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Rare clinically significant hepatic events and hepatitis B reactivation occur more frequently following rather than during direct-acting antiviral therapy for chronic hepatitis C: Data from a national US cohort

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Summary

Recently, cases of hepatitis B virus reactivation (HBVr) with direct-acting antiviral therapy (DAAs) for HCV have been reported. However, few data exist from large, Western cohorts. The study objectives were to evaluate the incidence of alanine aminotransferase (ALT) flares, clinically significant hepatic events, and HBVr among a national cohort of US veterans with prior exposure to HBV (anti-HBc+) treated with DAAs. We used a national administrative database to identify patients treated with DAAs from January 2014 through November 2016 and obtained clinical and demographic as well as HBV and HCV treatment data. HBVr was defined as an at least 1-log increase in HBV DNA titre. Among 17 779 anti-HBc+ patients, 17 400 were HIV– and 379 were HIV+. Among the HIV– patients, 17 266 (99%) were HBsAg– prior to DAA therapy and 134 were HBsAg+. Among HIV–, HBsAg– patients, ALT elevations greater than 10 times the upper limit of normal (ULN; 300 IU/mL) were rare and occurred more frequently after treatment completion: 31 cases (<0.1%) during vs 85 (0.6%) following treatment. Clinically significant

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

AUTHOR CONTRIBUTIONS

MS involved in study concept and design, analysis and interpretation of data, drafting of manuscript and critical revision of the manuscript for important intellectual content. KAF involved in study concept and design, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. DK involved in study concept and design, interpretation of data, drafting of manuscript and critical revision of the manuscript for important intellectual content.

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hepatic events defined as ALT increases >100 IU/L with total bilirubin >2.5 mg/dL occurred in 39 cases (0.3%), most often following DAA completion (n = 35 cases, 3/35 in setting of HCV relapse). Among 31 patients with post-DAA hepatic events without HCV relapse, 10 (32%) were confirmed unrelated to HBVr by HBsAg and/or HBV DNA testing, 1 (3%) confirmed due to HBVr, and 20 (65%) did not have documented HBV-related testing. One additional case of HBsAg – to + seroreversion was identified. Among HBsAg+ DAA recipients, 2/97 (2%), both with cirrhosis, experienced ALT elevations >300 IU/mL in the setting of HBVr. In conclusion, clinically significant hepatic events and HBVr were rare and much more likely among HBsAg– positive individuals. Anti-HBc + patients should be monitored for ALT flares and HBVr during and possibly for up to 6 months post-DAA therapy.

Keywords

corporate data warehouse; direct-acting antiviral; hepatitis B; hepatitis C; hepatotoxicity; human; veteran

1 | INTRODUCTION

Chronic concomitant hepatitis B (HBV) and hepatitis C (HCV) not infrequently coinfect individuals from endemic areas¹ or in those with a history of injection drug use.² HBV/HCV coinfection typically results in relative suppression of HBV viral replication^{3,4} most likely mediated by antiviral immunological responses which more potently suppress HBV replication rather than by direct intrahepatocytic viral competition.⁵ While pegylated interferon modulates antiviral effects against both hepatitis B and C, oral direct-acting antivirals (DAAs), available since 2013, specifically sterilize hepatocytes of HCV, raising the possibility of HBV reactivation (HBVr) in HBV/HCV coinfecting patients when HCV infection is eradicated.

On 4 October 2016, the United States Food and Drug Administration (FDA) issued a black box warning requiring screening for prior exposure and monitoring for HBVr in chronic HBV coinfecting (HBsAg+, anti-HBc+) and previously HBV-exposed (HBsAg–, anti-HBc+) individuals treated for chronic HCV with all-oral DAAs.⁶ The recommendation was based upon 24 reports of HBVr submitted to the FDA Adverse Event Reporting System (FAERS) database⁷ and other case reports.^{7–12} The reported cases included 2 patients who died and 1 who required liver transplantation. Three of the 24 had isolated anti-HBc+ raising concerns that even patients with long-controlled HBV infection may be at risk of reactivation from cccDNA reservoirs. In one of the largest published series of 327 HBV/HCV patients from Hong Kong, 0 of 317 HBsAg– individuals developed HBVr, although 7 developed clinical hepatitis from other causes¹² suggesting that the risk of reactivation lies nearly exclusively in HBsAg+ coinfecting individuals. The risk of reactivation in HBsAg+ was indeed 3 of 10 in this series.

As a result of these data, the American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) issued guidelines recommending HBV vaccination for all susceptible individuals, testing of HBV DNA before DAA therapy in any patient who could be actively replicating, and regular monitoring of

patients with HBV DNA titres to identify individuals who may require HBV-directed antiviral therapy. Recently published work by Belperio et al¹³ described a low risk of HBVr on HCV DAA therapy, however, only reported short-term, on-treatment data. As the data in this area are still scant and the frequency and severity of HBVr with all-oral DAAs in Western populations remain poorly described, the objectives of this study were to evaluate the incidence of alanine aminotransferase (ALT) flares, clinically significant hepatic events, and HBVr among a national cohort of Veterans with evidence of prior exposure to HBV (anti-HBc+) and treated with DAAs. We specifically focused on defining the incidence of clinically significant hepatic events (as HBV DNA is often not serially monitored in clinical practice) and to evaluate post-DAA treatment outcomes. We hypothesized that clinically significant ALT or HBV flares would be extremely rare among patients with resolved HBV infection (isolated anti-HBc+) and would be more common among patients with chronic HBV (HBsAg+).

2 | METHODS

2.1 | Study design/cohort identification

The Veterans Affairs health care system is the largest single provider of HCV care in the United States.¹⁴ This was a retrospective cohort study, which included all Veterans with prior exposure to HBV (anti-HBc+) who initiated all-oral DAAs for HCV from January 2014 through November 2016. Data were obtained by querying the corporate data warehouse (CDW), a centralized administrative and clinical repository of national VA data previously used by the study team with detailed methods previously described.^{15,16} Only the first course of DAA therapy was evaluated (patients receiving subsequent courses were excluded). Patients were also excluded if they had missing on-treatment ALT values, HBsAg status was missing, had previous exposure to hepatitis B-suppressing nucleos(t)ide analogues (lamivudine, adefovir, telbivudine, tenofovir or entecavir), had received any immunosuppressive regimens such as rituximab, infliximab, adalimumab and vincristine/doxorubicin within 2 years or if they received pegylated interferon either alone or in combination with the DAA regimen. The time of cohort entry was defined by the pharmacy release date of the first oral DAA regimen prescribed. The Institutional Review Board at the Corporal Michael J Crescenz VA Medical Center in Philadelphia approved the study protocol.

2.2 | Outcomes

Primary outcomes were as follows: (i) elevations in serum ALT (see below), (ii) clinically significant hepatic events defined as an increase of >100 IU/L of the serum ALT accompanied by an increase of the serum bilirubin level by >2.5 mg/dL, and (iii) 1-log increase in HBV DNA or absolute HBV DNA increase >10 000 IU/mL (4-log), or (iv) HBsAg+ seroreversion (HBsAg- to HBsAg+) while on DAA treatment and for up to 12 months post-DAA treatment. Due to the lack of standardized definitions of ALT “flares,” we evaluated several categories which we considered to be clinically significant: twofold and fourfold increases in consecutive ALT values while on DAA therapy (if >30 IU/L) as well as increases to 300 and 1000 IU/L. Post-treatment outcomes were evaluated for all patients with at least 12 weeks of post-treatment follow-up as well as selecting only patients with no

documented HCV relapses (N = 10 595 HIV– HBsAg– subjects) to avoid misclassification of hepatitis flares to HBV in the setting of relapsing HCV. Pharmacy release dates of DAA therapy were used to determine the timing of laboratory values relative to HCV treatment.

2.3 | Exposure variables

All demographic and clinical data were obtained from the CDW.¹⁷ Laboratory data included serial values of ALT, total serum bilirubin, HCV RNA and HBV DNA (for up to 12 months prior to DAA initiation, while on-treatment, and for up to 12 months post-treatment). Baseline laboratory values reported were the closest values that preceded the DAA start date; ALT data were available in 99% of cases within 30 days of DAA initiation. Cirrhosis was identified using a previously validated algorithm of at least 1 inpatient or 2 outpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or Tenth Revision (ICD-10) codes in the 12 months preceding DAA therapy.¹⁸ Decompensated cirrhosis was ascertained using a previously validated algorithm.¹⁹ Human immunodeficiency infection (HIV) was identified with ICD-9-CM or ICD-10 diagnosis codes. Alcohol use was ascertained using the maximum score on the alcohol use disorders identification test obtained from January 2014 through December 2016, and alcohol misuse was classified with a score of 4 for males and 3 females.²⁰ Sustained virologic response (SVR12) was defined as having a negative HCV viral load at least 12 weeks after DAA treatment completion. CDW pharmacy files were used to identify DAA prescriptions both with and without riba-virin (RBV) for all available DAA regimens such as sofosbuvir/ribavirin (SOF/RBV), sofosbuvir/simeprevir (SOF/SMV), sofosbuvir/ledipasvir (SOF/LDV), paritaprevir/ritonavir, ombitasvir +dasabuvir (PrOD), sofosbuvir/daclatasvir (SOF/DAC), elbasvir/grazoprevir (EBR/GZR) and sofosbuvir/velpatasvir (SOF/VEL). Outpatient pharmacy data were also used to determine whether patients were prescribed HBV antiviral therapy with oral nucleos(t)ide analogues such as lamivudine, adefovir, telbivudine, entecavir, tenofovir and emtricitabine/tenofovir or had previously been exposed to rituximab and/or tumour-necrosis factor antagonists.

2.4 | Statistical analysis

Descriptive statistics were calculated for all variables. Bivariate analyses were conducted with chi-square tests or Fisher's exact tests for categorical variables, *t* tests and Wilcoxon rank sum tests for continuous variables where appropriate. A 2-sided *P* value of <.05 was considered statistically significant. Analyses were performed using Stata 14.0 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Characterization of patient groups

During the study period, a total of 22 769 patients with prior HBV exposure (anti-HBc+) initiated a first course of HCV therapy, representing 29.8% of all DAA-treated patients. Among those, 870 were excluded for having unknown HBsAg status, 791 for receiving pegylated interferon, 299 for receiving fewer than 28 days of HCV DAA therapy, 2069 due to lack of serial, on-treatment ALT values, 961 for prior exposure to hepatitis B-suppressing nucleos(t)ides or for receipt of prior immunosuppressive therapy, yielding the final study

sample of 17 779 (Figure 1). Of HIV– negative subjects (N = 17 400), 134 were HBsAg– positive and 17 266 were HBsAg– negative. Of these, 10 092 (58%) were anti-HBs+, 6426 (37%) were anti-HBs– and 748 (5%) had no documented anti-HBs testing; for subsequent analyses, anti-HBs– and untested patients were analysed together. Given the potential impact of the presence of cirrhosis on prophylactic HBV nucleos(t) ide analogue treatment, we stratified the 134 HIV– negative HBsAg+ patients by the presence or absence of documented cirrhosis, finding 37 with a diagnosis of cirrhosis. Details of the HIV– infected subjects are provided in Figure 1.

3.2 | Baseline and treatment characteristics of HBsAg–, anti-HBc+ patients undergoing hepatitis C virus direct-acting antiviral therapy

The largest group of anti-HBc+ HCV DAA-treated patients were HBsAg– (N = 17 266). As shown in Table 1, median age was 63 years old and these patients were 98% male, 46% White, 47% Black, with the vast majority (83%) being infected with genotype 1 HCV. Cirrhosis was present in 4148 (24%), decompensated in 509 (3%), and liver cancer present in 37 (<1%). Active alcohol abuse was present in 8% of the cohort. The frequency of prescribed DAA regimens ± RBV was as follows: SOF/LDV: 62%; SOF/RBV: 11%; PrOD: 10%, EBR/ GZR: 8%, SOF/SMV: 5%; SOF/VEL: 3%, SOF/DAC: 1%. The median post-treatment follow-up time was 6.7 months (IQR 2.9–13.1) with 13 390 (78%) followed at least 12 weeks after completion of HCV DAA; 10 675 (62%) had documentation of HCV RNA 12 weeks after treatment completion, and of these, 93% had documented HCV cure (SVR12). These demographics did not differ between anti-HBs+ and anti-HBs– /unknown subjects. Demographics and treatment characteristics of HIV+ HBsAg– subjects are provided in Table S1.

3.3 | Hepatic events and HBV reactivation rates in HBsAg–, anti-HBc+ patients undergoing hepatitis C virus direct-acting antiviral therapy

We first examined the incidence of ALT elevations during and after antiviral therapy among HIV–, HBsAg– individuals (Table 2). During treatment, 2336 (14%) and 577 (3%) developed ALT elevations greater than 2 or 4 times the upper limit of normal (ULN), respectively. ALT elevations greater than 10 times the ULN (300 IU/ mL) or 1000 IU/mL were rare and occurred in 31 (<0.1%) and 3 (<0.01%), respectively. Only 4 individuals (<0.01%), developed clinically significant hepatic events, defined as an ALT 100 IU/mL with concomitant serum total bilirubin 2.5 mg/dL. Of these 4 patients, only 1 had HBV DNA viral load testing and was confirmed to have HBV reactivation (HBVr). No HBV testing was performed in the other 3 patients.

Following DAA treatment, the frequency of significant ALT elevations 300 IU/mL or 1000 IU/mL was higher compared to during treatment, occurring in 85 (0.6%) and 10 (0.1%) patients, respectively. Clinically significant hepatic events occurred in 35 (0.3%) patients, of whom 4 had HCV relapse, 1 had confirmed HBVr, 10 had negative testing for HBV DNA excluding HBVr and 24 did not have HBV-related testing. There were no differences in the incidence of clinically significant hepatic events nor documented HBVr events based on anti-HBs status.

3.4 | Hepatic events and HBV reactivation rates in HBsAg+ patients undergoing hepatitis C virus direct-acting antiviral therapy

A total of 134 HBsAg+ patients not already being treated with HBV-suppressing nucleos(t)ide analogues were treated with HCV DAA during the study period (Table 3), of whom 3 were HIV+ (all without cirrhosis); among the 131 that were HIV-; n = 97 (72%) did not have cirrhosis while n = 37 (28%) had cirrhosis. Age, gender, race, HCV genotype and HCV DAA regimens used were comparable to HBsAg- subjects. No HIV+ patients experienced an HBV-related clinical event and only 1 had a 2-fold ALT elevation after treatment completion. Of the 97 patients without cirrhosis, 8 (8%) developed ALT 4 times the ULN during treatment and 11 (15%) after treatment. A total of 2 individuals (2%) had ALT levels 300 IU/mL during or after treatment and 1 (1%) had ALT levels 1000 IU/mL during or after treatment. None of the HBsAg+ patients without cirrhosis developed clinically significant hepatic events. A total of 2 (5.4%) patients with cirrhosis had detectable HBV DNA at baseline and, therefore, had an indication for HBV nucleos(t)ide analogue treatment, but were not managed according to AASLD guidelines.

Overall, 13/134 (10%) HBsAg+ patients experienced HBVr during (n = 7) or after therapy (n = 6), clinically significant toxicity was observed in only 1 case who had underlying cirrhosis.

3.5 | Characteristics of anti-HBc+ patients with clinically significant hepatic events

Of the entire cohort of 17 779 subjects, 41 (0.2%) developed clinically significant toxicity in the absence of HCV relapse (Table 4); 39 of which occurred in HBsAg- subjects. Cirrhosis was strongly associated with clinically significant hepatic events ($P < .0001$), but there was no association with patient demographics, alcohol abuse or genotype. As noted previously, 1 case occurred in an HBsAg+ cirrhotic patient with a peak ALT of 1495 IU/mL and peak total bilirubin of 12.2 mg/dL. A second case confirmed as HBVr occurred in an HIV+ HBsAg- patient with cirrhosis with a peak ALT of 1540 IU/mL and peak total bilirubin of 17.3 mg/dL that occurred following completion of HCV DAA. The remaining 39 cases developed in non-HIV- infected HBsAg- patients with varying severity. Due to the rare frequency of HBV testing in the setting of ALT elevations, only 1/39 HBsAg- cases could be confirmed as HBVr with 10 cases confirmed unrelated to HBVr by negative HBV DNA and/or HBsAg testing, and 28 without sufficient testing to confirm or refute HBVr. In these cases, the median maximum ALT of these patients was 251 IU/mL (IQR 172-459, maximum 2452 IU/mL) and median total bilirubin was 5.1 mg/dL (IQR 3.4-14.4, maximum 28.1 mg/dL). Overall, clinically significant hepatic events in anti-HBc+ patients undergoing HCV DAA therapy was extremely rare (0.2% of cases), was strongly associated with the presence of cirrhosis, appeared unrelated to HBVr in 25% of cases and clearly related to HBVr in 8%, but could not be characterized through administrative data in 2/3 of cases.

3.6 | HBV reactivation events in anti-HBc+ patients undergoing hepatitis C virus direct-acting antiviral therapy

We identified 17 patients with HBV increases of at least 1-log (and/ or conversion from negative to detectable) during or after antiviral therapy (Table S3). This is most likely an underestimate, as baseline testing for HBV DNA was present in only 5% of total cases

(Table 2). HBVr was documented only in HIV– subjects, 4 of whom were HBsAg– (seroreversion) and 13 were HBsAg+. HBVr most frequently first occurred after treatment completion, occurring in 3/4 HBsAg– subjects and 9/13 HBsAg+ subjects. In only 1/4 HBsAg– patients, a significant elevation of ALT occurred (687 IU/mL) during HCV DAA therapy, which normalized after initiation of HBV nucleos(t)ide therapy. Two of four HBsAg– patients with HBVr had evidence of occult HBV with low-level HBV DNA detection prior to HCV DAA therapy. Seroreversion from HBsAg– to HBsAg+ was documented in 1/4 cases with HBVr and 1 additional case in which HBV DNA changes were not tested (data not shown). In HBsAg+ patients, HBVr was typically associated with mild hepatitis (median ALT 114 IU/mL, maximum ALT 245 IU/mL) with only 1 patient experiencing a total bilirubin 4.0 mg/ dL. All patients recognized to have HBVr received HBV nucleos(t)ide therapy and demonstrated normalization of ALT and total bilirubin (data not shown).

Six patients experienced HBVr with greater than 4-log increases in HBV DNA (Table 5). The age range of these 6 individuals was 56-64 years; 5/6 were HBsAg+ at baseline with HBV DNA titres of 0-27 900 IU/mL. Four of 6 had HCV genotype 1 and 2 of 6 genotype 2; 3 of 6 were cirrhotic, none had recent alcohol misuse. All were treated with sofosbuvir-based regimens and 5 of 6 achieved SVR12; 2 received concomitant HBV nucleos(t)ide therapy. The median HBV DNA increase was 1.6×10^6 IU/mL (IQR: 2.5×10^5 to 1.3×10^7). A total of $n = 3$ had ALT increases of 100 IU/L associated with HBVr. Notably, only 1 patient (HBsAg+ at baseline) had HBVr resulting in clinically significant hepatic events with a total absolute bilirubin increase to 18.6 mg/dL accompanied by a maximum ALT increase to 1492 IU/L. All 6 patients with 4-log or greater HBV DNA increases were initiated on HBV treatment concomitantly with DAA therapy ($n = 2$), during DAA therapy ($n = 3$) or after DAA therapy completion ($n = 1$). Five of 6 patients responded to HBV therapy with concomitant drops in HBV DNA ranging from 3 to 6 logs; 3 were noted to have HBV DNA values of 0 IU/mL at last follow-up. The single patient with HBVr and significant hepatic events was initiated on HBV therapy with emtricitabine/tenofovir 67 days after starting DAA therapy. He was noted to have a normal ALT and total serum bilirubin at 1.6 mg/ dL within 76 days of starting HBV therapy, and a normal ALT and total serum bilirubin of 0.6 mg/dL at last follow-up (553 after starting DAA therapy).

4 | DISCUSSION

In evaluating a large cohort of anti-HBc+ individuals with chronic HCV undergoing DAA therapy, we identified that the risk of HBVr defined by any increase of HBV DNA was extremely small (<0.1%) and occurred much more frequently, but not exclusively, in HBsAg+ individuals. For HBsAg– patients started on HCV DAA therapy, clinically significant hepatic events were extremely rare, occurring in 35 (0.3%) patients, of whom only 1 had confirmed HBVr but an additional 24 cases could not be excluded due to inadequate testing; thus, the maximal rate of HBVr associated with clinical hepatic events could approximate 0.2% of cases. Among HBsAg+ patients, the risk of HBVr was approximately 10% and was associated with 1 clinically significant hepatic events event in a patient with cirrhosis. In general, clinically significant hepatic events whether confirmed HBVr or not were much more common in cirrhotic patients.

Notably, anti-HBs were not protective against HBVr, and HBVr occurred significantly more often after completion of the HCV DAA course than during active therapy. The median time to HBVr was 112 days, more frequently occurring after the typical 84-day DAA therapy course. Seroreversions from HBsAg- to HBsAg+ status were also quite rare (documented in only 2 cases overall), were associated with ALT elevation in only 1 or the 2 cases and were not confirmed up until SVR12 follow-up. These data suggest that anti-HBc+ patients undergoing HCV DAA therapy should undergo a measurement of ALT and reassessment of HBsAg status at the time of SVR12 determination to exclude rare but possible subclinical seroreversion events.

We describe 6 patients with 4-log or greater HBV DNA increases, all but one of whom were HBsAg+ at the start of DAA therapy. Only 1 patient had concomitant clinically significant hepatic events and among the 5 patients with follow-up data, all responded to HBV therapy with decreases in HBV DNA, ALT and total serum bilirubin. When recognized, HBVr was highly responsive to nucleos(t)ide treatment and no serious sequelae could be identified from administrative data.

Overall, the low rates of adverse events we identify in this large Western cohort are comparable previously published data from China.¹² Although derived from a similar dataset as the previously published data from the VA on HBV reactivation,¹³ there are critical differences in our analysis that should be highlighted: (i) the previous analysis only evaluated patients during HCV DAA therapy until 7 days after therapy, likely missing many of the events we identified in longer follow-up of patients; (ii) relied on HBV DNA results which were missing in many patients with hepatitis flares who were not appropriately tested and therefore were unable to estimate the number of possibly undiagnosed HBVr events in the population; and (iii) used a different definition of HBVr requiring a 3-log change in HBV DNA titre. Similar to their findings, we found that most HBVr was associated with relatively modest increases in ALT.

As in all large, real-world observational datasets, most patients had incomplete HBV testing before, during and after HCV DAA initiation as well as infrequent initial/repeat testing at the time of clinical hepatitis events. Approximately 18% of veterans treated with HCV DAAs had no HBV testing results available within 5 years of HCV DAA treatment potentially leading us to underestimate the true incidence of HBV-related adverse events. Serial HBeAg data were not generally available and thus were not reported. Adverse events such as death and transplantation were not globally assessed for the cohort; however, among the patients with significant hepatic events and HBVr, serial assessment of pharmacy records and laboratory testing confirmed successful treatment with HBV therapy in all but 1 case that had no follow-up. SVR12 data were unknown for about one-third of patients at the time of data analysis, including among 10 patients with significant hepatic events; this could falsely overestimate attribution of hepatotoxicity to possible HBVr in the setting of undiagnosed HCV relapse. Lastly, we do not compare outcomes of anti-HBc+ to anti-HBc- patients, however, hepatotoxicity with DAAs is infrequently reported and more common in decompensated cirrhosis, which represents a minority of our cohort.^{21,22}

Based on the infrequency of clinically significant hepatic events in this large and diverse Western cohort of anti-HBc+ individuals, we propose several recommendations. First, we strongly concur with current recommendations for universal testing of HBsAg and anti-HBc prior to DAA initiation. Second, we recommend serial ALT determinations during HCV therapy and for at least 6 months after completion of therapy for all anti-HBc+ patients. Third, for HBsAg+ patients without cirrhosis and not currently on nucleos(t)ide therapy due to inactive chronic or immune-tolerant HBV, it is reasonable to follow serial ALT during and after DAA therapy and to continue HBV DNA and ALT testing indefinitely every 6 months as per the current AASLD HBV guidelines.²³ Fourth, HBsAg+ patients with cirrhosis should be pre-emptively treated with nucleos(t)ide analogues concomitant with HCV DAA therapy. Fifth, for HBsAg– individuals with resolved HBV, interval retesting for HBsAg and HBV DNA should be triggered by elevations of ALT during or after DAA therapy; furthermore, we recommend testing HBsAg status once more at the time of SVR12 determination to exclude subclinical seroreversion. We postulate that the above strategies may maximize identification of clinically significant HBVr without excessive testing burden, although the specific recommendations regarding the frequency and duration of post-DAA follow-up among those with resolved HBV should be informed by future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AUDIT-C	alcohol use disorder identification test
CDW	corporate data warehouse
DAA	direct-acting antiviral
EBR/GZR	elbasvir/grazoprevir
HBVr	hepatitis B virus reactivation
IQR	interquartile range
PrOD	paritaprevir/ritonavir, ombitasvir + dasabuvir
SOF/DAC	sofosbuvir/daclatasvir
SOF/LDV	sofosbuvir/ledipasvir
SOF/VEL	sofosbuvir/velpatasvir

SVR sustained virologic response

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FIGURE 1.

Identification and categorization of the study cohort. HBeAb, anti-HBe antibody; HCV, hepatitis C virus; DAA, direct-acting antivirals; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody

TABLE 1

Baseline demographics and characteristics of HIV– negative hepatitis B core antibody-positive (anti-HBc+) cohort stratified by hepatitis B surface antibody (anti-HBs) status

	Total (N = 17 266)	Anti-HBs–/unknown (N = 7174)	Anti-HBs+ (N = 10 092)
Age	63 (60-67)	64 (61-67)	63 (60-66)
Male, N (%)	16 902 (98)	7042 (98)	9860 (98)
Race, N (%)			
White	7882 (46)	3155 (44)	4727 (47)
Black	8097 (47)	3480 (49)	4617 (46)
Other	271 (2)	111 (2)	160 (2)
Unknown	976 (6)	412 (6)	564 (6)
Genotype, N (%)			
1	14 372 (83)	6051 (84)	8321 (82)
2	1444 (8)	560 (8)	884 (9)
3	838 (5)	303 (4)	535 (5)
4–6	171 (1)	64 (1)	107 (1)
Cirrhosis, N (%)	4148 (24)	1643 (23)	2505 (25)
Decompensated cirrhosis, N (%)	509 (3)	219 (3)	290 (3)
Hepatocellular carcinoma, N (%)	37 (0)	16 (0)	21 (0)
Alcoholism, N (%)	1386 (8)	553 (8)	833 (8)
Alcohol misuse, N (%) ^a	1376 (8)	548 (8)	828 (8)
Baseline total bilirubin (mg/dL), median (IQR)	0.9 (0.6-1.1)	0.9 (0.6-1.0)	1.0 (0.6-1.1)
Baseline ALT (IU/mL), median (IQR)	67 (34-81)	67 (35-80)	67 (34-82)
HCV direct-acting antiviral, N (%)			
PrOD	1711 (10)	753 (10)	958 (9)
EBR/GZR	1358 (8)	615 (9)	743 (7)
SOF/DAC	242 (1)	87 (1)	155 (2)
SOF/LDV	10 737 (62)	4471 (62)	6266 (62)
SOF/RBV	1802 (11)	694 (10)	1108 (11)
SOF/SMV	914 (5)	363 (5)	551 (5)
SOF/VEL	502 (3)	191 (3)	311 (3)
HCV DAA duration days, median (IQR)	85 (75-85)	85 (75-85)	85 (75-84)
Follow-up to 12 wk post-treatment, N (%)	13 390 (78)	5536 (77)	7854 (78)
SVR12 tested, N (%)	10 675 (62)	4364 (61)	6311 (63)
SVR12 (among tested), N (%)	9944 (93)	4079 (93)	5865 (93)

SOF/LDV, sofosbuvir/ledipasvir; PrOD, paritaprevir/ritonavir, ombitasvir +dasabuvir; SOF/DAC, sofosbuvir/ daclatasvir; EBR/GZR, elbasvir/grazoprevir; SOF/VEL, sofosbuvir/velpatasvir; DAA, direct-acting antiviral; IQR, interquartile range; SVR, sustained virologic response; ALT, alanine aminotransferase.

^a Alcohol misuse was identified with the alcohol use disorder identification test, and score 4 for males and 3 for females indicates hazardous drinking.

TABLE 2

Baseline demographics and characteristics of HIV-negative, hepatitis B core antibody-positive (anti-HBc+) cohort stratified by hepatitis B surface antibody (anti-HBs) status

During treatment	Total (N = 17 266)	Anti-HBs-/unknown (N = 7174)	Anti-HBs+ (N = 10 092)
ALT 2× ULN, N (%)	2336 (14)	922 (13)	1414 (14)
ALT 4× ULN, N (%)	577 (3)	236 (3)	341 (3)
ALT >300 IU/mL during treatment, N (%)	31 (0)	11 (0)	20 (0)
ALT >1000 IU/mL during treatment, N (%)	3 (0)	1 (0)	2 (0)
HBV DNA increase 1-log during therapy, N (%)	1 (0)	1 (0)	1 (0)
Significant hepatic events during therapy, N (%) ^a	4 (0.0)	1 (0.0)	3 (0.0)
HBV DNA flare	1	0	1
Undetermined cause	3	1	3
Post-treatment	Total (N = 13 390)	Anti-HBs-negative or unknown (N = 5536)	Anti-HBs+ (N = 7854)
ALT 2× ULN after treatment, N (%)	1264 (9)	509 (9)	755 (10)
ALT 4× ULN after treatment, N (%)	387 (3)	167 (3)	220 (3)
ALT >300 IU/mL after treatment, N (%)	58 (0.4)	23 (0.4)	35 (0.4)
ALT >300 IU/mL during or after treatment, N (%)	85 (0.6)	33 (0.6)	52 (0.7)
ALT >1000 IU/mL during treatment, N (%)	10 (0.1)	4 (0.1)	6 (0.1)
HBV DNA tested at baseline, N (%)	840 (5)	495 (7)	345 (3)
HBV DNA increase 1-log after therapy, N (%)	3 (0.0)	2 (0.0)	1 (0.0)
Significant hepatic events after therapy, N (%) ^a	35 (0.3)	11 (0.2)	24 (0.3)
Post-treatment ^b	Total (N = 10 595)	Anti-HBs-negative or unknown (N = 3930)	Anti-HBs+ (N = 6265)
ALT 2× ULN after treatment, N (%)	1102 (10)	445 (10)	657 (10)
ALT 4× ULN after treatment, N (%)	340 (3)	150 (3)	190 (3)
ALT >300 IU/mL after treatment, N (%)	50 (0.5)	19 (0.5)	30 (0.5)
ALT >300 IU/mL during or after treatment, N (%)	70 (0.7)	26 (0.7)	43 (0.7)
ALT >1000 IU/mL during treatment, N (%)	7 (0.1)	2 (0.1)	5 (0.1)
HBV DNA increase 1-log after therapy, N (%)	3 (0.0)	2 (0.0)	1 (0.0)
Significant hepatic events after therapy, N (%) ^a	31 (0.3)	10 (0.3)	21 (0.3)
HBV DNA flare, N (%)	1	0 (0)	1 (4.8)
Confirmed, N (%) no HBV DNA flare	10	2 (20.0)	8 (38.1)
Undetermined cause, N (%)	20	8 (80.0)	12 (57.1)

ALT, alanine aminotransferase.

^aSignificant hepatic events were defined as an increase in ALT >100 IU/L and increase in total bilirubin >2.5 µg/dL.

^bPost-treatment values reported for patients with complete ALT data in the absence of hepatitis C relapse

TABLE 3

Baseline demographics, characteristics and outcomes of HBsAg+/hepatitis B core antibody-positive (anti-HBc +) cohort stratified by HIV and cirrhosis Status

	HIV-negative		HIV-positive
	No cirrhosis (N = 97)	Cirrhosis (N = 37)	All noncirrhotic (N = 3)
Age	61 (58–66)	61 (59–65)	57 (56–58)
Male, N (%)	96 (99)	36 (97)	3 (100)
Race, N (%)			
White	50 (52)	29 (78)	2 (67)
Black	45 (46)	8 (22)	1 (33)
Asian	0 (0)	0 (0)	0 (0)
Other	1 (1)	0 (0)	0 (0)
Unknown	1 (1)	0 (0)	0 (0)
Genotype, N (%)			
1	79 (81)	30 (81)	2 (67)
2	6 (6)	4 (11)	0 (0)
3	7 (7)	3 (8)	1 (33)
4-6	1 (1)	0 (0)	0 (0)
Decompensated cirrhosis, N (%)	0 (0)	2 (5)	0 (0)
Hepatocellular carcinoma, N (%)	0 (0)	0 (0)	0 (0)
Alcoholism, N (%)	7 (7)	2 (5)	0 (0)
Alcohol misuse, N (%) ^a	7 (7)	2 (5)	0 (0)
Baseline total bilirubin (mg/dL), median (IQR)	0.6 (0.5–0.7)	1.6 (0.7–1.6)	0.5 (0.5–0.5)
Baseline ALT (IU/mL), median (IQR)	71 (33–94)	78 (37–92)	54 (40–68)
HCV direct-acting antiviral, N (%)			
PrOD	7 (7)	0 (0)	0 (0)
ELB/GZP	10 (10)	0 (0)	0 (0)
SOF/DAC	1 (1)	0 (0)	0 (0)
SOF/LDV	59 (61)	22 (59)	3 (100)
SOF/RBV	12 (12)	11 (30)	0 (0)

	HIV-negative		HIV-positive
	No cirrhosis (N = 97)	Cirrhosis (N = 37)	All noncirrhotic (N = 3)
SOF/SIM	2 (2)	4 (11)	0 (0)
SOF/VEL	6 (6)	0 (0)	0 (0)
HCV DAA duration days, median (IQR)	81 (74–83)	105 (81–95)	81 (80–83)
Follow-up to 12 wk post-treatment, N (%)	74 (76)	36 (97)	3 (100)
SVR12 tested, N (%)	66 (68)	31 (84)	2 (67)
SVR12 (among tested), N (%)	66 (68)	31 (84)	2 (67)
During treatment	HIV-negative		HIV-positive
	No cirrhosis (N = 97)	Cirrhosis (N = 37)	All noncirrhotic (N = 3)
HBV DNA tested at baseline, N (%)	43 (44)	12 (32)	2 (67)
ALT 2× ULN, N (%)	3 (3)	1 (3)	0 (0)
ALT 4× ULN, N (%)	8 (8)	4 (11)	0 (0)
ALT >300 IU/mL during treatment, N (%)	2 (2)	1 (3)	0 (0)
ALT >1000 IU/mL during treatment, N (%)	1 (1)	1 (3)	0 (0)
HBV DNA increase 1-log during therapy, N (%)	4 (4)	0 (0)	0 (0)
Significant hepatic events during therapy, N (%) ^b	0 (0)	1 (3)	0 (0)
HBV DNA flare, N (%)	0 (0)	1 (100)	0 (0)
Undetermined cause, N (%)	0 (0)	0 (0)	0 (0)
Post-treatment	HIV-negative		HIV-positive
	No cirrhosis (N = 74)	Cirrhosis (N = 36)	All noncirrhotic (N = 3)
>Twofold increase in ALT (IU/L), N (%)	24 (32)	16 (44)	1 (33)
>Fourfold increase in ALT (IU/L), N (%)	11 (15)	8 (22)	0 (0)
ALT >300 IU/mL after treatment, N (%)	2 (2)	1 (3)	0 (0)
ALT >300 IU/mL during or after treatment, N (%)	1 (1)	0 (0)	0 (0)
ALT >1000 IU/mL during treatment, N (%)	1 (1)	0 (0)	0 (0)
HBV DNA increase 1-log after therapy, N (%)	3 (4)	6 (17)	0 (0)
Significant hepatic events after therapy, N (%) ^a	0 (0)	1 (3)	0 (0)
HBV DNA flare, N (%)	0 (0)	1 (100)	0 (0)

	HIV-negative		HIV-positive
	No cirrhosis (N = 97)	Cirrhosis (N = 37)	All noncirrhotic (N = 3)
Confirmed no HBV DNA flare, N (%)	0 (0)	0 (0)	0 (0)
Undetermined cause, N (%)	0 (0)	0 (0)	0 (0)

ALT, alanine aminotransferase; DAA, direct-acting antiviral.

^a Alcohol misuse was identified with the alcohol use disorder identification test, score 4 for males and 3 for females indicates hazardous drinking.

^b Clinically significant hepatic events was defined as ALT >100 IU/L and total bilirubin >2.5 µg/dL.

TABLE 4

Baseline demographics, characteristics and outcomes of patients with clinically significant hepatic events

	HIV-negative			HIV-positive
	HBsAg-			
	HBsAg-or untested (N = 12)	Anti-HBs+ (N = 27)	HBsAg+ (N = 1)	HBsAg-(N = 1)
Cirrhosis, N (%)	9 (75)	22 (81)	1 (100)	1 (100)
Decompensated cirrhosis, N (%)	1 (8)	0 (0)	0 (0)	0 (0)
Hepatocellular carcinoma, N (%)	0 (0)	1 (4)	0 (0)	0 (0)
Alcoholism, N (%)	1 (8)	1 (4)	0 (0)	0 (0)
Alcohol misuse, N (%) ^a	1 (8)	1 (4)	0 (0)	0 (0)
Baseline total bilirubin (mg/dL), median (IQR)	1.0 (0.8–1.2)	3.1 (2.3–3.6)	0.7 (0.7–0.7)	N/A
Baseline ALT (IU/mL), median (IQR)	89 (54–98)	77 (45–103)	62 (62–62)	90 (90–90)
HCV direct-acting antiviral, N (%)				
PrOD	0 (0)	1 (4)	0 (0)	0 (0)
ELB/GZP	0 (0)	0 (0)	0 (0)	0 (0)
SOF/DAC	0 (0)	0 (0)	0 (0)	0 (0)
SOF/LDV	6 (50)	13 (48)	0 (0)	1 (100)
SOF/RBV	4 (33)	5 (19)	0 (0)	0 (0)
SOF/SIM	2 (17)	8 (30)	1 (100)	0 (0)
SOF/VEL	0 (0)	0 (0)	0 (0)	0 (0)
HCV DAA duration days, median (IQR)	91 (81–86)	129 (78–137)	55 (55–55)	142 (142–142)
Follow-up to 12 wk post-treatment, N (%)	12 (100)	26 (96)	1 (100)	1 (100)
SVR12 tested, N (%)	11 (92)	23 (85)	1 (100)	1 (100)
SVR12 (among tested), N (%)	6 (55)	18 (78)	1 (100)	1 (100)
Event timing				
Significant hepatic events during therapy, N (%) ^a	1 (8)	3 (11)	1 (100)	0 (0)
Significant hepatic events after therapy, N (%) ^a	11 (92)	24 (89)	1 (100)	1 (100)
Laboratory changes				

	HIV-negative		HIV-positive	
	HBsAg-			
	HBsAg-or untested (N = 12)	Anti-HBs+ (N = 27)	HBsAg+ (N = 1)	HBsAg-(N = 1)
Maximum ALT (IU/mL) during treatment, median (IQR)	35 (24–80)	51 (29–95)	1495 (1495–1495)	80 (80–80)
Maximum ALT (IU/mL) during treatment	1594	909	1495	80
Maximum total bilirubin (mg/dL) during treatment, median (IQR)	1.1 (1.0–1.7)	2.3 (1.5–4.1)	12.2 (12.2–12.2)	3.2 (3.2–3.2)
Maximum total Bilirubin (mg/dL) during treatment	8.1	11.8	12.2	3.2
Maximum ALT (IU/mL) after treatment, median (IQR)	255 (207–492)	247 (162–381)	132 (132–132)	1540 (1540–1540)
Maximum ALT (IU/mL) after treatment	1427	2452	132	1540
Peak total Bilirubin (mg/dL) after treatment, median (IQR)	8.7 (3.9–15.1)	4.3 (3.2–14.2)	4.1 (4.1–4.1)	17.3 (17.3–17.3)
Maximum total Bilirubin (mg/dL) after treatment	21.9	28.1	4.1	17.3
HBV DNA tested at baseline, N (%)	0 (0)	1 (4)	1 (100)	0 (0)
HBV DNA tested during event, N (%)	1 (4)	1 (4)	0 (0)	0 (0)
HBV DNA increase 1-log during therapy, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
HBV DNA increase 1-log after therapy, N (%)	0 (0)	1 (4)	1 (100)	1 (100)
HBV DNA increase 4-log after therapy, N (%)	0 (0)	0 (0)	1 (100)	0 (0)
Related to HBVr	0	1	1	1
Not related to HBVr (tested and negative)	1	9	0	0
Undetermined cause	11	17	0	0

ALT, alanine aminotransferase; DAA, direct-acting antiviral.

^aClinically significant hepatic events was defined as ALT >100 IU/L and total bilirubin >2.5 µg/dL.

TABLE 5

Characteristics of 6 patients with >4 log increases in HBV DNA during treatment or after treatment with direct-acting antivirals

Age	Cirrhosis	Alcohol misuse ^a	Baseline HBsAg+	Pre-DAA treatment baseline HBV DNA (IU/mL)	Max HBV DNA increase (IU/mL)	Max ALT increase (IU/L)	Max total bili increase (µg/dL)	Time between start of DAA therapy and HBV DNA flare (d)	Time between start of DAA therapy and HBV treatment initiation (d)	HBV therapy	Outcome
58	No	No	No	0	10 902	15	0.1	28	38	TDF	HBV DNA cleared
64	Yes	No	Yes	Unknown	18 900	3	0.4	45	45	TDF	Unknown
53	No	No	Yes	27 900	254 304	9	1.1	316	Started concomitant with DAA	FTC/TDF+ETV	HBV DNA dropped by 3-log
60	Yes	No	Yes	0	1 559 851	241	0.2	194	195	ETV	HBV DNA dropped by 6-log
53	No	No	Yes	0 ^b	2 885 983	24	0	168	Started concomitant with DAA	TDF	HBV DNA cleared
56	Yes	No	Yes	2361	>22 000 000	1467	17.3	57	67	FTC/TDF	HBV DNA cleared

DAA, direct-acting antiviral; HCV, hepatitis C virus; TDF, tenofovir; FTC, emtricitabine; ETV, entecavir; bili, bilirubin; ALT, alanine aminotransferase.

^aAlcohol misuse was identified with the alcohol use disorder identification test, score 4 for males and 3 for females indicates hazardous drinking.

^bHBV DNA was available within 1.5 y of DAA start date.