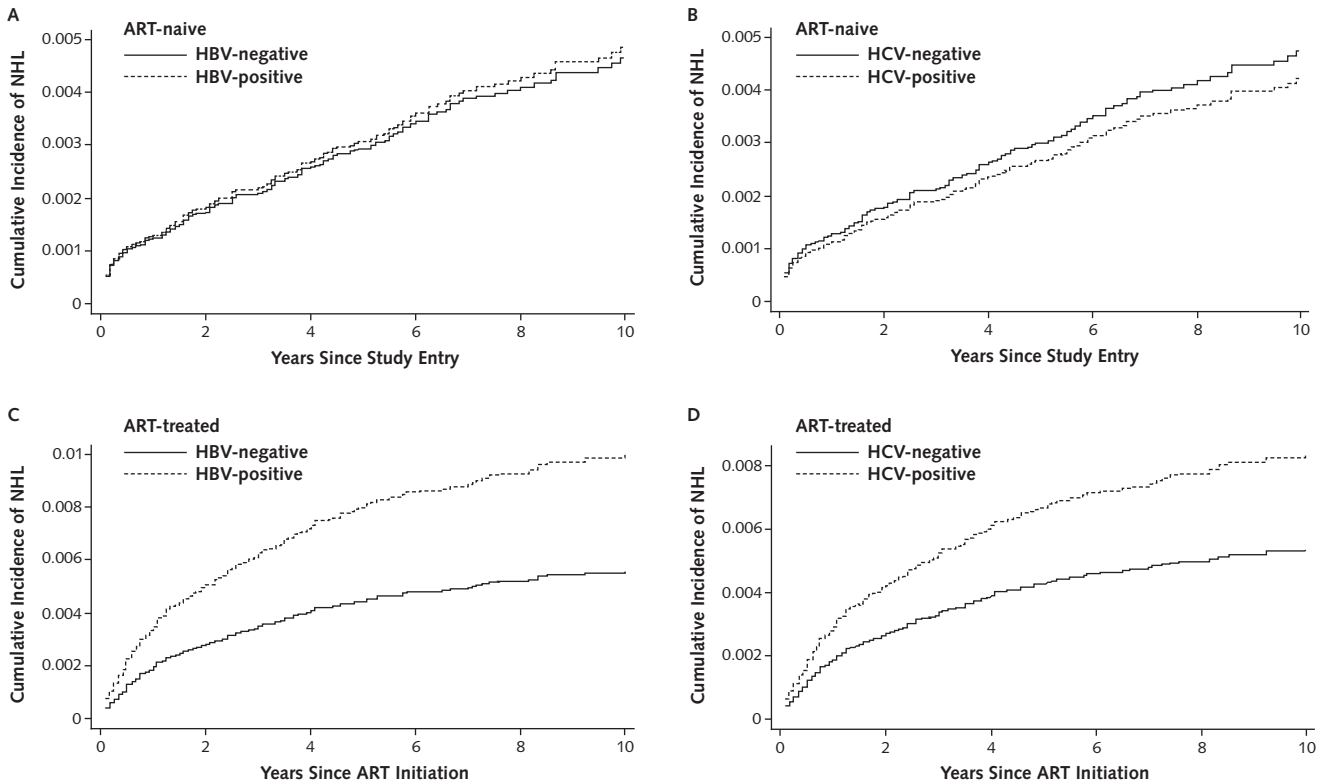
This study was funded exclusively by government grants or foundations with no industry involvement (European Union Seventh Framework Programme; Agence Nationale de Recherches sur le SIDA et les Hépatites Virales, Paris, France; HIV Monitoring Foundation, Amsterdam, the Netherlands; Augustinus Foundation, Copenhagen, Denmark; and Schweizerische Krebsliga). The funding sources had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

Table 1. Patient Characteristics at Baseline and During Follow-up

Characteristic	Patients With Chronic HBV Infection	Patients With Chronic HCV Infection	Patients With Dual Infection	Uninfected Patients
At time of HIV infection or inclusion				
Patients, *n*	1339	7506	210	43 844
Female, *n (%)*	250 (19)	1770 (24)	23 (11)	9711 (22)
White, *n (%)**	357 (58)	3036 (92)	66 (89)	15 976 (72)
HIV transmission via injection drug use, *n (%)*	162 (12)	4227 (56)	116 (55)	833 (2)
Median age (IQR), *y*	36 (30–42)	36 (31–41)	36 (31–40)	35 (29–42)
Median HIV RNA level (IQR), log_{10} *copies/mL*	4.7 (4.1–5.2)	4.5 (3.7–5.0)	4.5 (3.8–5.1)	4.6 (4.0–5.2)
Median CD4 count (IQR), × 10^9 *cells/L*	0.320 (0.144–0.496)	0.380 (0.208–0.585)	0.340 (0.190–0.509)	0.380 (0.210–0.560)
At initiation of ART				
Patients, *n*	1255	5481	187	33 670
Female, *n (%)*	227 (18)	1286 (23)	19 (10)	7850 (23)
White, *n (%)**	333 (59)	1978 (91)	57 (88)	11 989 (72)
HIV transmission via injection drug use, *n (%)*	136 (11)	2953 (54)	97 (52)	649 (2)
Median age (IQR), *y*	36 (30–42)	36 (31–41)	35 (30–40)	36 (30–43)
Median HIV RNA level (IQR), log_{10} *copies/mL*	4.9 (4.3–5.3)	4.8 (4.2–5.3)	4.8 (4.2–5.2)	4.9 (4.3–5.3)
Median CD4 count (IQR), × 10^9 *cells/L*	0.240 (0.120–0.349)	0.230 (0.125–0.334)	0.248 (0.131–0.349)	0.250 (0.140–0.345)
At NHL diagnosis				
ART-naive patients, *n*	10	36	1	207
Median HIV RNA level (IQR), log_{10} *copies/mL*	5.1 (4.1–5.2)	4.6 (4.0–5.3)	3.7 (3.7–3.7)	4.8 (4.2–5.4)
Median CD4 count (IQR), × 10^9 *cells/L*	0.115 (0.089–0.195)	0.246 (0.085–0.377)	0.240 (0.240–0.240)	0.212 (0.079–0.391)
ART-treated patients, *n*	18	54	3	241
Median HIV RNA level (IQR), log_{10} *copies/mL*	2.8 (1.7–4.9)	2.5 (1.7–4.1)	4.9 (4.1–5.5)	1.8 (1.7–3.6)
Median CD4 count (IQR), × 10^9 *cells/L*	0.136 (0.050–0.289)	0.231 (0.131–0.480)	0.131 (0–0.140)	0.256 (0.125–0.397)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; IQR = interquartile range; NHL = non-Hodgkin lymphoma.
* Among patients with known race.

Figure 2. NHL event-free survival in ART-naive and ART-treated HIV-infected patients, by chronic HBV and HCV infection status at baseline.



ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.

RESULTS

Patient Characteristics

Of 299 690 patients from 33 cohorts, we excluded 208 840 patients from 15 cohorts that did not routinely measure HBV and HCV markers and an additional 36 922 patients with no HBV or HCV measurements (Figure 1).

We included 52 479 ART-naive patients, 40 219 (77%) of whom later started ART. The median follow-up was 13 months (interquartile range, 2 to 41 months) for ART-naive patients and 50 months (interquartile range, 24 to 88 months) for treated patients. At the time of inclusion into cohorts, 1339 (2.6%) patients had chronic HBV infection, 7506 (14.3%) had chronic HCV infection (with HCV RNA confirmed in 3807 patients and missing in the remainder), and 210 (0.4%) had dual infection. During follow-up, an additional 70 and 52 ART-naive patients acquired a new chronic HBV or HCV infection, and 50 and 267 ART-treated patients acquired a new chronic HBV or HCV infection. Of persons co-infected with HBV who initiated ART, 89% received at least 1 HBV-active drug, including lamivudine, emtricitabine, or tenofovir. Of those co-infected with HCV, 1204 (15%) were treated for HCV and 753 (63%) had a sustained virologic response at week 12.

Among all included patients, 22% were female and 56% who were co-infected with HCV were injection drug users. Median CD4 counts in HBV-infected patients, HCV–co-infected patients, and uninfected patients were 0.320, 0.380, and 0.380 × 10^9 cells/L at baseline and 0.240, 0.230, and 0.250 × 10^9 cells/L at initiation of ART, respectively (Table 1). At the time of NHL diagnosis, median CD4 cell counts were not higher in ART-treated patients co-infected with HBV and HCV than in treatment-naive patients.

Outcomes in ART-Naive Patients and Their Association With Chronic HBV and HCV Infection

During 115 049 person-years of follow-up in ART-naive patients, 252 developed NHL. Of these, 47 (18.7%) developed Burkitt lymphoma, 27 (10.7%) developed diffuse large B-cell lymphoma, 9 (3.6%) developed primary brain lymphoma, and 169 (67.1%) developed unspecified NHL types. There were 547 deaths—67 (12.2%) were due to NHL and the rest were due to other causes. Incidence rates of NHL in ART-naive patients were 186 (95% CI, 180 to 193) cases per 100 000 person-years in uninfected patients, 187 (CI, 152 to 229) cases per 100 000 person-years in HBV-infected patients, 134 (CI, 123 to 145) cases per 100 000 person-years in HCV-infected patients, and 149 (CI, 88 to 252) cases per 100 000 person-years in patients co-infected with HBV and HCV. Figure 2 (pan-

Table 2. Hazard Ratios for NHL in ART-Naive and ART-Treated Patients With HIV Infection, by Chronic HBV or HCV Infection

Variable	Hazard Ratio for NHL (95% CI)	
	Cox Model	Cox Model With Censoring Weights
ART-naive patients (*n* = 52 479)		
Adjusted for baseline covariates*†		
Chronic HBV infection	1.02 (0.45–2.30)	1.33 (0.69–2.56)
Chronic HCV infection	0.89 (0.54–1.48)	0.67 (0.40–1.12)
Adjusted for baseline covariates* and time-dependent CD4 cell count and viral load		
Chronic HBV infection	0.99 (0.44–2.24)	1.28 (0.66–2.47)
Chronic HCV infection	0.87 (0.53–1.43)	0.66 (0.40–1.10)
ART-treated patients (*n* = 40 219)		
Adjusted for baseline covariates*†		
Chronic HBV infection	1.73 (1.08–2.80)	1.74 (1.08–2.82)
Chronic HCV infection	1.76 (1.23–2.51)	1.73 (1.21–2.46)
Adjusted for baseline covariates* and time-dependent CD4 cell count and viral load		
Chronic HBV infection	1.64 (1.02–2.65)	1.63 (1.01–2.64)
Chronic HCV infection	1.61 (1.12–2.30)	1.59 (1.11–2.27)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.
* Adjusted for sex, injection drug use, age, white race, baseline HIV viral load, and CD4 cell count.
† Hazard ratios with adjustment for all baseline covariates included in all models are provided in Tables 3 and 4 and Appendix Table 2 (available at www.annals.org).

els *A* and *B*) provides survival functions for NHL events in ART-naive persons with or without chronic HBV or HCV infection.

Table 2 shows results of multivariate models considering the outcomes of NHL in ART-naive 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 level. In ART-naive patients, the adjusted hazard ratios (with censoring weights applied) for NHL with chronic HBV and HCV infection were 1.33 (CI, 0.69 to 2.56) and 0.67 (CI, 0.40 to 1.12), respectively. Hazard ratios for NHL in models with time-updated CD4 cell count and HIV viral load were similar to those with adjustment for baseline covariates only. Hazard ratios with adjustment for all baseline covariates included in all models are provided in Tables 3 and 4 and Appendix Table 2 (available at www.annals.org).

The adjusted 5-year risk differences in rates of NHL for treatment-naive persons were 1.6 (CI, 0.3 to 5.9) cases per 1000 persons for those with chronic HBV infection and −1.8 (CI, −6.9 to −0.4) cases per 1000 persons for those with chronic HCV infection (Table 5).

Outcomes in ART-Treated Patients and Their Association With Chronic HBV and HCV Infection

During 191 257 person-years of follow-up, 310 ART-treated patients developed NHL. Of these, 59 (19.0%) developed Burkitt lymphoma, 33 (10.6%) developed diffuse large B-cell lymphoma, 20 (6.5%) developed primary brain lymphoma, and 198 (63.9%) developed unspecified NHL types. There were 1523 deaths, with 107 (7.0%) due to NHL and the rest due to other causes. Incidence rates of NHL in ART-treated patients were 149 (CI, 143 to 155) cases per 100 000 person-years in uninfected patients, 241 (CI, 198 to 293) cases per 100 000 person-years in HBV-infected patients, 200 (CI, 182 to 220) cases per 100 000 person-years in HCV-infected patients, and 294 (CI, 178 to 487) cases per 100 000 person-years in patients coinfected with HBV and HCV. Figure 2 (panels *C* and *D*) provides survival functions for NHL events in ART-treated patients with or without chronic HBV or HCV infection.

Table 3. Adjusted Hazard Ratio for NHL in ART-Naive Patients (*n* = 52 479)

Variable	Adjusted Hazard Ratio for NHL (95% CI)	
	Cox Model Stratified by Cohort	Cox Model With Censoring Weights
Chronic HBV infection		
Chronic HBV infection	1.02 (0.45–2.30)	1.33 (0.69–2.56)
Female sex	0.70 (0.47–1.03)	0.72 (0.50–1.03)
White race	1.14 (0.68–1.90)	0.93 (0.69–1.24)
HIV transmission via injection drug use	0.71 (0.44–1.13)	0.71 (0.45–1.12)
Age per 10-y increase	1.46 (1.29–1.67)	1.48 (1.32–1.65)
Baseline HIV RNA level per 1-$\log_{10}$ copy/mL increase	1.22 (1.05–1.42)	1.18 (0.98–1.44)
Baseline CD4 count per 0.100 × 10^9-cell/L increase	0.77 (0.72–0.83)	0.78 (0.71–0.85)
Chronic HCV infection		
Chronic HCV infection	0.89 (0.54–1.48)	0.67 (0.40–1.12)
Female sex	0.70 (0.47–1.03)	0.71 (0.50–1.02)
White race	1.14 (0.68–1.91)	0.92 (0.69–1.24)
HIV transmission via injection drug use	0.77 (0.43–1.38)	0.97 (0.54–1.73)
Age per 10-y increase	1.46 (1.29–1.66)	1.47 (1.32–1.65)
Baseline HIV RNA level per 1-$\log_{10}$ copy/mL increase	1.22 (1.04–1.42)	1.18 (0.97–1.43)
Baseline CD4 count per 0.100 × 10^9-cell/L increase	0.77 (0.72–0.83)	0.78 (0.71–0.85)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.

Chronic HBV and HCV infection were both associated with increased risk for NHL, with adjusted hazard ratios of 1.74 (CI, 1.08 to 2.82) for HBV infection and 1.73 (CI, 1.21 to 2.46) for HCV infection (Table 2). Hazard ratios for NHL in models with time-updated CD4 cell count and HIV viral load were also similar to those with adjustment for baseline covariates only.

The adjusted 5-year risk differences in rates of NHL for ART-treated patients were 5.9 (CI, 1.8 to 14.7) cases per 1000 persons for those with chronic HBV infection and 5.4 (CI, 1.6 to 14.1) cases per 1000 persons for those with chronic HCV infection (Table 5).

In sensitivity analyses that were based on different definitions of and exposure times to chronic HBV and HCV infection and that controlled for immortality bias, hazard ratios for NHL in treatment-naive and ART-treated co-infected patients were similar to those in the main models described earlier.

DISCUSSION

In this multicohort study, we found that ART-treated patients with chronic HBV or HCV infection were at greater risk for NHL than uninfected persons. Estimates in ART-naive patients were less certain, possibly due to the lower number of events, limited follow-up due to some patients initiating ART, or other unmeasured competing factors masking the effect of chronic HBV and HCV infection in this population. The median CD4 count at the time of NHL diagnosis was less than 0.250×10^9 cells/L in both ART-naive and treated patients co-infected with HBV and HCV, indicating that co-infected patients with NHL initiate ART late or have insufficient HIV viral control and immune recovery that may be due to multiple reasons. This unfavorable constellation is aggravated by the fact that chronic HBV infection attenuates immune recovery in ART-treated patients (14); whether this is also the case for chronic HCV infection is less clear (15, 16).

This study has several limitations. First, our analysis was based on a limited number of cohorts and a fraction of patients from COHERE who provided detailed information on chronic HCV and HBV infection. This precluded a more powerful analysis for co-infected patients who were ART-naive 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-naive persons are indicative of the competing risk for death due to any cause that we found in additional analyses (data not shown).

Second, suboptimal screening or data collection for hepatitis virus co-infection in HIV-infected populations is a problem and has been reported in different settings (17). Presence of chronic HCV and HBV infection was not measured uniformly at baseline across cohorts. However, we accounted for these limitations in extensive sensitivity analyses, all of which confirmed our findings. Most cohorts did not measure or collect HCV RNA levels to confirm chronic HCV infection status. Hepatitis B surface antigen and HCV clearance were not routinely measured in all cohorts, and HBV DNA levels in ART-treated patients and HCV RNA clearance after treatment were not routinely monitored or might have been underreported.

Third, a substantial proportion of ART-treated patients who are co-infected with HBV continue to express HBV DNA, and some might experience relapses (18). Reactivation of HBV in the presence of ART in severely immunosuppressed patients or HBV resistance to lamivudine might explain the observed increased risk for NHL in co-infected patients (19). Continued immune stimulation after antiviral treatment against HBV and HIV in co-infected patients might be another mechanism, given that chronic B-cell stimulation by HBsAg persists despite inhibition of viral replication by antiviral therapy, and indirect effects mediated by increased proinflammatory cytokine expression and secretion in

Table 4. Adjusted Hazard Ratio for NHL in ART-Treated Patients (n = 40 219)

Variable	Adjusted Hazard Ratio for NHL (95% CI)	
	Cox Model Stratified by Cohort	Cox Model With Censoring Weights
Chronic HBV infection		
Chronic HBV infection	1.73 (1.08–2.80)	1.74 (1.08–2.82)
Female sex	0.51 (0.36–0.73)	0.53 (0.37–0.75)
White race	0.97 (0.64–1.46)	0.95 (0.75–1.20)
HIV transmission via injection drug use	1.10 (0.72–1.68)	1.02 (0.68–1.54)
Age per 10-y increase	1.40 (1.26–1.55)	1.42 (1.28–1.57)
Baseline HIV RNA level per 1-$\log_{10}$ copy/mL increase	1.26 (1.09–1.46)	1.26 (1.08–1.48)
Baseline CD4 count per 0.100×10^9-cell/L increase	0.91 (0.84–0.98)	0.90 (0.82–0.99)
Chronic HCV infection		
Chronic HCV infection	1.76 (1.23–2.51)	1.73 (1.21–2.46)
Female sex	0.50 (0.35–0.72)	0.52 (0.37–0.74)
White race	0.92 (0.61–1.39)	0.94 (0.75–1.19)
HIV transmission via injection drug use	0.74 (0.45–1.21)	0.68 (0.42–1.11)
Age per 10-y increase	1.40 (1.26–1.55)	1.42 (1.28–1.57)
Baseline HIV RNA level per 1-$\log_{10}$ copy/mL increase	1.26 (1.09–1.46)	1.27 (1.08–1.49)
Baseline CD4 count per 0.100×10^9-cell/L increase	0.91 (0.84–0.98)	0.90 (0.82–0.99)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.

these patients may also contribute to lymphomagenesis (20–22). A limited number of cohorts routinely test HCV- and HBV-negative patients for incident infections or HCV reinfection after successful treatment (23, 24). All of these deficiencies would introduce misclassification bias; the direction of the bias, however, would be conservative in all instances and would result in an underestimate of the true association of HCV and HBV co-infection and NHL in ART-naive or treated patients.

Finally, because many NHL types were not classified, all NHL cases had to be coalesced, which precluded an analysis according to NHL subtype. In addition, ascertainment of NHL was not uniformly reported by all cohorts. Therefore, 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 infection are 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 patients. Previous studies not confirming such an association were smaller cohort or case–control studies (4, 25). Incidence rates for NHL in ART-treated versus treatment-naive patients did not differ substantially in patients with chronic HBV or HCV infection. This might be at least partially attributable to cases of unmasking NHL in the context of immune reconstitution syndrome when patients, as in our study population, initiate ART at a low CD4 cell count (26, 27). Patients co-infected with HBV and HCV are more likely to die of other causes due to the effect on mortality of injection drug use or other epidemiologic differences. Therefore, we used inverse probability weights to adjust for bias due to informative censoring.

Several meta-analyses of observational studies have investigated the association between chronic HBV and HCV infection in HIV-uninfected persons. The pooled odds ratios for chronic HBV infection and NHL in 5 cohort studies and 17 case–control studies were 2.06 (CI, 1.44 to 2.95) and 2.27 (CI, 1.74 to 2.94), respectively, but heterogeneity of 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 nationwide study from Sweden that was not included in the meta-analysis, patients with chronic HBV infection showed an increased standardized incidence ratio of 4.89 (CI, 3.81 to 6.18) for NHL (29). Incidence rates for NHL among HBV co-infected patients in our study indicate that the risk for NHL is about 10 times higher in the presence of HIV than in HBV monoinfected patients, regardless of whether ART is used (30).

In a meta-analysis of 15 case–control studies and 2 cohort studies in HIV-uninfected persons, the pooled odds ratios for chronic HCV infection and NHL were 2.5 (CI, 2.1 to 3.1) and 2.0 (CI, 1.8 to 2.2), respectively, with high heterogeneity of case–control study findings (1). Diffuse large B-cell lymphoma and marginal zone lymphoma are the NHL types most frequently associated with HCV infection. Several pathogenic mechanisms have been suggested to explain this association (31). Studies showing regression of B-cell NHL after HCV eradication strongly argue in favor of a causal relationship between HCV infection and these types of NHL (32). In HIV infection, B-cell NHL, particularly diffuse large cell subtypes, represents the majority of NHL cases, which is in line with a potential contribution of HCV infection to the pathogenesis of NHL. However, due to the large number of cases of uncharacterized NHL, this study lacked the power to detect an association between HCV infection and specific subtypes. Nonetheless, our findings do suggest that chronic HCV co-infection, along with immunosuppression, may be a relevant cause of 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 for NHL, which is the most frequently occurring AIDS-defining condition. Our study was not sufficiently powered to show such an association in ART-naive co-infected patients. Early diagnosis and treatment of HIV infection in conjunction with routine screening for chronic HBV and HCV infection is essential to further decrease NHL morbidity and mortality in HIV-infected persons. Uptake of chronic HCV treatment in co-infected patients in Europe has been low and primarily limited to those with higher CD4 counts (>0.350 × 10^9 cells/L) and advanced liver fibrosis, due to high failure and toxicity rates related to peginterferon- and ribavirin-based regimens as well as the high costs of direct-acting antiviral drugs (33–36). Our findings provide strong evidence that HCV co-infected patients with poor immune status

Table 5. Adjusted* Differences in Number of NHL Events per 1000 HIV-Infected Persons at 1, 2, 3, 5, 10, and 12 y of Follow-up, by Chronic HBV or HCV Infection

Variable	Difference in Rate of NHL per 1000 Persons (95% CI)	
	HBV-Positive vs. HBV-Negative Persons	HCV-Positive vs. HCV-Negative Persons
ART-naive patients		
1 y	0.8 (0.2 to 2.8)	−0.9 (−3.1 to −0.2)
2 y	0.9 (0.1 to 3.2)	−1.0 (−3.6 to −0.2)
3 y	0.6 (0.2 to 3.9)	−1.2 (−4.4 to −0.3)
5 y	1.6 (0.3 to 5.9)	−1.8 (−6.9 to −0.4)
10 y	2.5 (0.5 to 11.0)	−2.9 (−12.4 to −0.6)
12 y	2.4 (0.4 to 9.4)	−3.0 (−11.0 to −0.5)
ART-treated patients		
1 y	3.1 (1.0 to 7.9)	2.9 (0.9 to 7.5)
2 y	4.1 (1.3 to 10.3)	3.8 (1.2 to 9.9)
3 y	4.9 (1.5 to 12.0)	4.4 (1.4 to 11.5)
5 y	5.9 (1.8 to 14.7)	5.4 (1.6 to 14.1)
10 y	7.0 (2.2 to 17.4)	6.4 (1.9 to 16.6)
12 y	7.3 (2.3 to 17.6)	6.4 (1.9 to 16.8)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.
* Adjusted for age, sex, injection drug use, CD4 cell count, and HIV viral load.

or restoration (CD4 count <0.250 × 10^9 cells/L) are at high risk for NHL and death and deserve high priority for access to well-tolerated, interferon-free, direct-acting antiviral treatment programs similar to those for patients with advanced liver fibrosis or cirrhosis.

From Basel Institute for Clinical Epidemiology & Biostatistics, University Hospital Basel, Basel, Switzerland; University of Siena, Siena, Italy; University College London, London, United Kingdom; Innsbruck Medical University, Innsbruck, Austria; University of Athens, Athens, Greece; Université Bordeaux, Bordeaux, France; Stichting HIV Monitoring, Amsterdam, the Netherlands; University Hospital of Cologne, Cologne, Germany; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Rigshospitalet, Copenhagen, Denmark; IRCCS Ospedale San Raffaele, Milan, Italy; National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; University of Brescia, Brescia, Italy; University of Modena and Reggio Emilia, Modena, Italy; University of Barcelona, Barcelona, Spain; Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium; and University Hospital Zurich and University of Zurich, Zurich, Switzerland.

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Requests for Single Reprints: Heiner C. Bucher, MD, MPH, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Spitalstrasse 12, CH-4031 Basel, Switzerland; e-mail, heiner.bucher@usb.ch.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Wang and Bucher: Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Spitalstrasse 12, CH-4031 Basel, Switzerland.
Dr. De Luca: Department of Medical Biotechnologies, University of Siena, University Division of Infectious Diseases, Siena University Hospital, Viale M. Bracci 16, 53100 Siena, Italy.
Dr. Smith: Research Department of Infection and Population Health, University College London, Mortimer Market Centre off Capper Street, London WC1E 6JB, United Kingdom.
Dr. Zangerle: Medical University of Innsbruck, Department of Dermatology and Venereology, Anichstrasse 35, A-6020 Innsbruck, Austria.
Dr. Sambatakou: 2nd Department of Internal Medicine, Hippokration General Hospital, University of Athens, Evrou 63-67 Street, PC 11527, Athens, Greece.
Dr. Bonnet: Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint-André, CHU de Bordeaux, 1 rue Jean Burguet, 33075 Bordeaux, France.
Dr. Smit: Stichting HIV Monitoring, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
Dr. Schommers: University Hospital of Cologne, Department I of Internal Medicine, Kerpenerstrasse 62, 50937 Cologne, Germany.
Dr. Thornton: Research Department of Infection and Population Health, University College London, Royal Free Campus, Rowland Hill Street, London NW3 2PF, United Kingdom.
Dr. Berenguer: Infectious Diseases Unit, Head HIV Clinical Research Group, Hospital General Universitario Gregorio Marañón, Instituto Investigación Sanitaria Gregorio Marañón, Doctor Esquerdo 46, 28007 Madrid, Spain.
Dr. Peters: CHIP, Department of Infectious Diseases, Rigshospitalet, Finsencentret, Blegdamsvej 9, DK-2100, Copenhagen, Denmark.
Dr. Spagnuolo: Department of Infectious Diseases, IRCCS Ospedale San Raffaele, via Stamira d'Ancona 20, 20127 Milan, Italy.
Drs. Ammassari and Antinori: National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, via Portuense 292, 00149 Rome, Italy.
Dr. Quiros Roldan: Infectious Diseases Unit, Università degli studi di Brescia, Piazza del Mercato, 15 - 25121 Brescia, Italy.
Dr. Mussini: Infectious Diseases Clinics, University Hospital, via del Pozzo, 71 41124 Modena, Italy.
Dr. Miro: Infectious Diseases Service, Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain.
Dr. Konopnicki: Service de Maladies Infectieuses, Centre Hospitalier Universitaire Saint-Pierre, 322 rue Haute, 1000 Brussels, Belgium.
Dr. Fehr: Division of Infectious Diseases & Hospital Epidemiology, University Hospital Zurich, University of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.
Ms. Campbell: Steno Diabetes Center A/S, Niels Steensens Vej 2-4, DK-2820 Gentofte, Denmark.
Ms. Termote: VIH, Hépatites Virales et comorbidités, Epidémiologie clinique et santé publique, Université de Bordeaux, ISPED, 146, rue Léo Saignat – CS61292, 33076 Bordeaux cedex, France.

Author Contributions: Conception and design: A. De Luca, C. Smith, H.C. Bucher.
Analysis and interpretation of the data: Q. Wang, A. De Luca, C. Smith, F. Bonnet, P. Schommers, J. Fehr, H.C. Bucher.
Drafting of the article: Q. Wang, C. Smith, A. Antinori, C. Mussini, J. Fehr, H.C. Bucher.
Critical revision of the article for important intellectual content: Q. Wang, A. De Luca, C. Smith, H. Sambatakou, F. Bonnet, A. Thornton, J. Berenguer, L. Peters, V. Spagnuolo, A. Antinori, C. Mussini, J.M. Miro, D. Konopnicki, J. Fehr, H.C. Bucher.
Final approval of the article: Q. Wang, A. De Luca, C. Smith, R. Zangerle, H. Sambatakou, F. Bonnet, C. Smit, P. Schommers, A. Thornton, J. Berenguer, L. Peters, V. Spagnuolo, A. Ammassari, A. Antinori, E. Quiros Roldan, C. Mussini, J.M. Miro, D. Konopnicki, J. Fehr, M.A. Campbell, M. Termote, H.C. Bucher.
Provision of study materials or patients: H. Sambatakou, J. Berenguer, V. Spagnuolo, A. Antinori, E. Quiros Roldan, C. Mussini, J.M. Miro, D. Konopnicki, J. Fehr.
Statistical expertise: Q. Wang, C. Smith.
Obtaining of funding: H.C. Bucher.
Administrative, technical, or logistic support: J. Fehr, M.A. Campbell, H.C. Bucher.
Collection and assembly of data: R. Zangerle, F. Bonnet, P. Schommers, A. Thornton, L. Peters, A. Ammassari, J. Fehr, M.A. Campbell, M. Termote, H.C. Bucher.

Appendix: COHERE Steering Committee

Unless otherwise indicated, the committee members contributed to this work but did not author the manuscript.

Executive Committee

Stéphane de Wit (Chair, St. Pierre University Hospital), Jose M. Miró* (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Antonella Castagna (San Raffaele), Julia del Amo (CoRIS), Amanda Mocroft (EuroSIDA), Dorthe Raben (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre)

Steering Committee

Robert Zangerle* (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Linda Wittkop (ANRS CO13 HEPAVIH), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner Bucher* (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne-Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Bartmeyer (German ClinSurv), Nikoloz Chkhartishvili (Georgian National HIV/AIDS), Antoni Noguera-Julian (CORISPE-cat), Andrea Antinori* (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), Luis Prieto (Madrid PMTCT Cohort), Pablo Rojo Conejo (CORISPES-Madrid), Antoni

Soriano-Arandes (NENEXP), Manuel Battegay (SHCS), Andri Rauch (SHCS), Cristina Mussini* (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró* (PISCIS), Antonella Castagna (San Raffaele), Deborah Konopnicki* (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Anders Sönnerborg (Swedish InfCare), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH), David Haerry (European AIDS Treatment Group)

Project Leads and Statisticians

Juan Berenguer*, Julia Bohlius, Vincent Bouteloup, Heiner Bucher*, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Mary-Anne Davies, Julia del Amo, Maria Dorrucci, David Dunn, Matthias Egger, Hansjakob Furrer, Marguerite Guiguet, Sophie Grabar, Ali Judd, Ole Kirk, Olivier Lambotte, Valériane Leroy, Sara Lodi, Sophie Matheron, Laurence Meyer, Jose M. Miró*, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Roger Paredes, Andrew Phillips, Massimo Puoti, Michael Schomaker, Colette Smit*, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Marc van der Valk, Linda Wittkop, Natasha Wyss

Pediatric Cohort Representatives

Ali Judd, Pablo Rojo Conejo

Regional Coordinating Centers

Bordeaux RCC: Diana Barger, Christine Schwimmer, Monique Termote*, Linda Wittkop

Copenhagen RCC: Maria Campbell*, Nina Friis-Møller, Jesper Kjaer, Dorthe Raben, Rikke Salbøl Brandt

European AIDS Treatment Group

David Haerry

* Wrote the manuscript.

Appendix Table 1. Assessment of Chronic HBV Infection Based on Biomarkers

Hepatitis B Surface Antigen	Antibody to Hepatitis B Surface Antigen	Antibody to Hepatitis B Core Antigen	IgM Antibody to Hepatitis B Core Antigen	Interpretation
Negative	–	–	–	Not chronic regardless of other markers
–	Positive	–	–	Not chronic regardless of other markers
–	–	Negative	–	Not chronic regardless of other markers
Positive	Negative/missing	Missing	–	Acute or chronic
Positive	Negative/missing	Positive	Positive/missing	Acute or chronic
Positive	Negative/missing	Positive	Negative	Chronic

HBV = hepatitis B virus.

Appendix Table 2. Sensitivity Analyses With Adjusted Hazard Ratios for NHL

Variable	Hazard Ratio for NHL (95% CI)*				
	Sensitivity Analysis I†	Sensitivity Analysis II‡	Sensitivity Analysis III§	Sensitivity Analysis IV‖	Sensitivity Analysis V¶
ART-naive patients (*n* = 52 479)					
Chronic HBV infection	1.01 (0.59–1.72)	1.30 (0.67–2.49)	1.26 (0.53–2.96)	0.74 (0.24–2.22)	1.84 (0.91–3.69)
Chronic HCV infection	–	0.67 (0.40–1.12)	0.67 (0.38–1.17)	0.81 (0.44–1.51)	0.71 (0.36–1.39)
ART-treated patients (*n* = 40 219)					
Chronic HBV infection	1.73 (1.17–2.55)	1.43 (0.88–2.34)	1.66 (1.02–2.72)	1.70 (1.04–2.78)	1.32 (0.67–2.58)
Chronic HCV infection	–	1.32 (0.97–1.80)	1.73 (1.21–2.47)	1.72 (1.20–2.47)	1.79 (1.17–2.75)

ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.
* Cox model with censoring weights adjusted for sex, injection drug use, age, baseline HIV viral load, and CD4 cell count.
† The definition of chronic HBV infection was expanded to include patients with single measurements by combining information from other HBV markers (see Appendix Table 1).
‡ If the patient had ≥1 HBV or HCV measurement that indicated chronic infection, we assumed that the patient had been chronically infected for the whole follow-up period.
§ If the first HBV or HCV measurement indicated chronic infection, we assumed that the patient had been infected since baseline if the first hepatitis B surface antigen or HCV measurement was <6 mo after baseline or if the first measurement was >6 mo after baseline and the patient was an injection drug user. In the remaining patients, we reset the baseline to the date of the first measurement.
‖ Baseline date was reassigned to the first HBV or HCV measurement if this was later than baseline (45 107 ART-naive patients and 40 097 ART-treated patients were kept in the analyses).
¶ We excluded Patients enrolled in the cohort before 2000 were excluded (35 236 ART-naive patients and 27 537 ART-treated patients were kept in the analyses).