BRIEF REPORT

Hepatitis B Virus Infection Is Associated With Impaired Immunological Recovery During Antiretroviral Therapy in the Swiss HIV Cohort Study

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Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality in human immunodeficiency virus (HIV)–infected patients worldwide. It is unclear whether HIV-related outcomes are affected by HBV coinfection. We compared virological suppression and immunological recovery during antiretroviral therapy (ART) of patients of different HBV serological status in the Swiss HIV Cohort Study. CD4 cell recovery during ART was significantly impaired in hepatitis B surface antigen–positive patients and in those with anti-hepatitis B core antigen alone compared with HBV-uninfected patients, despite similar virological efficacy of ART. CD4 increase in patients with resolved HBV infection was similar to that in HBV-uninfected individuals.

Keywords. hepatitis B infection; antiretroviral therapy outcomes; immunological recovery; anti-hepatitis B core antigen alone.

Worldwide, hepatitis B virus (HBV) infection remains an important cause of liver-related morbidity and mortality in human immunodeficiency virus (HIV)-infected patients, despite the availability of potent HBV drugs [1, 2]. HIV infection accelerates the progression to liver fibrosis in HBV-infected patients and frequently leads to liver cirrhosis and hepatocellular carcinoma [3, 4].

The impact of chronic HBV infection on antiretroviral therapy (ART) outcomes in HIV-infected patients has been frequently debated. Although virological response to ART seems to be similar in HIV-monoinfected and HIV/HBV-coinfected patients, the impact of HBV infection on immunological recovery after the initiation of ART is controversial. Most studies have been limited by a short duration of follow-up and by inclusion of a small number of HIV/HBV-coinfected patients. Furthermore, no study has specifically compared immunological recovery in hepatitis B surface antigen (HBsAg)–negative patients exposed to HBV with those with chronic infection and with those without previous exposure to HBV.

The Swiss HIV Cohort Study (SHCS; www.shcs.ch) is a prospective cohort study with ongoing enrollment of HIV-positive adults in Switzerland since 1988 [5]. In that study, all patients are screened for HBV infection at baseline, and HIV viral loads and CD4 cell counts are measured every 3 to 6 months thereafter. We compared HIV-related outcomes during the first 3 years of ART between HIV-infected patients with or without evidence of previous or current HBV infection.

METHODS

Local ethics committees of all participating study sites approved the study, and written consent was obtained from all participants.

We included all patients who had a full serological assessment of HBV infection before the initiation of ART or within the first month of ART and excluded those who did not have at least a baseline and 1 follow-up CD4 count. Participants were categorized into 4 main groups: (1) HBV-uninfected (HBsAg- and anti-hepatitis B core antigen (HBc)–negative), (2) resolved HBV infection (HBsAg-negative, anti-HBc–positive, and anti-HBs–positive), (3) anti-HBc alone (HBsAg-negative, anti-HBc–positive, and anti-HBs–negative), and (4) HBsAg-positive. Because we intended to compare immunological recovery during the first 3 years of ART across the different HBV status groups, patients who experienced an HBsAg or anti-HBc seroconversion during follow-up were excluded.

Baseline characteristics of the 4 HBV status groups were compared using analysis of variance and χ^2 tests for continuous and categorical variables, respectively. The 2 ART outcomes evaluated were virological suppression (defined as an HIV viral load <50 copies/mL) during the first year of treatment and CD4

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cell count recovery during 3 years of follow-up. Differences in virological suppression between the 4 groups were evaluated using multivariable Cox regression models. CD4 cell count recovery during the 3 first years of ART for the 4 groups was compared using multivariable linear mixed-effect regression models. CD4 cell count response was square-root transformed, and trajectories were modeled using fractional polynomials. This model has been described in detail elsewhere [6]. Results are presented as marginal CD4 trajectories. All multivariable analyses were adjusted for sex, age category (16–29, 30–39, and ≥40 years), baseline CD4 cell count (<100, 100–199, and ≥200 cells/μL), HIV RNA category (≤4, 4–5, and ≥5 log copies/mL), education level (none, basic, and high-level professional education), HIV transmission group (men who have sex with men [MSM], intravenous drug users [IDU], heterosexuals, or other), region of origin (northwest/southern Europe, sub-Saharan Africa, southeast Asia, or other), Centers for Disease Control and Prevention stage, and hepatitis C virus (HCV) status (positive or negative anti-HCV antibodies). Multivariable models to evaluate CD4 recovery were additionally adjusted for the use of zidovudine (yes or no) as this drug has been shown in the SHCS to impair immunological recovery [7].

The following sensitivity analyses were performed: CD4 count increase was assessed in analyses restricted to patients who achieved HIV virological suppression under ART, to white MSM, to those treated with tenofovir (TNV), and stratified by baseline CD4 cell count category (greater than or less than 200 cells/μL), initial ART regimen, and HCV status. To assess the impact of ongoing HBV replication on immunological recovery, we repeated our analyses in the subset of HBV-coinfected patients with successful ART who had an available HBV DNA measurement after 1 year of ART (n = 159). Finally, we assessed relative CD4 cell count (expressed as percentage of total lymphocyte count) increase during ART. All statistical analyses were performed using Stata 12 (Stata Corp, College Station, TX).

RESULTS

Of 7671 patients who started ART, 4773 fulfilled the inclusion criteria of a complete serological HBV assessment and at least 1 follow-up CD4 cell count measurement. Of these, 287 (6.0%) were HBsAg positive, 633 (13.3%) anti-HBc alone, 1245 (26.1%) had a resolved HBV infection, and 2608 (54.6%) were HBV uninfected (Table 1). The proportion of patients from sub-Saharan

Table 1. Baseline Characteristics of Patients Starting Antiretroviral Therapy, by Hepatitis B Virus Status

Characteristic	HBV-Uninfected	Resolved HBV Infection	Anti-HBc Alone	HBsAg- Positive	*P* Value
Number of patients (%)	2608 (54.6)	1245 (26.1)	633 (13.3)	287 (6.0)	
Median age in years (IQR)	37 (31–44)	40 (33–47)	37 (32–43)	36 (31–42)	<.001
Female gender (%)	744 (28.5)	344 (27.6)	214 (33.8)	76 (26.5)	.03
Region of origin (%)					<.001
Northwest/southern Europe	2079 (79.9)	883 (71.0)	429 (67.9)	182 (63.4)	
Sub-Saharan Africa	230 (8.8)	217 (17.4)	142 (22.5)	63 (22.0)	
Southeast Asia	82 (3.2)	59 (4.7)	16 (2.5)	18 (6.6)	
Other	212 (8.1)	85 (6.8)	45 (7.1)	23 (8.0)	
Risk group (%)					<.001
Men who have sex with men	1053 (40.4)	549 (44.1)	139 (22.0)	109 (38.0)	
Heterosexual	1263 (48.4)	424 (34.1)	248 (39.2)	106 (36.9)	
Injecting drug users	178 (6.8)	218 (17.5)	226 (35.7)	58 (20.2)	
Other	114 (4.4)	54 (4.3)	20 (3.2)	14 (4.9)	
Professional education level (%)					<.001
None	130 (5.1)	108 (9.0)	80 (13.3)	42 (15.0)	
Basic	1650 (64.2)	790 (65.6)	415 (68.9)	169 (60.4)	
High	790 (30.7)	307 (25.5)	107 (17.8)	69 (24.6)	
Median CD4 count (IQR)	249 (134–364)	228 (113–340)	201 (107–302)	218 (92–322)	<.001
Median log human immunodeficiency virus–RNA (IQR)	4.78 (4.11–5.30)	4.75 (4.05–5.27)	4.80 (4.02–5.34)	4.82 (4.08–5.33)	.39
Centers for Diseases Control and Prevention stage (%)	387 (14.8)	240 (19.3)	124 (19.6)	46 (16.0)	.001
Antiretroviral therapy regimen					
Protease inhibitor–based (%)	1634 (62.7)	807 (64.8)	417 (65.9)	187 (65.2)	.33
Zidovudine-containing (%)	1024 (39.3)	533 (42.8)	314 (49.6)	121 (42.2)	<.001
Positive hepatitis C serology (%)	210 (8.1)	246 (19.8)	248 (39.2)	60 (20.9)	<.001

Abbreviations: HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IQR, interquartile range.

Africa was highest in the HBsAg-positive and anti-HBc alone groups, whereas IDUs were overrepresented in the anti-HBc alone group. Patients with anti-HBc alone had the lowest median CD4 cell count at the start of ART, followed by HBsAg-positive individuals. Baseline lymphocyte, leukocyte, and platelet counts differed by <10% among HBV status groups.

During the first year of ART, 2350 (90.1%) HBV-uninfected, 1083 (87.0%) with resolved HBV infection, 540 (85.3%) with anti-HBc alone, and 245 (85.4%) HBsAg-positive patients achieved virological suppression (<50 copies/mL; see Supplementary Table 1). In crude analyses, patients exposed to HBV infection were marginally less likely to experience virological suppression compared with HBV-uninfected patients. After adjustment for all baseline characteristics, there was no significant difference in time to virological suppression between HBV-uninfected patients and those in the other risk groups (resolved HBV infection: adjusted hazard ratio [aHR], 0.93 and 95% confidence interval [CI], .87–1.01; anti-HBc alone: 1.02 and 0.92–1.13; and HBsAg-positive: 0.94 and 0.82–1.08; Supplementary Table 1).

Included patients had a median of 4.3 (interquartile range [IQR], 3.5–5.1) CD4 cell count measurements performed per year, with similar measurement frequencies across HBV status groups. Estimated marginal CD4 cell count trajectories during the first 3 years of ART and by HBV status are shown in Figure 1. During the first 3 years of ART, HBV-uninfected patients and those with resolved HBV infection had significantly higher CD4 cell counts than patients in the other 2 groups (at 1 year: HBV-uninfected: 434 cells/μL and 95% CI, 427–440; resolved HBV infection: 429 and 420–436; anti-HBc alone: 406 and 393–416; HBsAg-positive: 392 and 374–410; at 3 years: HBV-uninfected: 504 and 496–511; resolved HBV infection: 496 and 485–506; anti-HBc alone: 461 and 446–475; HBsAg-positive: 449 and 428–469). The differences in absolute CD4 cell counts between HBV-uninfected and resolved HBV infection, anti-HBc alone or HBsAg positive patients were −8 cells/μL (95% CI, −21; 5), −43 (−60; −26), and −55 (−77; −33) after 3 years, respectively (see Supplementary Figure 1).

Differences in CD4 cell counts during the first 3 years of ART were consistent across sensitivity analyses (see Supplementary Figure 1). There was a trend for an impaired immune recovery in HBV-coinfected patients with a detectable HBV viral load after 1 year compared with those who were HBV suppressed (difference in CD4 counts at 1 year: −28 cells/μL [95% CI, −76; 20] and at 3 years: −45 [95% CI, −100; 9]; $P = .25$ and $P = .10$, respectively). Finally, HBV-uninfected patients and those with resolved HBV infection had higher relative CD4 cell counts compared with those of the other 2 groups, although differences were small (differences in CD4 percentage between HBV uninfected and resolved HBV infection, anti-HBc alone or HBsAg positive patients were 2% (95% CI, 1; 2), 3% (2; 4), and 3% (1; 4) after 3 years, respectively, $P < .001$).

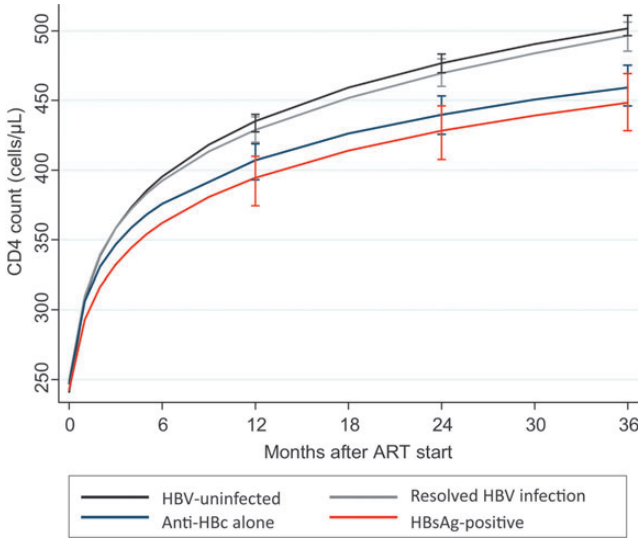

Figure 1. Immunological recovery during the first 3 years of antiretroviral therapy, by hepatitis B virus status. All analyses are adjusted for sex, age, region of origin, education level, transmission group, use of zidovudine, baseline CD4 count, log viral load, Centers for Disease Control and Prevention stage, and hepatitis C virus status.

DISCUSSION

In this nationwide representative, prospective cohort of HIV-infected patients, coinfection with HBV adversely affected baseline CD4 cell counts and immunological recovery during the first 3 years of ART. The impaired CD4 recovery was observed in HBsAg-positive patients as well as in those with anti-HBc alone. In contrast, virological response to ART was independent of HBV infection.

The impact of HBV coinfection on immunological response to ART has been a matter of debate. Although most studies, including a large study from the EuroSIDA Group, did not show any association between HBV coinfection and immunological recovery during ART [8, 9], a few studies, mainly from middle- and low-income countries, described an impaired CD4 response in HBV-coinfected subjects, at least during the first months of ART [10, 11]. Our study suggests that coinfection with HBV impairs CD4 recovery if immune responses fail to maintain detectable levels of anti-HBs antibodies. The differences in immunological recovery between the HBV groups were consistent across analyses in specific subpopulations, including HIV-suppressed patients, those treated with TNV, and MSM of white origin and in different baseline CD4 groups and treatment regimens. In addition, all analyses were adjusted for a wide range of confounders known to have an impact on CD4 recovery. In line with previous reports, time to HIV viral load suppression was independent of HBV status [8, 9]. The results from the sensitivity analyses and the similar virological

responses to ART strongly suggest that HBV coinfection is not only a marker for patients with unfavorable predictors of CD4 recovery but also directly impairs immunological recovery during ART. This is underlined by a trend for an impaired immune recovery in HBV-coinfected patients with a detectable HBV viral load after 1 year of ART compared with those with suppressed DNA levels.

Several mechanisms might contribute to impaired T-cell recovery in HBsAg-positive patients. First, HBV viral replication might adversely affect immune recovery. Apoptotic pathways are upregulated in chronic HBV infection [12] and could contribute to lower CD4 counts in untreated and treated HIV/HBV coinfection. Second, it is conceivable that chronic HBV infection contributes to some degree of systemic immune activation, which increases T-cell apoptosis [13]. Third, HBV-related liver fibrosis, which might increase splenic sequestration of lymphocytes, could contribute to impaired T-cell recovery. However, it is unlikely that splenic sequestration is the primary mechanism leading to impaired T-cell recovery during ART for the following reasons: impaired T-cell recovery was also observed in those with anti-HBc alone where significant liver fibrosis is very rare; total leukocyte, lymphocyte, and thrombocyte counts were similar at baseline; and relative CD4 T-cell count recovery was also significantly impaired. In our study, impaired immune recovery was also observed in patients treated with ART regimens that included TNV, which is highly effective in suppressing HBV replication [14]. However, even highly potent HBV drugs are not able to fully suppress HBV viremia during the first months of treatment, which could explain impaired CD4 recovery even in patients with optimal HBV treatment.

Interestingly, CD4 recovery was also impaired in the anti-HBc alone group. Previous reports have demonstrated that anti-HBc alone is associated with intermittent, mostly low-level HBV replication [15]. It is therefore possible that even low-level HBV replication and associated alterations of cytokine levels and/or regulatory pathways impair CD4 recovery. The observation that patients with anti-HBc alone are characterized by both failure to maintain sufficient levels of anti-HBs antibodies, and by impaired CD4 T-cell recovery suggests that several arms of the immune responses are impaired in these individuals. To our knowledge, this is the first study to report a clear association between the anti-HBc alone constellation and impaired CD4 cell recovery. This finding highlights the similarities, from an immunological standpoint, between HIV-infected patients with chronic HBV infection and those with previous exposure to HBV infection without detectable humoral immunity to HBV.

Our study did have limitations. Only a subset of HBsAg-positive patients had an HBV DNA measurement available after the first year of ART. Furthermore, HBV DNA levels were not available in most patients with anti-HBc alone, and therefore we could not assess the role of HBV replication in these individuals.

Taken together, our study suggests a negative impact of HBV coinfection on baseline immunological status before the start of ART and on CD4 cell recovery during the first 3 years of ART. This impairment in immunological recovery is sustained and consistent across different subpopulations, including patients who have an adequate virological response to ART. The differences in CD4 recovery among the HBV status groups after the first year of ART are not recompensated after 3 years of ART. This strengthens current recommendations to start ART early in HBV-coinfected patients. More research on the direct impact of HBV on cellular immunity is needed to understand why coinfection with HBV impairs immune recovery during ART and to determine whether intensified HBV treatment could reverse this effect.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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