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Low Incidence of Adverse Outcomes in Adults With Chronic Hepatitis B Virus Infection in the Era of Antiviral Therapy

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BACKGROUND AND AIMS: Outcomes of persons with chronic hepatitis B virus (HBV) infection in the era of antiviral therapy (AVT) are not well characterized. We determined the incidence and factors associated with clinical outcomes in a multiethnic, North American cohort of adults with chronic HBV infection, who were not on AVT at enrollment.

APPROACH AND RESULTS: Adults with chronic HBV infection, not receiving AVT, and without a history of decompensation, HCC, or liver transplantation (LT), were prospectively followed. Participants with known human immunodeficiency virus (HIV), hepatitis C virus, or hepatitis D virus (HDV) coinfection were excluded. During follow-up, treatment could be initiated per standard of care. Clinical outcomes included: incident cirrhosis, decompensation, HCC, OLT, and HBV-related death. Among 1,418 participants analyzed, 51.5% were women, median age was 41.1 years, 75% were Asian, 10% White, 13% Black, 24% HBeAg(+), and 1.5% cirrhosis at baseline. During the study, 274 started treatment, 83 had an alanine aminotransferase flare, 118 of 330 initially HBeAg(+) became HBeAg(−), and 90 of 1,329 became HBsAg(−). After 6,641 person-years follow-up, 8 participants (4 of 21 with baseline cirrhosis) had 12 clinical outcomes (2 decompensation, 5 HCC, 2 OLT, and 3 HBV-related deaths) and 19 of 1,397 had incident cirrhosis. Twenty-one of 26 participants had first outcome before treatment, none had become HBsAg(−), whereas 5/9 HBeAg(+) had become HBeAg(−) at time of first outcome. Cumulative percentage of clinical outcomes was 16% at year 4 in participants with baseline cirrhosis and 2% (including incident cirrhosis) at year 7 in those without.

CONCLUSIONS: Incidence of adverse outcomes was low in this closely monitored, large cohort of North American adults with predominantly inactive, chronic HBV without cirrhosis. Our data highlight the benefits of HBsAg loss and the importance of early diagnosis and treatment to prevent cirrhosis and other complications of chronic HBV infection. (Hepatology 2021;73:2124-2140).

Chronic hepatitis B virus (HBV) infection is uncommon in the United States with an estimated population prevalence of 0.35% based on the National Health and Nutrition Examination Survey, corresponding to 840,000 persons. However, this may be an underestimation of the true prevalence given that persons at increased risk of infection, such as those who are homeless or incarcerated,

Abbreviations: ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; AVT, antiviral therapy; CHB, chronic hepatitis B; CI, confidence interval; FIB-4, Fibrosis 4 markers; HBeAg, hepatitis B e antigen; HBRN, Hepatitis B Research Network; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HD, hepatic decompensation; HDV, hepatitis D virus; HIV, human immunodeficiency virus; LT, liver transplantation; NA, nucleos(t)ide analogue; PY, person-year; ULN, upper limit of normal.

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were not included, and until 2011, Asians, who have the highest prevalence of HBV infection, were under-represented.[1]

The majority of natural history studies in untreated chronic HBV infection have originated from Asia or Europe.[2-6] These studies have shown varying rates of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. Whereas some of the discrepancies may be attributable to differences in study design, other factors, notably age at infection and HBV genotypes, may have contributed to the variable results.[2-8] Apart from the studies in Alaskan natives, there are limited data on the natural history of chronic HBV infection in adults living in North America.[9,10]

The course of chronic HBV infection is dynamic, characterized by fluctuations in HBV replication and liver inflammation, and patients with inactive liver disease at presentation may progress to active disease or experience progressive disease during follow-up. Indeed, several studies have reported high rates of hepatic decompensation (HD), HCC, and liver-related mortality in patients who did not meet criteria for antiviral therapy (AVT) at presentation and who did not receive treatment during follow-up.[3,10,11]

Availability of safe and potent AVT, in particular nucleos(t)ide analogues (NAs), in the past two decades has dramatically changed the outcomes of chronic HBV infection. AVT has been shown to be

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effective not only in suppressing HBV replication and decreasing liver inflammation, but also in reversing liver fibrosis and in preventing cirrhosis, liver failure, HCC, and liver-related mortality.[12-18] However, currently available therapies do not eradicate the virus and rarely result in clearance of hepatitis B surface antigen (HBsAg). Thus, professional society guidelines recommend treatment only in patients with cirrhosis or those with active disease at risk of progressive liver injury, and monitoring of patients who do not meet criteria for treatment.[19-21]

The Hepatitis B Research Network (HBRN) was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 2008 to investigate clinical, virological, and immunological characteristics of patients with HBV infection in the United States and Canada. The HBRN cohort study enrolled persons with chronic HBV infection who were not receiving AVT and followed them prospectively per standard of care, which included initiating AVT during follow-up if necessary. We analyzed data from the HBRN Adult Cohort Study to determine the incidence and factors associated with clinical outcomes in this large and diverse population of persons with chronic HBV infection.

Materials and Methods

STUDY DESIGN

The HBRN comprises 21 adult and seven pediatric liver centers in the United States and in Toronto, Ontario, Canada. Details of the HBRN Adult Cohort Study protocol have been described.[22] In brief, consecutive, consenting, HBsAg-positive patients, seen in outpatient clinics, who were not receiving AVT unless pregnant or were coinfected with hepatitis D virus (HDV) and did not have a history of HD, HCC, liver transplantation (LT), or known human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection, were enrolled.

The baseline evaluation included detailed medical history, physical examination, health surveys, and blood tests. Recommended laboratory tests included complete blood count, liver panel, creatinine, international normalized ratio, alpha fetoprotein, HBV-DNA level, HBV serologies (HBsAg, antibody against HBsAg, hepatitis B e antigen [HBeAg], and antibody against HBeAg), and antibodies against HIV, HCV, and HDV. In addition, relevant clinical, laboratory, radiological, and histological data were extracted from past medical records. Participants were reassessed at week 12, 24, and then every 24 weeks and, additionally, when participants experienced a flare in alanine aminotransferase (ALT), became HBeAg or HBsAg negative, or became pregnant.

The protocol recommended testing for quantitative HBV DNA and qualitative HBeAg (for those who were HBeAg positive at enrollment) every 24 weeks and qualitative HBsAg every 48 weeks, and testing for hepatitis B e antibody and hepatitis B surface antibody among participants who cleared HBeAg or HBsAg. The protocol also recommended HCC surveillance per American Association for Study of Liver Diseases (AASLD) Guidelines on Hepatitis B. Standard-of-care tests were done at the local laboratories. Standardized cut-off values were chosen to define the upper limit of normal (ULN) for ALT: 30 U/L for men and 20 U/L for women. Research blood samples were collected at each visit, processed, and stored at −70°C at each site and shipped in batches to a central repository for subsequent transfer to central testing laboratories. Follow-up ended with LT or death.

Baseline cirrhosis was based on histology, if available, and in the absence of biopsy by presence of two of the following three criteria: splenomegaly or nodular liver on radiological imaging, or platelet count <120,000/mm^3. Vibration-controlled transient elastography had not been approved for clinical care in the United States at the start of HBRN studies. Participants meeting these criteria within 24 weeks after enrollment were considered to have baseline cirrhosis after adjudication by an HBRN panel of investigators.

During follow-up, AVT could be initiated if a participant was enrolled in a HBRN treatment trial or if the physician initiated AVT per standard of care. There were two HBRN treatment trials: one for participants in the immune-tolerant phase[23] and one for participants in either the HBeAg-positive or HBeAg-negative immune-active phase.[24]

The protocol was approved by the institutional review boards or ethics committee of each participating institution and by a data and safety monitoring board appointed by the NIDDK to oversee

the HBRN studies. All participants gave written, informed consent. All authors had access to study data and reviewed and approved the final manuscript.

HBV TESTING

Quantitative HBV DNA, HBeAg, and HBsAg were performed at a central laboratory (University of Washington, Seattle, WA). HBV-DNA levels were determined using a real-time PCR assay (COBAS Ampliprep/COBAS TaqMan HBV Test, v2.0; Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of detection of 10 IU/mL and lower limit of quantification of 20 IU/mL. Quantitative HBsAg and HBeAg were tested using the Roche Diagnostics Elecsys platform with lower limit of detection for HBsAg and HBeAg of 0.05 and 0.3 IU/mL, respectively. Qualitative assays for HBsAg and HBeAg were also performed locally using commercially available enzyme immunoassays. HBV genotype was determined based on mass spectrometry, at the Molecular Epidemiology and Bioinformatics Laboratory in the Division of Viral Hepatitis at the Centers for Disease Control and Prevention.[25]

Central laboratory results were used when available and supplemented by local laboratory results when missing.

STUDY POPULATION

HBsAg-positive patients aged ≥18 years, enrolled in the HBRN Adult Cohort Study, were included in this analysis unless they met one of the following exclusion criteria: acute HBV infection, HIV, HCV, or HDV coinfection at enrollment; or had all labs while on treatment or within 24 weeks of stopping treatment for those who received treatment before enrollment, or while pregnant or within 24 weeks of end of pregnancy. Chronic HBV infection was defined by presence of HBsAg or HBV DNA for at least 6 months. Participants who either transferred from the HBRN Pediatric Cohort Study, who entered an HBRN treatment trial concurrently with the Adult Cohort Study, who did not have at least one follow-up visit >24 weeks after enrollment or who started AVT that lasted ≥24 weeks within 24 weeks after enrollment were also excluded (Fig. 1).

Baseline date was the date of enrollment into the HBRN Adult Cohort study. Values of HBsAg,

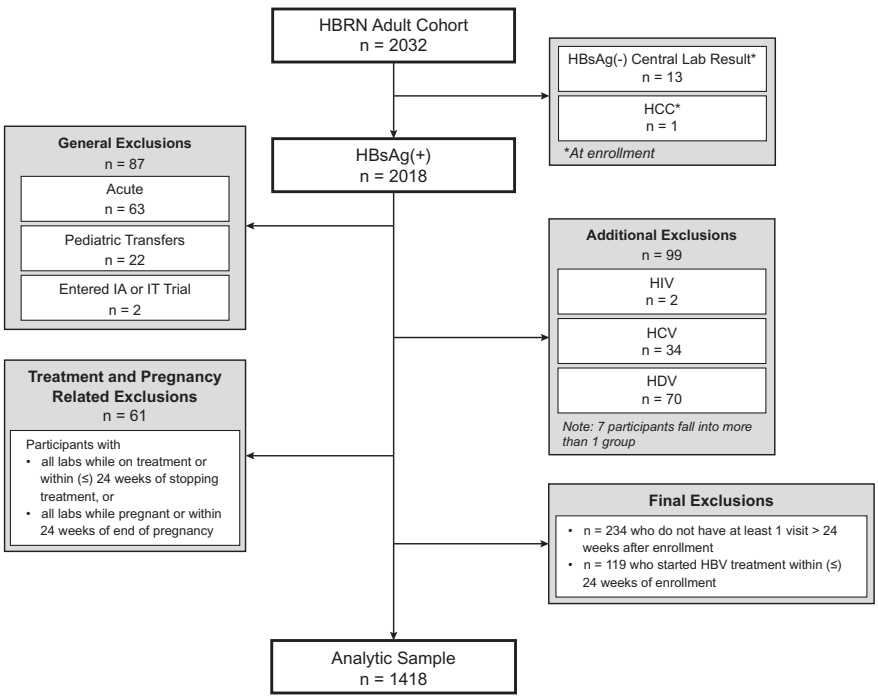

FIG. 1. Flow chart showing selection of HBRN adult participants for analysis.

HBeAg, HBV DNA, aspartate aminotransferase (AST), ALT, and platelets on the same day or closest to each other during the period from 24 weeks before to 18 weeks after enrollment were used as baseline labs. Baseline HBV clinical phenotypes were determined based on a combination of HBeAg status, HBV-DNA level, and ALT level as described.[26] AST to platelet ratio index (APRI) and Fibrosis 4 marker (FIB-4) were calculated as described.[27,28] If there were multiple results for any component laboratory test within a study visit window, then the results closest to each other were used to calculate APRI and FIB-4.

Follow-up ended on January 28, 2019 or at the last date data were collected. For this analysis, follow-up data from participants at or after new diagnosis of HIV or HCV infection were excluded. Data from 111 participants (median 2 years' follow-up before enrollment in the trial) after enrollment into an HBRN clinical trial were excluded from all analyses. Data from participants who started treatment per standard of care were included in all analyses except for analysis of ALT flare, and changes in APRI and FIB-4, where data after start of treatment were excluded.

OUTCOMES

The clinical outcomes analyzed were: HD, HCC, LT, or HBV-related death. Given the low occurrence of individual outcomes, they were grouped and termed major clinical outcomes (Supporting Table S1). Among participants without baseline cirrhosis, incident (new diagnosis) cirrhosis was also determined. Other outcomes analyzed were non-HBV deaths, incident ALT flare (ALT ≥10 × ULN), initiation of AVT, ever becoming HBeAg negative for participants who were HBeAg positive at baseline, and ever becoming HBsAg negative. Initiation of AVT per standard of care was considered as an outcome because treatment might have averted a clinical outcome. In this study, only treatment lasting ≥24 weeks was considered as an outcome, because shorter courses of treatment, most commonly prescribed in highly viremic pregnant women to prevent mother-to-child transmission, were not expected to impact clinical outcomes. Fibrosis progression was assessed based on changes in APRI (≤0.5, 0.5-2.0, and >2.0) and FIB-4 (<1.45, 1.45-3.25, and >3.25) categories. All outcomes were predefined and the occurrence and timing of the major clinical outcomes, including incident cirrhosis and ALT flares, were adjudicated by a committee of HBRN clinical investigators to determine whether criteria for these outcomes were met (Supporting Table S1).

STATISTICAL ANALYSES

Descriptive statistics are reported as medians (25th and 75th percentiles) for continuous variables and frequencies (percentages) for categorical variables. Distributions of baseline characteristics of participants with versus those without cirrhosis at baseline were compared using exact Pearson chi-square or Kruskal-Wallis tests, as appropriate.

For each outcome, rates per 100 person-years (PYs) and corresponding confidence intervals (CIs) assuming a Poisson distribution are reported overall and by baseline characteristics and laboratory measures. Univariate associations between each outcome and each baseline measure were assessed from Poisson regression models. Exact CIs were calculated if the number of events in a category was <5, and *P* values were exact if the number of events in any one category of a baseline measure was <5. Otherwise, asymptotic Wald statistics were used. The Kaplan-Meier method was used to estimate the cumulative probability of each outcome over time. For major clinical outcomes, time to first event was recorded. For incident hepatitis flare, follow-up ended when treatment was initiated. All outcomes were conditional on participants having more than 24 weeks of follow-up. The follow-up for incident cirrhosis, LT, deaths, and treatment initiation was reduced by 24 weeks given that, by design, none of these events could occur within the first 24 weeks after enrollment. For APRI and FIB-4, the change in category from first result to last result, if at least 24 weeks after first, within each duration category (<96, 96-192, and >192 weeks) before initiating treatment was summarized.

Statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Results

BASELINE CHARACTERISTICS OF PARTICIPANTS

A total of 2,032 participants were enrolled between January 2011 and Janurary 2018; of these, 614 were

excluded (Fig. 1). Among the 1,418 participants included in this study, median age was 41.1 years, 51.5% were female, and most were Asian (74.6%), followed by Blacks (12.7%), Whites (10.0%), and other/mixed races (2.8%; Table 1). Roughly one-quarter (24.0%) were HBeAg positive, median HBV DNA was 3.6 $\log_{10}$ IU/mL, and median HBsAg was 3.4 $\log_{10}$ IU/mL. Genotypes B (40.2%) and C (33.4%) were most common followed by genotypes A (16.8%), D (6.7%), E (2.5%), and others (0.4%). Only 21 (1.5%) participants were considered to have cirrhosis at baseline. This was corroborated by a low percentage with APRI >2.0 (1.8%) or FIB-4 >3.25 (1.7%). Participants with baseline cirrhosis were older, more likely to be men, White, diabetic, and had higher AST and lower platelet count. The most common phenotype was indeterminant (37.0%), followed by inactive carriers (24.2%) and HBeAg-negative (17.4%) and HBeAg-positive (17.2%) chronic hepatitis.

INCIDENCE OF MAJOR CLINICAL OUTCOMES AND INCIDENT CIRRHOSIS AND ASSOCIATED BASELINE FACTORS

After 6,641 PYs of follow-up, 26 participants had a total of 31 clinical outcomes, including incident cirrhosis (Fig. 2). Among the 21 participants with baseline cirrhosis, 4 had major clinical outcomes, including 3 HCC (2 followed by LT and 1 followed by HBV-related death) and 1 HBV-related death. Of the 1,397 participants without baseline cirrhosis, 22 had major clinical outcomes or incident cirrhosis: 18 with incident cirrhosis only, 1 incident cirrhosis at the same time as decompensation followed by HBV-related death, 2 HCC, and 1 HD.

Incidence rate per 100 PYs for each individual outcome was low, HD (0.03), HCC (0.08), LT (0.03), HBV-related death (0.05), and incident cirrhosis (0.32; Table 2). Eight participants (4 with and 4 without baseline cirrhosis) had major clinical outcomes with incidence of 0.12 per 100 PYs (95% CI = 0.06, 0.24). Cumulative percentages of major clinical outcomes at years 4 and 7 were 0.5% and 1%, respectively, for the overall cohort. The incidence rate of major clinical outcomes was 4.79 per 100 PYs (95% CI = 1.80, 12.75), and the cumulative percentage at year 4 was 16% for those with baseline cirrhosis, whereas the incidence rate was 0.06 per 100 PYs (95% CI = 0.02, 0.16) and the cumulative percentages were 0.2% at year 4 and 0.5% at year 7 for those without baseline cirrhosis (Fig. 3A).

Among the participants without cirrhosis at baseline, incident cirrhosis was assessed in addition to major clinical outcomes. Incident cirrhosis or major clinical outcomes occurred in 22 participants with incidence rate of 0.34 per 100 PYs (95% CI = 0.22, 0.51), and the cumulative percentages were 2% at both year 4 and year 7 (Fig. 3B).

Among the 21 participants with baseline cirrhosis, the 4 participants who developed major clinical outcomes were older, more likely to be White, and had lower baseline HBV DNA, quantitative HBsAg, and platelet count than the other 17 who did not develop major clinical outcomes.

Among the 1,397 participants without baseline cirrhosis, the 22 participants who met a criterion for major clinical outcomes or incident cirrhosis were older, more likely to be men, and had higher APRI and lower platelet counts at baseline compared to those who did not meet criteria for these outcomes (Table 3).

CHARACTERISTICS OF PARTICIPANTS WITH MAJOR CLINICAL OUTCOMES OR INCIDENT CIRRHOSIS

Of the 26 participants who had a major clinical outcome or incident cirrhosis, 5 had started AVT, none had become HBsAg negative, and 5 of 9 HBeAg-positive participants had become HBeAg negative before their first outcome.

Eight participants (7 men, median age 57 years, 4 White, 1 Black, and 3 Asians) had a total of 12 major clinical outcomes (Fig. 2; Table 4). Of these, 4 had one outcome each and 4 had two outcomes each. Two participants had started AVT before and 2 others after their first outcome, whereas 4 (including 2 with persistently undetectable HBV DNA) never received treatment. None of the 8 participants with major clinical outcomes had experienced ALT flares. All 8 were still HBsAg positive at the time of first outcome. Of the 2 participants who were initially HBeAg positive, 1 had become negative and the other remained HBeAg positive at the time of first outcome.

TABLE 1. Baseline Characteristics of Participants With and Without Cirrhosis

Characteristics	All n = 1,418	With Baseline Cirrhosis n = 21	Without Baseline Cirrhosis n = 1,397
Age at enrollment (years)	n = 1,418	n = 21	n = 1,397
Median (25th:75th)	41.1 (32.9:51.5)	50.7 (42.4:57.3)	41.0 (32.9:51.4)
Sex	n = 1,418	n = 21	n = 1,397
Female	730 (51.5%)	6 (28.6%)	724 (51.8%)
Race	n = 1,415	n = 21	n = 1,394
White	142 (10.0%)	5 (23.8%)	137 (9.8%)
Black	179 (12.7%)	3 (14.3%)	176 (12.6%)
Asian	1,055 (74.6%)	11 (52.4%)	1,044 (74.9%)
Other/mixed	39 (2.8%)	2 (9.5%)	37 (2.7%)
Continent of birth	n = 1,414	n = 21	n = 1,393
Africa	139 (9.8%)	1 (4.8%)	138 (9.9%)
Asia	972 (68.7%)	11 (52.4%)	961 (69.0%)
Europe	43 (3.0%)	1 (4.8%)	42 (3.0%)
North America	249 (17.6%)	8 (38.1%)	241 (17.3%)
South America	8 (0.6%)	0 (0.0%)	8 (0.6%)
Australia	3 (0.2%)	0 (0.0%)	3 (0.2%)
HBeAg status	n = 1,379	n = 20	n = 1,359
Positive	331 (24.0%)	6 (30.0%)	325 (23.9%)
HBV DNA (log_{10} IU/mL)	n = 1,417	n = 21	n = 1,396
Median (25th:75th)	3.6 (2.6:5.6)	3.7 (1.8:5.8)	3.6 (2.6:5.5)
Quant HBsAg (log_{10} IU/mL)	n = 1,354	n = 20	n = 1,334
Median (25th:75th)	3.39 (2.67:4.11)	3.14 (2.45:3.92)	3.40 (2.67:4.11)
HBV genotype	n = 1,301	n = 17	n = 1,284
A	219 (16.8%)	4 (23.5%)	215 (16.7%)
B	523 (40.2%)	3 (17.6%)	520 (40.5%)
C	434 (33.4%)	7 (41.2%)	427 (33.3%)
D	87 (6.7%)	2 (11.8%)	85 (6.6%)
E	33 (2.5%)	1 (5.9%)	32 (2.5%)
Mixed/other	5 (0.4%)	0 (0.0%)	5 (0.4%)
APRI	n = 1,209	n = 21	n = 1,188
≤0.5	943 (78.0%)	3 (14.3%)	940 (79.1%)
>0.5-2.0	244 (20.2%)	15 (71.4%)	229 (19.3%)
>2	22 (1.8%)	3 (14.3%)	19 (1.6%)
FIB-4	n = 1,209	n = 21	n = 1,188
<1.45	966 (79.9%)	6 (28.6%)	960 (80.8%)
1.45-3.25	222 (18.4%)	11 (52.4%)	211 (17.8%)
>3.25	21 (1.7%)	4 (19.0%)	17 (1.4%)
HBV phenotype	n = 1,337	n = 20	n = 1,317
Immune tolerant	55 (4.1%)	0 (0.0%)	55 (4.2%)
$HBeAg^+$ CHB	230 (17.2%)	5 (25.0%)	225 (17.1%)
$HBeAg^-$ CHB	233 (17.4%)	3 (15.0%)	230 (17.5%)
Inactive carrier	324 (24.2%)	4 (20.0%)	320 (24.3%)
Indeterminant	495 (37.0%)	8 (40.0%)	487 (37.0%)
Platelets ($\times 10^3/mm^3$)	n = 1,219	n = 21	n = 1,198
Median (25th:75th)	219.0 (182.0:256.0)	142.0 (106.0:181.0)	220.0 (183.0:257.0)
AST × ULN*	n = 1,379	n = 21	n = 1,358
≤1 × ULN	1,103 (80.0%)	8 (38.1%)	1,095 (80.6%)
>1-2 × ULN	211 (15.3%)	9 (42.9%)	202 (14.9%)
>2 × ULN	65 (4.7%)	4 (19.0%)	61 (4.5%)
ALT × ULN†	n = 1,401	n = 21	n = 1,380

TABLE 1. *Continued*

Characteristics	All n = 1,418	With Baseline Cirrhosis n = 21	Without Baseline Cirrhosis n = 1,397
≤1 × ULN	466 (33.3%)	4 (19.0%)	462 (33.5%)
>1-2 × ULN	622 (44.4%)	9 (42.9%)	613 (44.4%)
>2 × ULN	313 (22.3%)	8 (38.1%)	305 (22.1%)
Albumin (g/dL)	n = 1,344	n = 21	n = 1,323
Median (25th:75th)	4.3 (4.1:4.6)	3.9 (3.8:4.3)	4.3 (4.1:4.6)
Total bilirubin (mg/dL)	n = 1,371	n = 21	n = 1,350
Median (25th:75th)	0.6 (0.4:0.8)	0.8 (0.6:1.0)	0.6 (0.4:0.8)
Ever received HBV treatment	n = 1,418	n = 21	n = 1,397
Yes	194 (13.7%)	2 (9.5%)	192 (13.7%)
BMI (kg/m^2)	n = 1,296	n = 20	n = 1,276
Median (25th:75th)	24.1 (21.6:27.0)	26.2 (24.6:31.1)	24.0 (21.6:27.0)
Diabetes	n = 1,415	n = 21	n = 1,394
Yes	77 (5.4%)	5 (23.8%)	72 (5.2%)
NIAAA alcohol risk level in past 12 months‡	n = 1,410	n = 21	n = 1,389
At-risk	100 (7.1%)	2 (9.5%)	98 (7.1%)

One participant had a baseline qHBsAg below detection limit (<0.05 IU/mL), but was HBsAg$^+$ by central laboratory HBsAg qualitative test.
*ULN for AST was laboratory specific, range 30-60 U/L.
†ULN for ALT was 30 U/L for males and 20 U/L for females.
‡Males considered at-risk if consumed >4 drinks/day or >14 drinks/week; females considered at-risk if consumed >3 drinks/day or >7 drinks/week.
Abbreviations: BMI, body mass index; NIAAA, National Institute on Alcohol Abuse and Alcoholism.

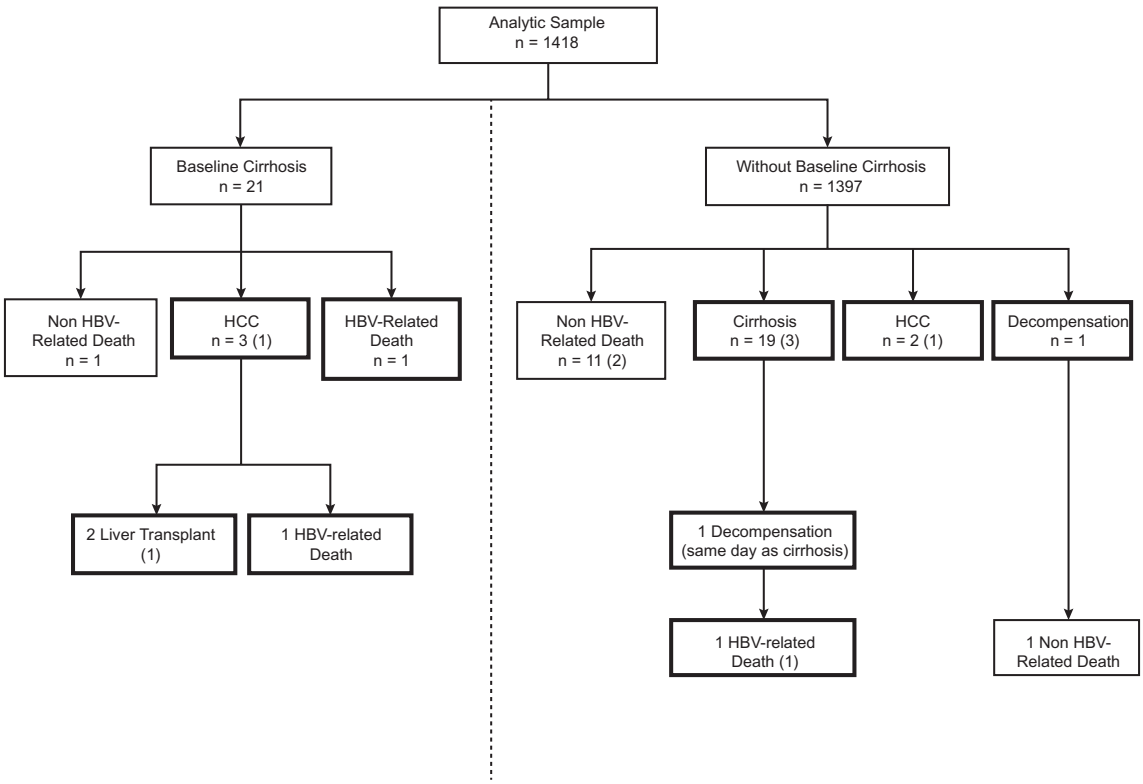

FIG. 2. Clinical outcomes by baseline cirrhosis. Outcomes of interest: decompensation, HCC, LT, HBV-related death, and incident cirrhosis shown in bolded boxes. Twenty-six participants had outcomes of interest: 8 major clinical outcomes and 18 with incident cirrhosis and no further clinical outcomes. Numbers in parentheses indicate number of outcomes that occurred after HBV treatment initiation.

TABLE 2. Incidence Rates Among 1,418 Participants With >24 Weeks of Follow-up

Outcome	No. of Participants With Outcome	Incidence per 100 PYs (95% CI)
HD*	2	0.03 (0.01, 0.12)
HCC*	5	0.08 (0.03, 0.18)
LT*	2	0.03 (0.01, 0.13)
HBV-related death*	3	0.05 (0.02, 0.16)
Incident cirrhosis (n = 1,397 w/o baseline cirrhosis)	19	0.32 (0.21, 0.51)
Major clinical outcome*,†	8	0.12 (0.06, 0.24)
Major clinical outcome or incident cirrhosis‡ (n = 1,397 w/o baseline cirrhosis)	22	0.34 (0.22, 0.51)
HBV treatment initiation >24 weeks after enrollment*,§	274	5.45 (4.84, 6.14)
ALT flare after enrollment and before initiating HBV treatment*,§ (n = 1,405 w/ follow-up ALT)	83	1.51 (1.22, 1.88)
Ever become HBeAg−* (n = 330 $HBeAg^+$ with follow-up HBeAg)	118	11.69 (9.76, 14.00)
Ever become HBsAg−* (n = 1,329 $HBsAg^+$ with follow-up HBsAg)	90	1.52 (1.23, 1.86)
Non-HBV-related death*	13	0.22 (0.13, 0.37)

*Includes those with baseline cirrhosis.
†First of decompensation, HCC, LT, or HBV-related death.
‡First of major clinical outcomes or incident cirrhosis.
§Treatment only considered if lasted ≥24 weeks.

HCC

Of the 5 participants with HCC (nos. 112, 933, 1,157, 1,287, and 1,432), 3 had cirrhosis at baseline, including 2 with persistently undetectable HBV DNA, and did not receive AVT and the third started treatment, but HCC was diagnosed nearly a year later despite having undetectable HBV DNA (Table 4). The other 2 participants with HCC had no evidence of cirrhosis at baseline or throughout the study; one of these 2 started treatment, but despite suppression of HBV DNA to an undetectable level was diagnosed to have HCC 2.6 years later.

HD

Two participants (nos. 113 and 729) without baseline cirrhosis developed HD; 1 was found to have cirrhosis at the time of decompensation, but despite starting treatment immediately after decompensation had an HBV-related death 1.6 years later.

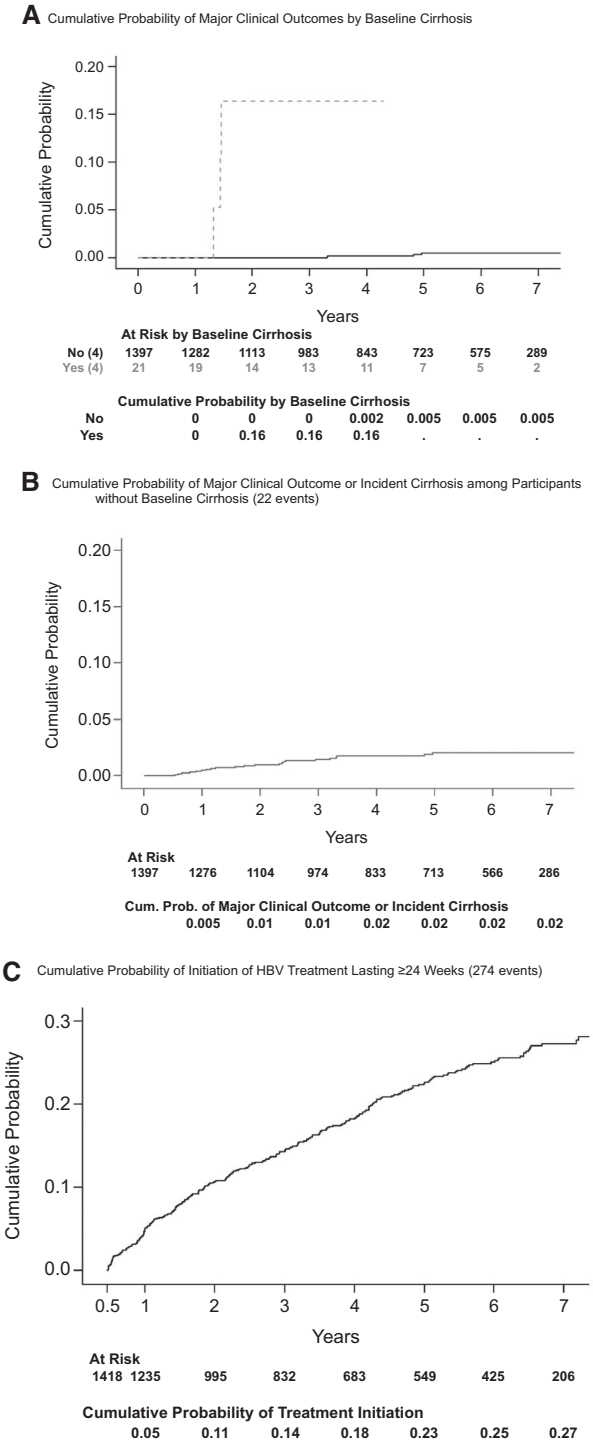

FIG. 3. (A) Cumulative probability of major clinical outcomes by baseline cirrhosis. Major clinical outcomes: first of decompensation, HCC, LT, or HBV-related death. (B) Cumulative probability of major clinical outcomes or incident cirrhosis among participants without baseline cirrhosis. (C) Cumulative probability of initiation of HBV treatment. Only treatment lasting ≥24 weeks was considered.

TABLE 3. Incidence Rates of Major Clinical Outcomes or Incident Cirrhosis Among 1,397 Participants Without Baseline Cirrhosis

Baseline Characteristic		No. of Participants	No. With Outcome	Total PYs	Incidence per 100 PYs (95% CI)*
Age (years)	<30	249	1	1,080	0.09 (0.01, 0.66)
	30-50	752	10	3,470	0.29 (0.16, 0.54)
	>50	396	11	1,941	0.57 (0.31, 1.02)
Sex	Male	673	19	3,063	0.62 (0.40, 0.97)
	Female	724	3	3,429	0.09 (0.03, 0.27)
Race	White	137	4	689	0.58 (0.22, 1.55)
	Black	176	6	760	0.79 (0.35, 1.76)
	Asian	1,044	12	4,856	0.25 (0.14, 0.44)
	Other/mixed	37	0	177	—
HBeAg status	Negative	1,034	12	4,954	0.24 (0.14, 0.43)
	Positive	325	8	1,366	0.59 (0.29, 1.17)
HBV DNA (log_{10} IU/mL)	<3	488	6	2,296	0.26 (0.12, 0.58)
	3-5	485	9	2,404	0.37 (0.19, 0.72)
	>5	423	7	1,788	0.39 (0.19, 0.82)
qHBsAg (log_{10} IU/mL)	<3	459	5	2,217	0.23 (0.09, 0.54)
	3-4	495	10	2,361	0.42 (0.23, 0.79)
	>4	380	5	1,627	0.31 (0.13, 0.74)
HBV genotype	A	215	8	941	0.85 (0.43, 1.70)
	B	520	6	2,425	0.25 (0.11, 0.55)
	C	427	6	1,994	0.30 (0.14, 0.67)
	D	85	1	444	0.23 (0.03, 1.60)
	E	32	1	126	0.79 (0.11, 5.62)
	Mixed/other	5	0	30	—
APRI	≤0.5	940	8	4,580	0.17 (0.09, 0.35)
	>0.5-2.0	229	9	920	0.98 (0.51, 1.88)
	>2	19	2	82	2.43 (0.61, 9.72)
FIB-4	<1.45	960	3	4,556	0.07 (0.02, 0.20)
	1.45-3.25	211	12	969	1.24 (0.70, 2.18)
	>3.25	17	4	58	6.91 (2.59, 18.40)
Platelets ($\times 10^3/mm^3$)	<150	94	6	371	1.62 (0.73, 3.60)
	≥150	1,104	13	5,266	0.25 (0.14, 0.43)
AST × ULN	≤1 × ULN	1,095	10	5,256	0.19 (0.10, 0.35)
	>1-2 × ULN	202	6	815	0.74 (0.33, 1.64)
	>2 × ULN	61	4	250	1.60 (0.60, 4.27)
ALT × ULN	≤1 × ULN	462	6	2,177	0.28 (0.12, 0.61)
	>1-2 × ULN	613	6	2,971	0.20 (0.09, 0.45)
	>2 × ULN	305	9	1,279	0.70 (0.37, 1.35)

*CI based on Wald.
Abbreviation: qHBsAg, quantitative HBsAg.

TABLE 4. Characteristics of Participants With Major Clinical Outcomes*

ID	Sex	Age	Race	Genotype	Cirrhosis at Wk 0	HBeAg at Wk 0	Outcomes (Timing, Wk)	HBV DNA, $\log_{10}$ IU/mL Wk 0/At First Outcome	ALT ×ULN Wk 0/At First Outcome	Platelet $\times 10^3/mm^3$ Wk 0/At First Outcome	Treatment Start
113	M	48	B	B	No	Neg	Decomp (172), other death (180)	3.1/2.2	0.5/1.5	175/195	No
729	M	55	W	A	No	Pos	Cirrh and decomp (173), HBV death (258)	8.5/8.4	2.1/5.3	248/138	Wk 174
112	M	64	W	A	Yes	Neg	HCC (75), LT (86)	UD/UD	1.0/1.6	67/81	No
933	F	54	A	C	Yes	Pos	HCC (76), LT (338)	5.8/UD	2.5/1.9	136/86	Wk 28
1157	M	66	W	Unk	Yes	Neg	HCC (69), HBV death (103)	UD/UD	0.9/1.0	61/53	No
1287	M	59	A	B	No	Neg	HCC (252)	5.0/UD	0.9/1.1	225/198	Wk 116
1432	M	65	A	C	No	Neg	HCC (259)	3.5/3.2	1.1/1.7	231/226	Wk 285
134	M	35	W	Unk	Yes	Unk	HBV death (257)	1.5/Unk	1.4/Unk	93/Unk	No

*HD, HCC, LT, or HBV-related death.
Abbreviations: M, male; F, female; B, Black; W, White; A, Asian; UD, below lower limit of detection or lower limit of quantification; Unk, unknown; Wk, week.

HBV-Related Death

Three participants were considered to have HBV-related deaths, 1 following HD (no. 729), 1 after HCC (no. 1,157), and 1 following sepsis attributed to cirrhosis (no. 134). One participant started AVT upon diagnosis of HD whereas the other 2 had not been treated.

Incident Cirrhosis

Eighteen participants met criteria for incident cirrhosis only (15 men, median age 49 years, 3 White, 5 Black, and 10 Asian) a median of 1.4 years after enrollment with no major clinical outcomes during median subsequent follow-up of 3.5 years. Three participants had started treatment before and 5 others started treatment after the finding of incident cirrhosis. Ten participants did not start treatment; of these, 1 had undetectable HBV DNA and 2 had HBV DNA <3 $\log_{10}$ IU/mL throughout the study and the remaining 7 had HBV DNA ≥3 $\log_{10}$ IU/mL. Of these 18 participants, 2 had an ALT flare 40 and 16 weeks before cirrhosis diagnosis, 3 of 7 initially HBeAg positive remained HBeAg positive, and all remained HBsAg positive at the time of cirrhosis diagnosis.

Deaths

A total of 16 participants were known to have died during the study; 3 were adjudicated to be HBV related (2 in those with and 1 in those without baseline cirrhosis). Cumulative probabilities of HBV-related and all-cause mortality at year 7 were 0.4% and 2.0%, respectively.

INCIDENCE OF OTHER OUTCOMES AND ASSOCIATED BASELINE FACTORS

Treatment Initiation Per Standard of Care

During the study, 274 participants initiated AVT (13 with baseline cirrhosis and 8 with incident cirrhosis) per standard of care that lasted at least 24 weeks. Of these, only 1 received pegylated interferon and the remainder NA therapy. The incidence rate of treatment initiation was 5.45 per 100

PYs, and cumulative percentage by year 7 was 27% (Table 2; Fig. 3C). These participants were more likely to be Asian, HBeAg positive, and to have cirrhosis, HBV genotype C, higher HBV DNA, HBsAg, ALT, APRI, and lower platelet counts at baseline than those who did not start treatment (Supporting Table S2).

Serum ALT Flare ≥10 × ULN

Eighty-three participants had at least one incident ALT flare (incidence = 1.51 per 100 PYs), yielding a cumulative percentage at year 7 of 8% (Table 2; Fig. 4). These participants were younger, more likely to be HBeAg positive, and to have cirrhosis, higher HBV DNA, HBsAg, ALT, and APRI, but lower platelet count at baseline, than those who did not have ALT flare (Supporting Table S3). The vast majority (96%; 80 of 83) did not have any clinical outcome or incident cirrhosis after the flare, though 33 started treatment after the flare.

Transition to HBeAg or HBsAg Negative Status

Of the 330 participants who were HBeAg positive at enrollment and had follow-up HBeAg testing, 118 became HBeAg negative (incidence = 11.69 per 100 PYs) with cumulative percentage by year 7 of 55% (Table 2; Supporting Fig. S1A). Rates of clinical outcomes were similar in those who became HBeAg negative as those who remained positive. Participants who became HBeAg negative were older, more likely to have genotype A infection, and to have lower HBV DNA and HBsAg levels at baseline than those who remained HBeAg positive. Of the 118 participants who became HBeAg negative, 82 did so spontaneously and the other 36 a median of 1.7 years after treatment initiation.

Ninety of the 1,329 participants with follow-up HBsAg tests became HBsAg negative (incidence = 1.52 per 100 PYs) with cumulative percentage by year 7 of 12% (Table 2; Supporting Fig. S1B). None of the participants who became HBsAg negative subsequently experienced any clinical outcome. Participants who became HBsAg negative were older, more likely to be men, non-Asian, HBeAg negative, and to have lower HBV DNA and HBsAg levels and normal AST and ALT at baseline than those who remained HBsAg positive. Of the 90 participants who became HBsAg negative, 86 did so spontaneously and the other 4 a median of 3.1 years after treatment initiation.

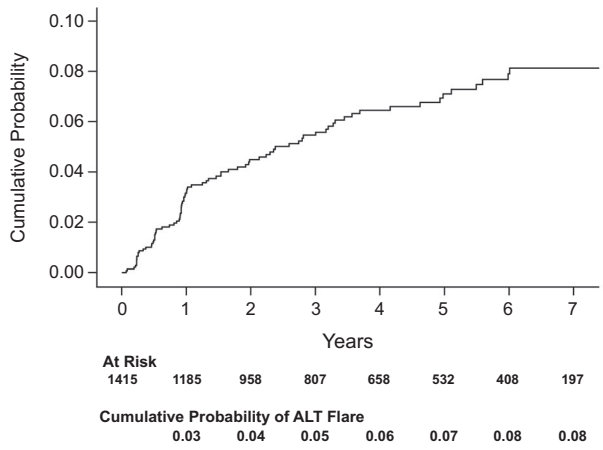

FIG. 4. Cumulative probability of incident ALT flares.

Changes in APRI or FIB-4 Categories

Liver fibrosis remained largely unchanged, with 80%-88% participants remaining in the same APRI or FIB-4 category during follow-up and similar proportions moved either up or down one category and ≤1% moved two categories.

Discussion

The large number of participants in the HBRN Adult Cohort Study with diverse race and HBV genotypes and a median follow-up of 5 years (maximum 8 years) provided a unique opportunity to examine the outcomes of mostly untreated patients with inactive chronic HBV infection residing in North America.

We found a very low rate (2% at 7 years) of clinical outcomes (incident cirrhosis, HD, HCC, LT, or HBV-related deaths) in this contemporary cohort followed at liver centers in the United States and in Toronto, Ontario, Canada. This contrasts with reports in the 1980s and 1990s before the availability of AVT, where combined rates of cirrhosis and HCC development among patients with chronic hepatitis B (CHB) were 10%-20% after 5-year follow-up, with evolution to cirrhosis being more common in European

studies and HCC more common in Asian studies.[4,5,29] Our results also differ from the more recent REVEAL (Risk Evaluation of Viral Load Elevation and Associated Liver. Disease) study in Taiwan, which enrolled 3,653 untreated persons with chronic HBV infection enrolled from the community between 1991 and 1992, in which 10.2%, 4.5%, and 4.5% participants had incident cirrhosis, HCC, and liver-related mortality after a median follow-up of 11.0-12.5 years.[3,30-32]

There are several reasons why the outcomes of our study were more favorable, foremost being the exclusion of patients who were receiving AVT at the time of enrollment. Given that guidelines recommend that patients with advanced fibrosis or cirrhosis and those with active liver disease should receive AVT, the HBRN Adult Cohort Study, by design, targeted patients with less active and/or less advanced liver disease for enrollment. Indeed, only 1.5% of participants were deemed to have baseline cirrhosis, and only 35% were classified as having HBeAg-positive or -negative chronic hepatitis. In fact, one-third of participants had normal baseline ALT using lower sex-based ULN.

Although our cohort was not dissimilar to the REVEAL cohort in sex, age, preponderance of subjects being HBeAg negative, low percent with cirrhosis (1.5% vs. 2%), and not receiving AVT at baseline, there were major differences. All participants in the REVEAL cohort were Chinese who likely acquired HBV infection perinatally or during early childhood and were infected with HBV genotypes B or C. Though the majority of our cohort were Asians with genotypes B and C, our cohort also included 10% Whites and 13% Blacks, and 26% were infected with HBV genotypes other than B or C. Another major difference was that our cohort began one decade later than the REVEAL cohort, when NA therapy was widely available. Indeed, 19% of participants in our study started AVT per standard of care, and treatment might have averted clinical outcomes in some of these participants. One additional difference was that duration of follow-up in our study was shorter than the REVEAL study.

Multiple studies have shown that AVT, particularly long-term NA therapy, decreases the risk of clinical outcomes, but does not completely eliminate HCC risk.[13-18] One study of 1,951 Caucasians with CHB, including 27% with cirrhosis who had received either entecavir or tenofovir for >5 years, found that risk factors for HCC after year 5 included age >50 and lower platelets at both baseline and year 5.[14] In our study, both participants who developed HCC while receiving NA therapy were >50.

As expected, we found a marked difference in clinical outcomes between participants with and those without baseline cirrhosis. Previous studies have shown that clinical outcomes are associated with male sex, older age, HBV genotype C, higher HBV DNA, higher ALT, and cirrhosis,[2-4,6,30,33] and HCC is more common among Asians and Blacks than Whites.[34] Whereas the low incidence of clinical outcomes in this study precludes meaningful analysis of baseline and longitudinal factors, among the 8 participants with major clinical outcomes, 7 were men and median age was 57 years. However, despite the predominance of Asians, half (4 of 8) of the participants (2 of 5 with HCC) with major clinical outcomes were White. The significance of our finding is unclear given the small numbers.

Increasing attention has been given to whether or not patients with minimally elevated or normal ALT would benefit from AVT, but the data are difficult to interpret because of the varied definition of normal ALT.[35-37] In our study, 18 participants who did not receive AVT before having the first major clinical outcome or incident cirrhosis had detectable baseline HBV DNA. Of these, 8 (1 with and 7 without baseline cirrhosis) would have met AASLD guidelines (HBV DNA >20,000 IU/mL for HBeAg-positive and >2,000 IU/mL for HBeAg-negative patients and ALT >2× ULN) for treatment. However, not all 18 would have met criteria for treatment even if the criteria were expanded to include lower HBV-DNA cutoff or ALT 1-2× ULN.

Severe hepatitis flares can precipitate HD in patients with advanced fibrosis or cirrhosis, and recurrent hepatitis flares may increase the risk of cirrhosis and HCC. In this study, 83 untreated participants had at least one incident ALT flare. None of the participants with major clinical outcomes had a documented ALT flare during follow-up whereas 2 of 18 participants with incident cirrhosis had transient ALT flare before diagnosis of incident cirrhosis. The other participants did not have any clinical outcomes following the flare, though 33 started treatment after the first flare, which might have averted outcomes.

HBeAg clearance and HBsAg clearance have been shown to improve clinical outcomes.[2,4,38-40] In this

study, of the 26 participants with clinical outcomes, none had become HBsAg negative before the outcomes whereas 5 of 9 participants who were initially HBeAg positive became HBeAg negative before their first outcome. Of note, the majority of participants who became HBeAg negative or HBsAg negative did so spontaneously.

The strengths of our study include the large number of participants of diverse race and HBV genotypes in contrast to studies in Asia, which included only Asians with genotypes B and C, and studies in Europe, which included mostly Caucasians with genotypes A and D. In addition, we used central laboratories for HBV testing and adjudicated clinical outcomes. Nevertheless, our study has several limitations. First, it was clinic based and not population based; however, the enrollment of patients not receiving treatment more closely mimics patients in the community than those seen in academic liver centers. Second, neither liver biopsy nor liver elastography measurements were routinely available to corroborate disease activity and extent of fibrosis, but the low percentage of patients with baseline cirrhosis was corroborated by APRI and FIB-4. Another perceived limitation is that 19% of our participants started AVT during the study (an additional 8% enrolled into HBRN clinical trials, but data after enrollment into trials were excluded from analysis), which might have altered the clinical course. We, however, view this as a strength given that this represents the current standard of care.

In summary, we found a low incidence of adverse outcomes in this large cohort of racially diverse persons with chronic HBV infection living in North America. The majority of clinical outcomes occurred in patients with cirrhosis at baseline or during follow-up and none in participants who lost HBsAg, confirming the clinical benefits of HBsAg loss in the absence of cirrhosis—the definition of functional cure of hepatitis B. Our data support that early diagnosis, linkage to care, close monitoring, and treatment initiation, when indicated, can prevent adverse outcomes and that treatment upon diagnosis may not be necessary for all patients.

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