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Association Between Severe Serum Alanine Aminotransferase Flares and Hepatitis B e Antigen Seroconversion and HBV DNA Decrease in Untreated Patients With Chronic HBV Infection

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Abstract

BACKGROUND & AIMS: The incidence and outcomes of alanine aminotransferase (ALT) flares during the natural history of chronic HBV infection has not been determined in a large, racially heterogeneous group of patients in North America.

METHODS: We collected data from the Hepatitis B Research Network—an observational cohort study of untreated adults with chronic HBV infection enrolled at 21 sites in the United States and Canada. Clinical and laboratory data were collected from 1587 participants (49.9% male, 73.7% Asian, 35.2% genotype B infection, mean age of 42.6 years) at enrollment, at weeks 12 and 24, and every 24 weeks thereafter for a planned 5 years of follow up (from January 2011 through May

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2019.02.005>.

Conflicts of interest

The authors disclose no conflicts.

2016). Participants were excluded if they had a history of hepatic decompensation, hepatocellular carcinoma, solid organ or bone marrow transplantation, chronic immune suppression, or antiviral therapy within 6 months before enrollment. Levels of ALT were measured in serum samples and flares were defined as at least 10 times the upper limit of normal (300 U/L in males and 200 U/L in females).

RESULTS: ALT flares occurred in 102 participants (6%), with 31 flares (30%) occurring at baseline. The 4-year cumulative incidence of ALT flares was 5.7%. The median peak level of ALT was 450 U/L (25th–75th percentile, 330 U/L to 747 U/L) with a maximum of 2578 U/L. In multivariable analysis, factors associated with the occurrence of an ALT flares were: male sex (odds ratio [OR], 3.02; $P=.0007$), higher baseline HBV DNA values (OR per log₁₀, 1.41; $P<.0001$), at risk alcohol use (OR, 2.27 vs none or moderate; $P=.02$), and higher FIB-4 values (OR, 1.85 per log₂; $P<.0001$). Older age was associated with lower odds of an ALT flare (OR, 0.63 per 10 years; $P=.004$). Rate of decrease in level of HBV DNA by 1 log₁₀ or more (59 vs 23 per 100 person-years for HB e antigen (HBeAg)-positive vs HBeAg-negative patients; $P=.003$) and HBeAg loss (47 vs 15 per 100 person-years; $P=.002$) were higher in patients with an ALT flare than in patients without, but the rate of HBsAg loss was similar (4 vs 2 per 100 person-years; $P=.26$). No hepatic decompensation, liver transplants, or deaths were observed in participants with ALT flares.

CONCLUSION: In a large racially heterogeneous cohort of adults with chronic HBV infection, the cumulative incidence of severe ALT flares was low and associated with greater decreases in HBV DNA and loss of HBeAg, but not with loss of HBsAg.

Keywords

Biomarker; Prognosis; Immune Response; HBRN

Chronic hepatitis B virus (HBV) infection affects more than 250 million individuals, with different prevalence rates depending on the geographic region.¹ The chronicity of infection may be due to interplay between host immune responses and the virus. Accordingly, the course is often complicated by increases in transaminases termed *flares* or acute exacerbations of HBV infection, which can occur spontaneously, during or after antiviral therapy, in the setting of immunosuppression, and pregnancy.² Various definitions of flares exist, such as alanine aminotransferase (ALT) level $>10\times$ the upper limit of normal (ULN), ALT $>5\times$ ULN, or >3 -fold increase from baseline.^{3–6} The clinical presentation of ALT flares also varies from no symptoms to liver failure and death; thus, physicians need to understand patient factors and clinical outcomes because there may be a need for close monitoring and antiviral treatment.^{6–10} The primary aims of this study were to determine the incidence and characterize the features and outcomes of ALT flares (ie, $>10\times$ ULN) in a large multi-ethnic cohort of chronic HBV infected adults.

Methods

The Hepatitis B Research Network and Adult Cohort Study Design

The Hepatitis B Research Network (HBRN) is a research consortium funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) involving 21 clinical sites

in the United States and Toronto, Canada. The HBRN does not enroll patients with a history of hepatic decompensation, hepatocellular carcinoma, solid organ or bone marrow transplantation, chronic immunosuppression, or human immunodeficiency virus.¹¹ The HBRN adult cohort study is an observational study of hepatitis B surface antigen (HBsAg)–positive participants who were not on antiviral therapy during the previous 6 months of enrollment but could be started after enrollment. Participants with acute hepatitis B were excluded for this analysis.

Baseline Evaluation and Definitions

The HBRN cohort evaluation includes a detailed medical history, physical examination, and laboratory tests using a structured questionnaire at enrollment and every 6 months thereafter. ALT flares were defined as ALT >300 U/L in male patients or >200 U/L in female patients, ie, roughly 10× the ULN, as described in the American Association for the Study of Liver Diseases Hepatitis B practice guidelines.¹² The HBRN Adjudication Committee, composed of members from the HBRN Steering Committee, reviewed the clinical and laboratory data associated with ALT flares to establish that the event met predefined criteria and to determine the most likely cause. In cases of ALT flares, participants were assessed every 4 weeks until resolution of ALT flare, with regular scheduled follow-up thereafter. In case of ALT flares >1000 U/L or total bilirubin >2.5 mg/dL, the follow-up intervals were every 2 weeks until ALT levels were <1000 U/L and then every 4 weeks thereafter as described above.

Statistical Analysis

Descriptive statistics are reported as means (standard deviation) or medians (25th and 75th percentiles) for continuous variables and frequencies (percentages) for categorical variables. Participants were at risk of ALT flare until the earliest time point of ALT flare, antiviral treatment initiation, or the last study visit, whichever came first. For the study, 3 separate sub-cohorts were used to address 3 specific aims.

Aim 1.—The cumulative probability of an ALT flare (>10× ULN) was estimated by using the product-limit estimate.

Aim 2.—Potential predictive factors for ALT flare (>10× ULN) measured between 4 and 52 weeks before the ALT flare were studied. Additional exclusions were having ALT flare at baseline (n = 31) and participants who had ALT flare outside the 4- to 52-week interval. Furthermore, non-ALT flare participants who did not have ALT value recorded within 4- to 52-week follow-up were excluded. The latter was to avoid categorizing a participant without ALT value within the 4- to 52-week follow-up as a non-flare. Generalized estimating equations were used to account for multiple visits per patient and to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). Models were fit both including and excluding ALT at the visit before ALT flare as a potential predictor. Because ALT defined the event (ie, ALT flare), the results of the model excluding ALT are presented. The predictive performances of the models were estimated under the receiver operating characteristic curve.

Aim 3.—The associations of ALT flare with the following outcomes were examined: antiviral therapy initiation (at the discretion of the clinician), HBV DNA decrease >1 log from baseline, hepatitis B e antigen (HBeAg) loss, HBsAg loss, hepatic decompensation (development of variceal bleeding, ascites or hepatic encephalopathy, jaundice defined as bilirubin levels >2.5 mg/dL), liver transplant, and death. An event was considered to be associated with ALT flare if it occurred within 48 weeks with a 12-week window of the ALT flare, which corresponded to when clinical visits were scheduled (ie, every 24 weeks).

Event rates are presented in person-years (PYR) calculated by the number of participants with an event divided by the total amount of years of follow-up for all participants at risk for an event. The 95% CIs were calculated by using the Poisson model, and statistical significance was set at 5%. Analyses were performed with SAS 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline and Alanine Aminotransferase Flare Characteristics

There were 1918 untreated adult chronic HBV infected participants enrolled into the HBRN cohort between January 2011 and May 2016. Figure 1 shows 1587 untreated participants meeting inclusion and exclusion criteria who were at risk of having an ALT flare, among whom 102 met our definition of ALT flare. Ten (10%) of these participants had a second flare during follow-up, and 2 had more than 2 flares. After additional exclusion criteria, 1193 participants were included in the prediction analysis (Aim 2), 67 of whom had a flare within 4–52 weeks.

Table 1 reports the values of the 1587 participants at risk for ALT flare and the 1193 participants included in the prediction analysis. Among the 1587, the mean age at enrollment was 42.6 years (standard deviation, 12.7), 792 (49.9%) were male, 1167 (73.7%) were Asian, 1179 (75.3%) were HBeAg negative at baseline, and 311 (22.1%) had the inactive carrier HBV phenotype. The median ALT at baseline was 33 U/L (interquartile range [IQR], 22–52), mean log₁₀ HBV DNA was 4.30 IU/mL (standard deviation, 2.30), and 1044 participants (77.4%) had F1 disease based on the FIB-4 score. Participants had the following major HBV genotypes: 244 A (15.4%), 558 B (35.2%), 474 C (29.9%), and 110 D (6.9%). Similar baseline characteristics were seen for the 1193 participants included in the prediction analysis and between e-antigen status (Table 1, Supplementary Tables 1 and 2). The median peak ALT during a flare was 450 U/L (IQR, 330–747), and maximum was 2578 U/L, with the evolution of ALT flares illustrated in Figure 2. The adjudication committee scored 3 ALT flares unrelated to chronic HBV infection (2 pregnancy related and 1 due to hepatitis D superinfection), ie, there was no superinfection with hepatitis A, C, or E infection, no evidence of autoimmune hepatitis, other autoimmune diseases (Wilson's disease), and no alcoholic hepatitis or biliary disease (gallstones).

Incidence and Predictors of Alanine Aminotransferase Flare

The cumulative incidence of ALT flares was 3.6%, 4.5%, 5.2%, and 5.7% at years 1, 2, 3, and 4, respectively. Factors independently associated with increased odds of ALT flare are

shown in Table 2: male sex (OR, 3.02; 95% CI, 1.59–5.74; $P = .0007$), higher HBV DNA values (OR per log₁₀, 1.41; 95% CI, 1.24–1.60; $P < .0001$), at-risk alcohol use (vs none or moderate OR, 2.27; 95% CI, 1.16–4.42; $P = .02$), and higher FIB-4 values (OR, 1.85 per doubling of FIB-4 value; 95% CI, 1.38–2.49; $P < .0001$). Older age was associated with lower odds of ALT flare (OR, 0.63 per 10 years; 95% CI, 0.46–0.86; $P = .004$). The overall C-statistic (area under the curve) for our model was 0.82. The estimated probability of having an ALT flare is shown in Supplementary Figure 1 for a fixed set of clinical and demographic data.

Alanine Aminotransferase Flares and Clinical Outcomes

Initiation of therapy.—In the ALT flare group, 43 of 88 participants were started on antiviral treatment within 48 weeks (+ 12-week window) after ALT flare, corresponding to 85 per 100 PYR among HBeAg-positive and 69 per 100 PYR among HBeAg-negative participants. The choices for therapy in participants with ALT flare were up to the investigator in each case and included nucleos(tide) analogues monotherapy, peginterferon, and combination therapy. In the group with no ALT flares, 214 participants were started on therapy within 48 weeks (+ 12-week window) after baseline, corresponding to 35 per 100 PYR among HBeAg-positive participants and 9 per 100 PYR among HBeAg-negative participants. The predominant therapy in this group was nucleos(tide) analogues monotherapy. The rate of antiviral treatment was higher for the ALT flare vs non-ALT flare group: in HBeAg-positive participants, 85 vs 35 per 100 PYR, $P < .0001$; in HBeAg-negative participants, 69 vs 9 per 100 PYR, $P < .0001$ (Tables 3 and 4). Further subanalysis as to why some participants in the ALT flare group were treated did not find any other statistically significant characteristics such as age, sex, HBeAg status, or amplitude of ALT flare to account for treatment decisions. The median ALT at treatment initiation was 338 U/L (IQR, 197–557) and 348 U/L (IQR, 133–606) in HBeAg-positive and -negative participants, respectively.

HBV DNA decrease.—For the 47 HBeAg-positive ALT flare participants with available data, 32 (68.1%) had HBV DNA decrease >1 log compared with baseline, of whom 12 (59 per 100 PYR) were untreated and 20 (167 per 100 PYR) were treated. In the 351 participants free of ALT flares, there were 127 (36.2%) who had HBV decrease >1 log compared with baseline, of whom 54 (23 per 100 PYR) were untreated and 73 (171 per 100 PYR) were treated. Thus, the rate of HBV decrease >1 log was greater in untreated ALT flare participants vs untreated non-ALT flare participants (59 per 100 PYR vs 23 per 100 PYR; $P = .003$). There was no statistical difference in rates of HBV DNA decrease >1 log between ALT and non-ALT flare participants after initiating HBV treatment (167 vs 171 per 100 PYR; $P = .91$). For the 33 HBeAg-negative ALT flare participants, 24 (72.7%) had HBV DNA decrease >1 log compared with baseline, of whom 10 (59 per 100 PYR) were untreated and 14 (129 per 100 PYR) were treated. In the 1115 participants free of ALT flares, there were 267 (23.9%) who had HBV decrease >1 log compared with baseline, of whom 203 (23 per 100 PYR) were untreated and 64 (132 per 100 PYR) were treated. The rate of HBV decrease >1 log was greater in untreated ALT flare participants vs untreated non-ALT flare participants (59 per 100 PYR vs 23 per 100 PYR; $P = .003$). There was no

statistical difference in rates of HBV DNA decrease >1 log between ALT and non-ALT flare participants after initiating of HBV treatment (129 vs 132 per 100 PYR; $P = .94$).

Hepatitis B e antigen loss.—For the 51 HBeAg-positive ALT flare participants with available data, 13 (25.5%) experienced HBeAg loss, of whom 10 (47 per 100 PYR) were untreated and 3 (30 per 100 PYR) were treated. Among the non-ALT flare participants, 46 of 340 (13.5%) had HBeAg loss, of whom 33 (15 per 100 PYR) were untreated and 13 (33 per 100 PYR) were treated. The difference in HBeAg loss rates between untreated participants with and without ALT flare was statistically significant (47 vs 15 per 100 PYR; $P = .002$) but not in those who were treated (30 vs 33 per 100 PYR; $P = .87$). The amplitude of ALT flare was not associated with HBeAg loss ($P = .57$) (Supplementary Table 3).

Hepatitis B surface antigen loss.—The HBsAg loss rate was low, and there was no difference between participants with and without ALT flare. Of the 47 HBeAg-positive ALT flare participants, 1 participant (5 per 100 PYR) had HBsAg loss, which occurred in the absence of treatment. Similarly, only 1 participant (9 per 100 PYR) out of a total of 31 HBeAg-negative ALT flare participants had HBsAg loss, which also occurred in the untreated group. In the non-ALT flare group, 4 of 292 HBeAg-positive participants had HBsAg loss, with 2 (1 per 100 PYR) receiving treatment, whereas 15 of 904 HBeAg-negative participants (2 per 100 PYR) had HBsAg loss, all occurring in those not receiving treatment (Tables 3 and 4).

Hepatic decompensation/transplant/death.—In our cohort, with primarily early stage disease, 0 participants in the ALT flare and 4 in non-ALT flare group had hepatic decompensation, liver transplant, or death (2 HBeAg positive and 2 HBeAg negative participants). There was 1 HBeAg positive and 2 HBeAg negative participants with jaundice defined as a serum bilirubin level >2.5 mg/dL.

Discussion

The HBRN provides the first opportunity to study ALT flares in a large, racially diverse population. The cumulative incidence of ALT flares $>10\times$ ULN was 5.7% after 4 years of follow-up. Advancing fibrosis, male sex, younger age, higher HBV DNA levels, and at-risk alcohol use were associated with higher odds of experiencing ALT flare. Moreover, we observed higher rates of HBV DNA decrease >1 log and HBeAg loss in participants experiencing ALT flare. ALT flares did not lead to any hepatic decompensation, need for liver transplant, or death in this cohort with mostly minimal fibrosis.

With the advent of sensitive HBV assays and new therapeutic agents, our understanding of the natural history, clinical outcomes, and management of ALT flares in chronic HBV infection has evolved. The clinical spectrum of ALT flares has been reported to vary from no symptoms to liver failure and death, posing a clinical dilemma in deciding whom to treat and when.^{6–10} Yet no study has ever been performed to assess incidence, prediction, and outcome of flares in the natural history of a large multi-ethnic population with chronic HBV infection.

In this cohort, treatment initiation was significantly more common in the ALT flare group in both HBeAg-positive and HBeAg-negative participants. However, 49% of ALT flare participants (treatment was at the discretion of the site investigator) were not treated, and this did not lead to hepatic decompensation, transplant, or death. Furthermore, we did not find any significant clinical, demographic, or virologic differences between treated and non-treated participants (data not shown). Our results should be interpreted in the context of a cohort with relatively mild disease (77.4% had FIB-4 values <1.45), and that ALT flares were part of the natural history of chronic HBV infection because we excluded ALT flares during/after antiviral therapy and in the setting of immunosuppression, chemotherapy, or superimposed infection. Thus, from this study no conclusions can be drawn as to when treatment is needed in patients with ALT flares.

The findings in the current study differ from previous studies where ALT levels at baseline along with HBV genotypes and mutations in the precore and core promoter region of the HBV genome were associated with ALT flares.^{13–16} Our study incorporates recently accepted gender norms for ALT that are lower than the ULN in laboratory reference ranges, and this might have contributed to differences reported between the studies. HBV genotype did not show any relationship to flares, and there were insufficient data to assess the role of precore or core promoter mutations. Information on the predictive probability of a patient having an ALT flare would be valuable information to the clinician to determine if/when follow-up is warranted because there are prognostic factors (ie, advanced liver disease) for mortality associated with ALT flares.¹⁷ Figure 3 represents the estimated percentages of participants having ALT flare $>10\times$ ULN during a 1-year period according to sex and age in a specific HBV population.

ALT flares are a result of interplay between host immune responses and viral replication. It has been previously shown that ALT flares are also the results of dynamic changes of the innate and adaptive immune responses with HLA-I restricted, cytotoxic T lymphocyte mediated immune cytolysis of HBV antigens expressing hepatocytes.^{18–20} Thus, higher ALT levels may represent a more vigorous immune response against HBV, and although it is still unknown what triggers the immune response, there may be an opportunity to eliminate or suppress HBV DNA, HBeAg, and HBsAg during this phase. Lok and Lai⁵ have previously shown 30% HBeAg seroconversion rate at the end of a 12-month period after an ALT flare. In this cohort, the HBeAg loss rate for participants with ALT flare was 47%, and was greater than participants without ALT flare (15%), during a 1-year observation period, suggesting ALT flares are associated with a host immune response leading to HBeAg loss. Similarly, HBV DNA decrease was also greater in ALT flare participants, supporting the hypothesis there may be a combination of immune mediated cytolysis of HBV containing hepatocytes along with the action of cytokines and endogenous interferon in abolishing HBV gene expression and replication.

Previous studies identifying factors predicting HBeAg loss and HBV decrease after ALT flare included alpha-fetoprotein >100 ng/mL, presence of bridging necrosis on liver biopsy, degree of ALT elevation, and HBV genotype B. However, these studies were done before the advent of effective antiviral therapy, and because of the evolving treatment paradigm, current

practice would dictate to initiate therapy before ALT levels peaked or remained elevated for a period of time.^{16,17}

The current analysis adds to our knowledge about ALT flares in the natural history of chronic HBV infection. Although ALT flares are infrequent, they do occur and can be associated with significant increases in ALT values (Supplementary Table 3; 32% had ALT flares $>30\times$ ULN), which probably warrant close monitoring in patients with advanced liver disease because of the risk of decompensation. However, in patients with minimal fibrosis, ALT flares may represent a beneficial host response to clear or reduce viral proteins (HBeAg, HBV DNA), so it may be possible to monitor these patients because ALT flares rarely lead to clinically significant decompensation. We must stress the current study was not designed to identify the optimal patient whom we may observe for the beneficial outcomes of ALT flares vs those whom we should treat.

The strengths of this study include the prospective nature, the adjudication of all ALT flares, along with standardized follow-up in a large racially diverse population, with diverse HBV genotypes and disease phases increasing the generalizability of results. Limitations include potential selection bias because patients with more severe liver disease were excluded; however, unlike previous studies, we involved 21 clinical sites with varying practice patterns to limit this bias. There may also be an element of referral bias due to the ALT flare itself; however, we attempted to control for this bias by stratifying our analysis to entry and follow-up flares and also by reporting our incidence rates after excluding the baseline entry flares. Moreover, immunologic data, central assessment of hepatitis A and E infection, and baseline histology to correlate ALT flares were not available, which would have strengthened the study. Last, because of the protocols of the HBRN, many participants are followed every 24 weeks; thus there is a potential to miss ALT flares.

To conclude, in the natural history of a large multi-ethnic cohort of untreated adult HBV participants, the frequency of ALT flares was low, with the odds of experiencing ALT flare being higher in male patients, younger age, higher HBV DNA levels, at-risk alcohol use, and higher fibrosis. ALT flares led to higher rates of HBeAg loss and HBV DNA decrease but not HBsAg loss. ALT flares did not lead to hepatic decompensation, liver transplants, or death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

ALT	alanine aminotransferase
CI	confidence interval
HBeAg	hepatitis B e antigen
HBRN	Hepatitis B Research Network
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
IQR	interquartile range
OR	odds ratio
PYR	person-years
ULN	upper limit of normal

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What You Need to Know

Background

Flares in level of alanine aminotransferase (ALT) occur during progression of chronic hepatitis B virus (HBV) infection. However, flares in ALT have not been well-characterized in a large population of North American patients.

Findings

ALT flares did not lead to loss of HB surface antigen (HBsAg), hepatic decompensation, liver transplantation, or death in patients with chronic HBV infection. However, they were associated with higher rates of decrease in level of HBV DNA and loss of HBeAg.

Implications for patient care

The frequency of ALT flares is low in patients with chronic HBV infection, but flares are associated with clearance or reductions in viral proteins (HBeAg) and HBV DNA. It might be prudent to monitor, rather than treat, patients with minimal fibrosis, because ALT flares rarely lead to significant decompensation.

Figure 1.

Participants included in the analyses. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBRN, Hepatitis B Research Network; HBV, hepatitis B virus.

Figure 2.

(A) Individual ALT values during follow-up in those participants experiencing ALT flare (*red line* denotes moving average ALT of participants). (B) Individual ALT values during follow-up in those participants experiencing ALT flare (*red line* denotes moving average ALT of participants; *gray lines* denote treatment initiation; *yellow line* denotes moving average ALT of untreated participants; *yellow dashed line* denotes moving average ALT of treated participants). ALT, alanine aminotransferase.

Figure 3.

Estimated predicted probabilities of ALT flare >10x ULN in relation to HBV DNA. ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal.

Table 1.

Baseline Characteristics of Study Participants

Variable	Participants meeting study criteria (n = 1587)	Participants meeting criteria for ALT flare prediction (n = 1193)
Age, mean, y (SD)	42.6 (12.7)	42.8 (12.5)
Sex (%)		
Male	792 (49.9)	577 (48.4)
Female	795 (50.1)	616 (51.6)
Of whom were pregnant ^a	74 (9.3)	44 (7.1)
Race (%)		
White	168 (10.6)	137 (11.5)
Black	210 (13.3)	159 (13.4)
Asian	1167 (73.7)	865 (72.6)
Other	39 (2.5)	30 (2.5)
BMI, mean, kg/m ² (SD)	24.9 (4.7)	24.8 (4.7)
HBeAg status (%)		
Negative	1179 (75.3)	937 (79.6)
Positive	386 (24.7)	240 (20.4)
HBV phenotype (%) ^b		
Immune tolerant	53 (3.8)	40 (3.8)
HBeAg positive active	273 (19.4)	160 (15.1)
HBeAg negative active	239 (17.0)	170 (16.0)
Inactive carrier	311 (22.1)	256 (24.2)
Indeterminate	529 (37.7)	434 (40.9)
HBV genotype (%)		
A	244 (15.4)	182 (15.3)
B	558 (35.2)	432 (36.2)
C	474 (29.9)	344 (28.8)
D	110 (6.9)	86 (7.2)
Other	46 (2.9)	36 (3.0)
Serum HBsAg levels (log ₁₀ U/L), mean (SD)	3.30 (1.16)	3.26 (1.15)
FIB-4, categorized (%)		

Variable	Participants meeting study criteria (n = 1587)	Participants meeting criteria for ALT flare prediction (n = 1193)
<1.45	1044 (77.4)	821 (80.8)
1.45–3.25	262 (19.4)	177 (17.4)
>3.25	42 (3.1)	18 (1.8)
HBV DNA (<i>log</i> 10 IU/mL), mean (SD)	4.30 (2.30)	4.05 (2.21)
ALT (U/L), median (IQR)	33 (22, 52)	30 (22, 46)
NIAAA alcohol risk level (%) ^c		
None	1153 (73.0)	861 (72.6)
Moderate	314 (19.9)	236 (19.9)
At-risk	112 (7.1)	89 (7.5)
Smoking (%)		
Current	169 (10.7)	114 (9.6)
Former	292 (18.5)	218 (18.3)
Never	1120 (70.8)	857 (72.1)

ALT, alanine aminotransferase; BMI, body mass index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IQR, interquartile range; NIAAA, National Institute on Alcohol Abuse and Alcoholism; SD, standard deviation.

^aPregnancy status at baseline.

^bImmune tolerant: HBeAg positive, ALT levels <ULN on 2 occasions at least 6 months apart and HBV DNA levels >10⁶ IU/mL; HBeAg positive active: HBeAg positive, ALT levels >2 times ULN on 2 occasions at least 6 months apart, and HBV DNA levels >10⁴ IU/mL; HBeAg negative active: ALT levels >2 times ULN on 2 occasions at least 6 months apart and HBV DNA levels >10³ IU/mL; Inactive carrier: HBeAg negative, ALT levels <ULN, and HBV DNA <10³ IU/mL on 2 occasions at least 6 months apart; Indeterminate: participants who did not fit into one of these categories.

^cAlcohol consumption amount was categorized into (1) none (fewer than 12 drinks in lifetime and/or no alcohol in last 12 months), (2) moderate use (had 12 or more drinks in the past year and used alcohol in past 12 months but not in At-risk category), and (3) at-risk use based on the NIAAA definition of heavy drinking.

Table 2.

Predictors of Serum ALT Flares >10× ULN

Variable	Univariate analysis Odds ratio (95% CI); P value	Multivariable analysis Odds ratio (95% CI); P value
Age (vs 10 y younger)	0.67 (0.53–0.83); .0003	0.63 (0.46–0.86); .004
Sex		
Non-pregnant female	Reference; .007	Reference; .003
Male	2.24 (1.30–3.86); .004	3.02 (1.59–5.74); .0007
Female, pregnant	1.99 (0.88–4.48); .10	1.82 (0.63–5.29); .27
Race		—
Asian	Reference; .84	
White	0.91 (0.40–2.05); .82	
Black	0.88 (0.37–2.07); .77	
Other/unknown	0.41 (0.06–3.12); .39	
BMI (vs 1 unit lower)	0.98 (0.92–1.04); .44	—
FIB-4 (vs 1/2 value)	1.30 (0.94–1.78); .11	1.85 (1.38–2.49); <.0001
FIB-4		—
<1.45	Reference; .004	
1.45–3.25	1.63 (1.09–2.44); .02	
>3.25	3.74 (1.54–9.08); .004	
HBeAg status (positive)	5.02 (2.98–8.46); <.0001	—
HBV DNA, log10 (vs 1 log lower)	1.46 (1.33–1.61); <.0001	1.41 (1.24–1.60); <.0001
HBsAg level (vs 1 log lower)	1.78 (1.31–2.40); .0002	—
HBV genotype		—
B	Reference; .42	
A	0.60 (0.26–1.39); .23	
C	1.20 (0.66–2.16); .55	
D	0.46 (0.10–2.16); .32	
Other	1.39 (0.38–5.04); .62	
Alcohol use		
Non/moderate drink	Reference	
At-risk drinker	2.14 (1.24–3.70); .007	2.27 (1.16–4.42); .02

Variable	Univariate analysis Odds ratio (95% CI); <i>P</i> value	Multivariable analysis Odds ratio (95% CI); <i>P</i> value
Smoking		—
Never	Reference; .14	
Current	1.68 (0.87–3.25); .12	
Former	1.59 (0.94–2.70); .09	
BCP mutation ^a	0.94 (0.49–1.80); .85	
PC stop mutation ^a	0.68 (0.34–1.34); .26	

NOTE. Reference *P* values represent global *P* values.

ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

^aNumber of missing values for BCP and PC stop mutation was greater than 50%; therefore it was not used in multivariable modeling.

Table 3.
Association Between ALT Flares >10× ULN and Clinical Outcomes for HBeAg-Positive Participants

Clinical outcome	Participants free of ALT flares			Participants with ALT flares			P value
Treatment initiation	N = 353			N = 51			<.0001
	N	PYR	Rate	N	PYR	Rate	
Specific treatments	104	297.2	35	26	30.7	85	
TDF or ETV		83			19		
Other NA		10			4		
PEG-IFN		4			1		
Combination		7			2		
HBV DNA decline (>1 log)	N = 351			N = 47			
	N	PYR	Rate	N	PYR	Rate	
Untreated ^a	54	235.1	23	12	20.4	59	.003
Treated ^a	73	42.6	171	20	12.0	167	.91
HBeAg loss	N = 340			N = 51			
	N	PYR	Rate	N	PYR	Rate	
Untreated ^a	33	218.9	15	10	21.2	47	.002
Treated ^a	13	39.3	33	3	10.1	30	.87
HBsAg loss	N = 292			N = 47			
	N	PYR	Rate	N	PYR	Rate	
Untreated ^a	2	199.8	1	1	19.2	5	.18
Treated ^a	2	37.6	5	0	8.5	0.0	1.0
Disease progression ^b	2			0			1.0

ALT, alanine aminotransferase; Combination, being in >1 of the previous therapy groups in the course of the 48-week window; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon (including pegylated [PEG] form); Other NA, telbivudine, adefovir, emtricitabine, truvada, lamivudine; PYR, person-years; TDF, tenofovir; ULN, upper limit of normal.

^aEvent rates per 100 PYR. Event was considered to be related to ALT flare if occurring within 48 weeks ($\pm$ 12-week window) of ALT flare. Participants may contribute PYR as both treated and untreated.

^bDisease progression is defined as composite outcome of hepatic decompensation (variceal bleeding, ascites, hepatic encephalopathy), death, or transplant.

Table 4.

Association Between ALT Flares >10× ULN and Clinical Outcomes for HBeAg-Negative Participants

Clinical outcome	Participants free of ALT flares			Participants with ALT flares			P value
Treatment initiation	N = 1172			N = 37			<.0001
	N	PYR	Rate	N	PYR	Rate	
Specific treatments	110	1190.7	9	17	24.7	69	
ETV or TDF		87			11		
Other NA		8			5		
PEG-IFN		10			0		
Combination		5			1		
HBV DNA decline (>1 log)	N = 1115			N = 33			
	N	PYR	Rate	N	PYR	Rate	
Untreated ^a	203	889.7	23	10	16.9	59	.003
Treated ^a	64	48.5	132	14	10.8	129	.94
HBsAg loss	N = 904			N = 31			
	N	PYR	Rate	N	PYR	Rate	
Untreated ^a	15	761.8	2	1	11.0	9	.14
Treated ^a	0	41.4	0.0	0	9.3	0.0	1.0
Disease progression ^b	2			0			1.0

ALT, alanine aminotransferase; Combination, being in >1 of the previous therapy groups in the course of the 48-week window; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon (including pegylated [PEG] form); NA, nucleoside analogue (entecavir and tenofovir); Other NA, telbivudine, adefovir, emtricitabine, truvada, lamivudine; PYR, person-years; ULN, upper limit of normal.

^aEvent rates per 100 PYR. Event must occur within 48 weeks (± 12-week window) of ALT flare. Participants may contribute PYR as both treated and untreated.

^bDisease progression is defined as composite outcome of hepatic decompensation (variceal bleeding, ascites, hepatic encephalopathy), death, or transplant.