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Characteristics of Older Patients With Immunotolerant Chronic Hepatitis B Virus Infection

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Abstract

BACKGROUND & AIMS: Most patients in the immunotolerant (IT) phase of chronic hepatitis B (CHB) transition to the immune active (IA-hepatitis B surface antigen [HBeAg]+) phase by early adulthood. We examined characteristics of adults in the IT vs IA-HBeAg+ phase and rate of transition from IT to other phases of CHB, with a focus on those 40 years.

METHODS: Demographic, clinical, and virologic characteristics of participants in the Hepatitis B Research Network adult cohort study with IT CHB (alanine aminotransferase 1.5 × upper limit of normal, hepatitis B virus DNA >10^7 IU/mL) were compared by age category, and to those with IA-HBeAg+ CHB in cross-sectional analysis. This study received institutional review board approval at all participating centers.

RESULTS: Of 107 adult IT participants, 52 (48%) were <30, 33 (31%) were 30 to 39, and 22 (21%) were 40 years old (maximum, 71 years). Among IT groups, the proportion born in Asia and duration of CHB were greater in older IT groups, but virologic and liver disease characteristics were similar. Compared with IA-HBeAg+ participants (n = 192), IT participants were younger, fewer were men, more were Asian, and platelets, qHBsAg, and qHBeAg levels were higher. Similar differences were observed when comparisons were made with the 40 years IT group. Among IT participants, 60 (56%) transitioned during 206 person-years of follow-up. The phase transition rate per 100 person-years was highest in the <30 years group (33.0 [95% confidence interval [CI], 23.4–46.7]) vs the 30 to 39 years group (24.8 [95% CI, 15.6–39.4]) and 40 group (27.4 [95% CI, 14.8–50.9]), but 95% CIs overlapped.

CONCLUSIONS: In a large North American population, over 50% of adults in the IT phase of CHB were 30 years and 20% were 40 years old, but older IT patients had similar characteristics and rates of transition as younger IT patients.

Keywords

Chronic HBV Infection; Immune Active; Immunotolerant (IT); Phase Transition

Chronic hepatitis B (CHB) is a dynamic condition that transitions through phases of disease activity. The first phase of CHB, often referred to as the immunotolerant (IT) phase or chronic hepatitis B infection, is characterized by hepatitis B e antigen (HBeAg)-positivity and high hepatitis B virus (HBV) DNA levels, but normal or near-normal transaminase levels and minimal or no inflammatory activity or fibrosis on liver biopsy.[1] The IT phase is typically observed in children and young adults who acquired the infection early in life. Although the duration of the IT phase is highly variable, most patients transition to the HBeAg-positive (HBeAg+) immune active (IA-HBeAg+) phase characterized by elevated alanine aminotransferase (ALT) and liver inflammation by late adolescence or early adulthood. However, some patients remain in the IT phase until much later in life.

Current international guidelines generally do not recommend treating patients in the IT phase due to the lack of effective therapy and the relatively benign short-term course of disease. However, the associations of HBeAg-positivity, high levels of HBV DNA, and older age with a higher risk of hepatocellular carcinoma (HCC)[2,3] have led to recommendations to consider treating older IT patients, despite lack of clear evidence that treatment during the

IT phase alters the risk of HCC and other outcomes. Specifically, the American Association for the Study of Liver Disease (AASLD),[4] European Association for the Study of the Liver (EASL),[5] and Asian Pacific Association for the Study of the Liver (APASL)[6] clinical practice guidelines recommend consideration of treatment for IT patients above 30 (EASL)[5], 35 (APASL)[6] or 40 (AASLD)[4] years, respectively.

Characterization of older individuals in the IT phase may improve understanding of the natural history of infection and guide management. We sought to characterize adults in the IT phase with cross-sectional comparisons across age groups, as well as between adults in the IT and IA-HBeAg+ phases. We hypothesized that older individuals in the IT phase would be distinct from younger IT patients, possibly more closely resembling those in the IA phase, with lower HBV DNA levels and low-grade chronic inflammation.[7] Using longitudinal data, we also characterized transitions from the IT phase and identified factors associated with these transitions.

Methods

Participants

The Hepatitis B Research Network (HBRN) is a National Institutes of Health-funded clinical research network with 21 adult clinical sites throughout the United States and in Toronto, Canada, that enrolled hepatitis B surface antigen (HBsAg)-positive adult (18 years old) patients without human immunodeficiency virus infection who were not currently on antiviral therapy into a prospective cohort study between 2012 and 2017.[8] Participants underwent initial evaluation and then returned for follow-up assessments at weeks 12 and 24, and then every 24 weeks. Treatment decisions were made at the discretion of the primary treating physicans, with participants remaining in the cohort during standard-of-care treatment. Participants enrolled in HBRN clinical trials were censored at the time of study entry. The study protocols were approved by the institutional review boards of participating institutions and participants provided written, informed consent.

Participants with acute HBV or with hepatitis C virus or hepatitis D virus coinfection were excluded. Participants meeting the criteria for IT or IA-HBeAg+ CHB (described below) were included.

To be included in the IT cohort, a participant had to have at least one IT period, defined as 2 or more consecutive assessments (>12 weeks apart) in which the IT phase definition (described below) was met, with allowance for a single missed study assessment or use of HBV therapy between IT determinations (eg, IT phase definition met at week 24 and 72 but week 48 assessment missed). The rationale for requiring 2 or more consecutive assessments was to ensure the cohort included participants who were truly in the IT phase and not in the IA-HBeAg+ phase with fluctuating ALT. Among HBeAg+ participants who never met the IT period definition throughout follow-up, those who had an IA-HBeAg+ period, defined as either 2 or more consecutive assessments in which the IA phase definition (described below) was met, with allowance for a single missed assessment between IA determinations, or a single assessment in which the IA phase definition was met followed by initiation of HBV therapy, were included in the IA-HBeAg+ cohort. The first assessment in either the first IT

or IA period was used for cross-sectional analysis, and among the IT cohort designated as the baseline for longituidanl analysis.

CHB Phase Definitions

At every assessment, CHB phase was determined among HBsAg+ participants not on HBV therapy. The IT CHB phase required HBeAg-positivity, with HBV DNA $\geq 10^7$ IU/mL and ALT $\leq 1.5 \times$ upper limit of normal (ULN), standardized as 30 U/L for men and 20 U/L for women. The IA-HBeAg+ CHB phase required HBeAg-positivity, HBV DNA $\geq 10^5$ IU/mL and ALT >1.5 × ULN. Those who were HBeAg+ without meeting either the IT or IA definition were categorized as being in an indeterminant HBeAg+ phase. IA-HBeAg-negative was defined by HBeAg negativity, HBV DNA >10^4 IU/mL and ALT >1.5 × ULN; inactive carrier by HBeAg-negativity, HBV DNA $\leq 10^4$ IU/mL and ALT $\leq 1.5 \times$ ULN; and Indeterminant HBeAg-negative if neither IA nor inactive carrier criteria were met.

Measures

Demographic (sex, age, self-reported race, continent of birth, presumed mode of HBV transmission, estimated duration of infection), clinical (body mass index, liver enzymes, platelets, aspartate aminotransferase [AST] to platelet ratio index [APRI], history of cirrhosis, HBV therapy) and virologic (HBsAg, HBeAg, and HBV DNA levels, HBV genotype, presence of precure [PC]/basal core promoter [BCP] mutations) characteristics were recorded. Age was categorized as 18 to 29, 30 to <40, and $\geq$ 40 years and APRI as <0.5, 0.5 to 1.5, and >1.5.[9]

Quantitative HBeAg and HBsAg (Roche Elecsys) assays were performed at the HBRN central virology laboratory at the University of Washington, with lower limits of detection of 0.3 IU/mL for HBeAg and 0.05 IU/mL for HBsAg. HBV DNA testing was performed centrally by real-time polymerase chain reaction (COBAS Ampliprep/COBAS TaqMan Test, v.2.0; Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of quantification of 20 IU/mL and a lower limit of detection of 10 IU/mL.

HBV genotyping and PC and BCP determination were performed at the Molecular Epidemiology and Bioinformatics Laboratory in the Division of Viral Hepatitis at the Centers for Disease Control and Prevention using mass spectrometry as previously described.[10,11]

Statistical Analysis

Cross sectional.—Among the IT cohort, trends across age groups (18–29, 30–<40, and $\geq$ 40 years) in demographic, clinical and virologic, characteristics were evaluated with the Johnkeere-Terpstra trend test for continuous variables, the Cochran-Armitage trend test for binary variables and Kendall's Tau b for ordinal variables. The χ^2 or Fisher's exact test was used to test for differences in categorical variables with $\geq$ 3 categories. The same characteristics of the IT cohort, and the subgroup $\geq$ 40 years, were compared with the IA-HBeAg+ cohort, with the Wilcoxon Rank Sum test for continuous variables, the χ^2 or Fisher exact test for categorical variables and Cochran-Armitage trend test for ordinal variables.

Longitudinal.—Among the IT cohort, heat maps, overall and stratified by age group, were created to show patterns of CHB phase stability and transitions, and HBV therapy use over time from study entry through the end of follow-up.

Phase transition rate from IT was estimated by dividing the number of participants with a phase transition by the number of person-years of observation. Follow-up was censored the day after (1) first non-IT phase determination, (2) HBV therapy initiation as part of clinical care (excluding short-term therapy use within an IT period), (3) clinical trial enrollment, or (4) IT phase determination followed by 60 or more weeks without a study assessment, whichever came first. Phase transition rate was calculated overall, by sex, age group, continent of birth, genotype (B vs C), and BCP mutation. Cox proportional hazards models were used to report unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of phase transition by these factors plus baseline ALT ($\times$ULN), qHBsAg ($\log_{10}$IU/mL), qHBeAg ($\log_{10}$IU/mL), and HBV DNA ($\log_{10}$IU/mL). A single multivariable model was built considering all variables with $P < .20$; variables in the model with $P > .10$ were removed using backward elimination. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary NC, 2000).

Results

Participant flow is shown in Figure 1. Among the IT cohort (n = 107), 52 (48%) were under 30 years, 33 (31%) were 30 to 39 years, and 22 (21%) were 40 years and older (range, 40 to 71 years). Characteristics of the IT cohort by age group are reported in Table 1. A higher percentage of older vs younger IT participants were born in Asia (69% under 30, 93% in 30–39, and 86% in >40 years of age; $P = .03$) and had genotype C (42%, 56%, and 62%, respectively; $P = .052$). Older IT participants had a longer estimated duration of infection (median: 23, 34, and 47 years, respectively; $P < .001$), likely due to older age, as the proportion with presumed vertical transmission was similar across age groups. Laboratory parameters were similar across IT age groups, however older vs younger IT participants had lower median albumin (median, 4.4, 4.3, and 4.2 g/dL, respectively; $P = .02$), and there appeared to be a trend toward lower platelets (median, 235, 221, and 215 $\times 10^3$/mm^3; $P = .11$) in older vs younger IT participants. There were no significant trends in viral characteristics (qHBsAg, qHBeAg, HBV DNA, genotype, and PC/BCP mutations) across IT age groups.

Compared with the IA-HBeAg+ cohort (n = 192), the IT cohort (n = 107) was younger (median age, 30 vs 36 years; $P < .001$), a smaller percentage were men (38% vs 51%; $P = .04$), and a higher percentage were Asian (95% vs 80%; $P < .0001$). Based on phase definition, IT participants had lower median ALT than IA-HBeAg+ participants (24 vs 77 U/L; $P < .001$). They also had lower median AST (22 vs 48 U/L; $P < .001$), alkaline phosphatase (64 vs 74 U/L; $P < .001$), and APRI (0.3 vs 0.6; $P < .001$), and higher median albumin (4.3 vs 4.2 mg/dL; $P = .02$) and platelets (225 vs 202 $\times 10^3$/mm^3; $P = .002$). qHBsAg (4.8 vs 4.3 log10 IU/mL; $P < .001$), qHBeAg (3.3 vs 2.9 log10 IU/mL; $P < .001$), and HBV DNA (8.3 vs 8.0 log10 IU/mL; $P < .001$) levels were also higher in the IT vs IA-HBeAg+ groups. The genotype distribution differed (eg, Genotype A: 2% IT vs 17% IA-HBeAg+ CHB; $P < .001$), and fewer IT vs IA-HBeAg+ participants had PC mutation

(4% vs 9%; *P* = .19) and BCP mutation (17% vs 44%; *P* < .001). No IT participants had a history of cirrhosis versus 0.5% (n = 1) of the IA-HBeAg+ cohort (*P* = .99).

To address the hypothesis that older adults in the IT phase would be more like those in the IA-HBeAg+ phase than younger adults in the IT phase, comparisons between IT participants who were 40 years old (n = 22) and the full IA-HBeAg+ cohort were performed (Table 1). Several characteristics that differed between participants in the overall IT vs IA-HBeAg+ phase (ie, sex, race, alkaline phosphatase, albumin, platelets), were no longer significantly different between the oldest IT group (40 years) and the IA HBeAg+ group (Table 1; last column); however, statistical power to detect potentially meaningful differences was low due to the small sample size of the older IT group.

Clinically relevant outcomes were uncommon in the HBRN cohort as a whole.[12] No HCCs, liver transplants or HBV-related deaths were reported in the IT cohort during follow-up (median, 234 weeks; range, 25–245 weeks); there was one death, not associated with HBV.

CHB Phases and HBV Antiviral Therapy Use Over Time Among the IT Cohort

Figure 2 shows CHB phase, HBV therapy use, and clinical trial participation in the IT cohort (n = 107) over time. Participants' first IT period, which started prior to study enrollment in 67% (n = 72) of the IT cohort, was a median duration of 74 weeks during study participation (range, 20–384 weeks). Following participants' first IT period, 55% (n = 59) transitioned to IA-HBeAg+, 3% (n = 3) to indeterminant HBeAg+, and 1% (n = 1) to inactive carrier. Six participants (6%) started HBV therapy, 9 (8%) enrolled in a clinical trial, and 29 (27%) remained in the IT phase through the end of follow-up. Status at end of follow-up is summarized in Supplementary Table 1. Among participants who started HBV therapy for clinial care during (n = 9) or immediately following (n = 6) an IT period, 60% (n = 9) were pregnant (HBV therapy duration median, 95 days; range, 59–128 days). The reason for HBV therapy in the other 6 participants, all of whom stayed on treatment until end of follow-up, is unknown; none cleared HBeAg or HBsAg (Supplementary Table 2).

Age group-specific heat maps are provided in Supplementary Figure 1. There was not an age trend in treatment initiation among the IT cohort (<30 years: 35% [n = 18], 30 to <40 years: 58% [n = 19], 40 years: 23% [n = 5]; *P* = .81).

Phase Transitions

Among the IT cohort, 60 participants had a phase transition during 206 person-year follow-up, a rate of 29.1 (95% CI, 22.6–37.5) per 100 person-years. The phase transition rate per 100 person-years (29.1; 95% CI, 22.6–37.5, overall) was lower in the 30 to 39 year group (24.8; 95% CI, 15.6–39.4) and 40 year group (27.4; 95% CI, 14.8–50.9) vs the <30 year group (33.0; 95% CI, 23.4–46.7), but 95% CIs overlapped. Among participants in the IT cohort who transitioned, the percentage who transitioned to IA HBeAg+ was 97% (n = 31), 94% (n = 17), and 80% (n = 8) in 18 to 30, 30 to <40 and 40 year olds, respectively. Phase transition rates appeared lower in females (26.0; 95% CI, 18.6–36.1) vs males (35.1; 95% CI, 23.8–52.0), but again, 95% CI overlapped and no other clinical or demographic factors were associated with phase transition (Supplementary Table 3). Higher baseline ALT (HR:1.18 (1.06, 1.32) per 1x ULN, p=.003) and lower qHBsAg (HR:2.34 (1.29, 4.26) per

log10 IU/mL, p=.005) and lower qHBeAg (HR:3.06 (1.65, 5.69) per log10 IU/mL, p<.001) were associated with transition from the IT phase. On multivariable analysis, only higher baseline ALT (HR, 1.19; 95% CI, 1.05–1.34; *P* = .006) and lower qHBsAg levels (HR, 2.73; 95% CI, 1.44–5.17; *P* = .002), were significantly associated with transition out of the IT phase (Supplementary Table 4).

Discussion

Among the large HBRN adult cohort study, we identified 107 participants who ever met criteria for having a period in the IT phase (ie, remained in IT phase for >20 weeks), 22 (21%) of whom were at least 40 years old. The older IT group was largely similar to the younger IT groups. As expected, IT participants had less active liver disease than IA-HBeAg+ participants. Although some of the differences between the IT group and IA-HBeAg+ were not statistically significant when the comparison was limited to the older IT subgroup, the lack of significance more likely reflects the small number of older IT participants rather than an imminent transition to active IA disease. In fact, the lowest rate of transitioning out of the IT phase was observed in the oldest IT group.

The association of HBeAg-positivity, high levels of HBV DNA, and increasing age with a higher risk of HCC in previous studies led AASLD, EASL, and APASL to recommend consideration of treatment of older IT patients.[4–6] Kim et al reported that, in a large Korean cohort, untreated patients in the IT phase had a higher rate of HCC and death than treated patients in the IA phase of disease.[13] They found that in addition to IT disease, age, male sex, and lower HBV DNA and platelet counts were associated with HCC risk, suggesting silent progression of liver disease despite meeting IT criteria or that those transitioning from the IT phase were at higher risk of outcomes. Additionally, previous studies have shown that patients with late (age 40 years) HBeAg seroconversion have a higher risk of cirrhosis and HCC.[14] Our finding that older IT participants did not appear to be imminently transitioning out of the IT phase may support recommendations to consider treatment in older IT patients; however; no events were reported in our IT cohort over a median follow-up of 234 weeks. A total of 15 participants were started on HBV therapy during or immediately following an IT period, the majority due to pregnancy. Only one was at least 40 years old. Given the absence of data on the effectiveness of HBV therapy to reduce HCC risk in IT patients, the decision to initiate HBV therapy in an older IT patient should be individualized.

Some of the controversy around management of patients in the IT phase relates to phase definitions. There is not universal agreement on the HBV DNA or ALT thresholds that define the IT phase. We used a threshold of HBV DNA above 10^7 IU/mL and ALT below $1.5 \times$ ULN in line with the HBRN IT treatment trials.[15,16] With ULN of 20 U/L for women and 30 U/L for men, our use of $1.5 \times$ ULN was in line with most studies that have used a threshold of 40 U/L to define the IT phase. Lee and colleagues found that HBV DNA levels above 10^7 IU/mL were associated with a low risk of transition to IA disease and a very low risk of HCC in long-term follow-up.[17] These and other authors have argued that studies reporting negative outcomes in IT patients were often including individuals with declining HBV DNA levels who were transitioning to early IA disease.[17,18] Indeed, in the Korean study by Kim et al, lower HBV DNA levels were associated with a higher risk of

HCC among untreated IT patients.[13] We found that lower qHBsAg and qHBeAg levels, as well as higher ALT levels, were associated with transition out of the IT phase, whereas age and HBV DNA levels were not, although statistical power was limited by our sample size. Although, on average, those who transitioned had higher ALT and lower qHBsAg/HBeAg levels prior to transition compared with those who did not transition during follow-up, their values were within the ranges that define the IT phase, making it difficult to use these markers to predict transition and signal the potential need for intervention, such as antiviral therapy.

Why some individuals remain in the IT phase until an advanced age is poorly understood. From the viral perspective, deep sequencing revealed that variants, particularly in the BCP, PC, and PreS regions, were more common in older than in younger IT patients. Higher viral diversity was associated with older age, as were lower levels of qHBeAg, qHBsAg, and HBV DNA, possibly indicating transition to IA-HBeAg+ disease.[19] We found that a higher proportion of IT participants in the 40 years age group had PC or BCP mutations, yet they were not more likely to transition to IA-HBeAg-negative phases. Aging is associated with immune senescence with ineffective pathogen-specific responses and low-grade inflammatory responses.[20,21] Furthermore, CHB is associated with global and HBV-specific T cell dysfunction regardless of clinical IT or IA phases.[22] Highly multiplexed imaging mass cytometry analysis of liver tissues from HBeAg+ CHB patients showed significantly lower hepatic adaptive and innate immune infiltrates in adults and children in the IT compared with the IA phase, with an age-associated increase in innate immune subsets.[23] Progressive fibrosis has also been reported to develop in at least some patients meeting the criteria for IT phase, particularly among those who are older.[24,25] Further immunological and virological characterization of older IT patients would be valuable to better understand if the delay in transition is virally or host-driven.

The following limitations should be considered. The number of older IT participants was limited. Whether 40 is the appropriate age threshold to define 'older IT' is unknown, but results were similar when we examined those above age 30, 35, or 50 years (data not shown). The age 40 threshold is also in line with AASLD guidelines that recommend consideration of treatment for older IT patients.[4] We used a standard HBV DNA and ALT threshold to define the IT phase, but our main results were robust to sensitivity analysis using lower HBV DNA and ALT thresholds previously defined by the HBRN[26] (data not shown). No clinically relevant outcomes occurred during follow-up in the IT cohort; however, 39% of participants initiated HBV treatment, which may have averted adverse outcomes. Additionally, follow-up duration was limited.

In summary, in a large North American cohort, we found that older adults (40 years) in the IT phase of CHB are not clinically or virologically distinct from younger adults in the IT phase. Transition to IA disease was relatively common, occurring in ~30% per year, but was not more frequent in the older patients. Additional studies of older IT patients would be helpful to better understand the virological and immunologic basis for persistent high viremia without overt hepatocellular injury to potentially guide optimal management of this challenging group of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Abbreviations used in this paper:

AASLD	American Association for the Study of Liver Disease
ALT	alanine aminotransferase
APASL	Asian Pacific Association for the Study of the Liver
APRI	AST to platelet ratio index
AST	aspartate aminotransferase
BCP	basal core promoter
CHB	chronic hepatitis B
EASL	European Association for the Study of the Liver
HBeAg	hepatitis B e antigen
HBRN	Hepatitis B Research Network
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
IA	immune active
IT	immunotolerant
PC	precure
ULN	upper limit of normal

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What You Need to Know

Background

Those in the immunotolerant (IT) phase of chronic hepatitis B virus infection typically transition to immune active phase of disease by in early adulthood. Characteristics of those who remain in the IT phase beyond age 40 are not well understood.

Findings

Patients who remain in the IT phase were not clinically or virologically distinct from younger adults in the IT phase. Transition to the immune active phase was common but was no more frequent among the older than younger IT patients.

Implications for Patient Care

Prior studies have shown that patients who remain in the IT phase are at high risk of active disease and liver cancer. Our observation that transition to immune active disease was not imminent in older IT patients would support the recommendation of international guidelines to consider treatment in older IT patients.
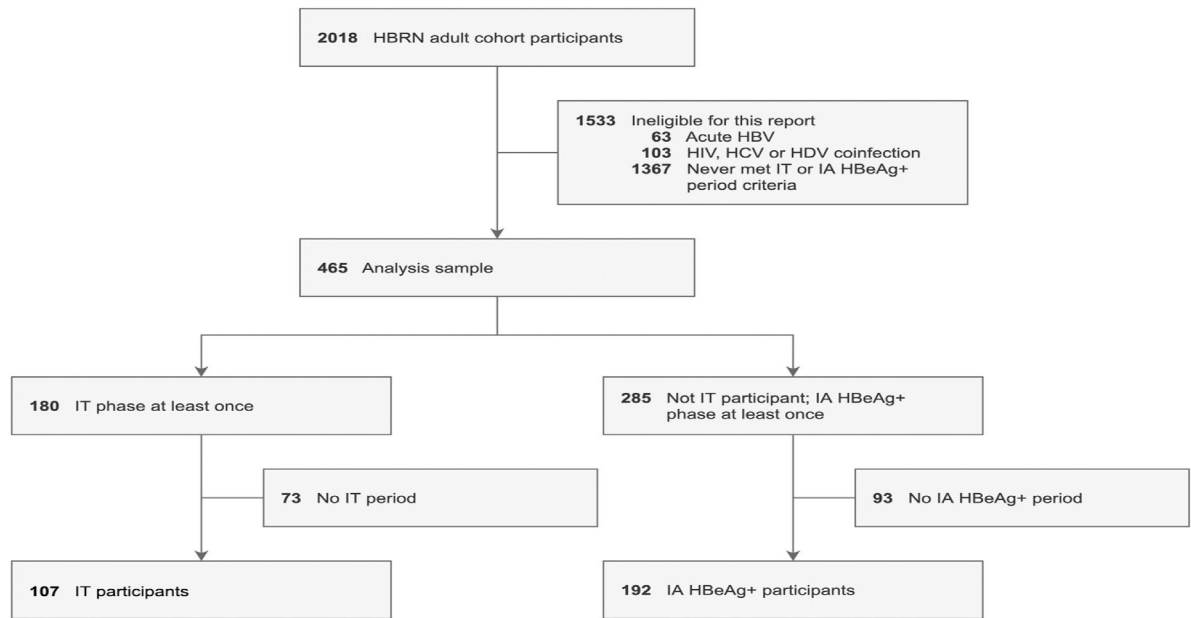
Figure 1.
Patient flow. Participant flow from HBRN adult cohort study entry to inclusion in the IT analysis (N = 299). HDV, Hepatitis D virus; HIV, human immunodeficiency virus

Figure 2.
Heat map of CHB phases over time among the IT cohort (N = 107). Transitions from the IT phase to other CHB phases are shown over time for each participant. Follow-up time is shown from the first sustained period in the IT phase for each participant until the end of follow-up.

Table 1.

Characteristics of Adults With CHB in the IT Phase, by Age Group, and Overall, vs Adults in the HBeAg+ IA Phase

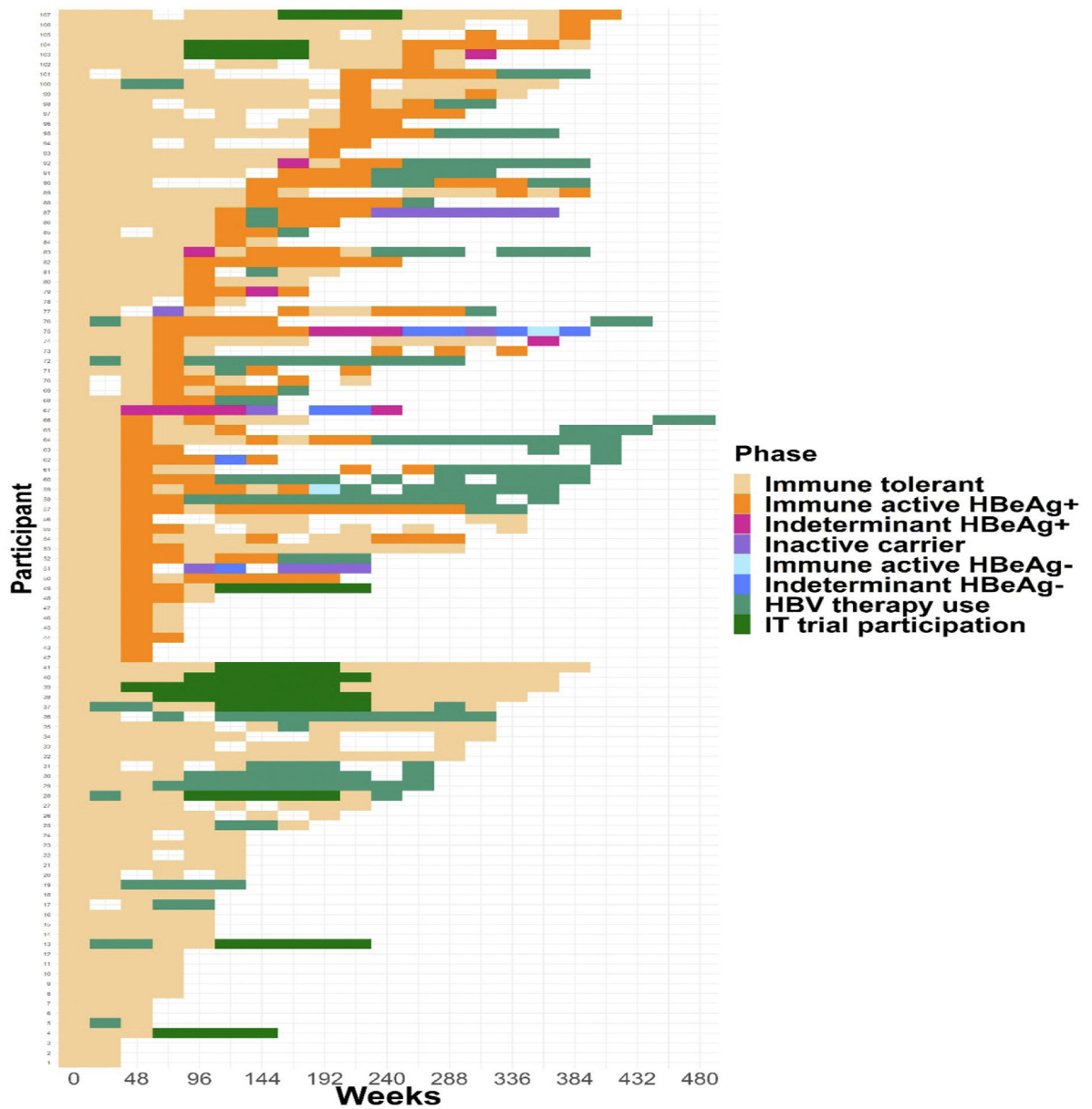| Variable	<30 (n = 52), n (%)	IT by age, y 30 to <40 (n = 33), n (%)	40 (n = 22), n (%)	P age trend	IT (n = 107), n (%)	IA (n = 192), n (%)	P IT vs IA	P 40 IT vs IA
Sex				.45			.04	.96
Male	19 (36.5)	11 (33.3)	11 (50.0)		41 (38.3)	97 (50.5)		
Female	33 (63.5)	22 (66.7)	11 (50.0)		66 (61.7)	95 (49.5)		
Race	n = 51	n = 28	n = 19	.57	n = 106	n = 191	<.001	.20
Asian	49 (96.1)	32 (97.0)	20 (90.9)		101 (95.3)	152 (79.6)		
Non-Asian	2 (3.9)	1 (3.0)	2 (9.1)		5 (4.7)	39 (20.4)		
Continent of birth				.03		n = 186	.27	.23
Asia	36 (69.2)	31 (93.9)	19 (86.4)		86 (80.4)	139 (74.7)		
Other	16 (30.8)	2 (6.1)	3 (13.6)		21 (19.6)	47 (25.3)		
BMI, kg/m^2	n = 49	n = 28	n = 19	.31	n = 97	n = 174	.07	.98
Median (IQR)	23.1 (19.9–24.9)	22.2 (20.6–25.6)	23.6 (22.3–25.9)		23.3 (20.2–25.7)	23.8 (21.1–26.8)		
Presumed mode of transmission	n = 48	n = 25	n = 16	.26	n = 89	n = 141	.26	.65
Vertical	40 (83.3)	16 (64.0)	12 (75.0)		68 (76.4)	98 (69.5)		
Horizontal	8 (16.7)	9 (36.0)	4 (25.0)		21 (23.6)	43 (30.5)		
Estimated duration of infection	n = 47	n = 27	n = 15	<.001	n = 89	n = 140	.39	<.001
Median (IQR)	23.0 (20.0–25.9)	34.1 (30.0–37.0)	47.0 (41.8–52.0)		26.0 (22.0–36.9)	29.0 (22.0–39.0)		
Estimated duration of infection among those with horizontal transmission	n = 6	n = 7	n = 2	.08	n = 15	n = 28	.18	.51
Median (IQR)	19.0 (16.0–22.7)	31.0 (21.5–37.0)	30.0 (12.0–48.0)		22.7 (16.0–34.0)	18.0 (10.0–30.8)		
ALT × ULN				.95			<.001	<.001
Median (IQR)	1.1 (0.8–1.3)	1.1 (0.8–1.3)	1.1 (0.9–1.3)		1.1 (0.8–1.3)	3.1 (2.1–4.8)		
ALT, U/L				.67			<.001	<.001
Median (IQR)	24 (18–30)	24 (19–29)	24 (19–37)		24 (19–30)	76.5 (52–118.5)		
AST, U/L	n = 51	n = 30	n = 20	.63	n = 101	n = 188	<.001	<.001
Median (IQR)	23 (19.5–25)	22 (21–24)	23 (20–29)		22 (20–26)	48 (36–70.5)		
Alkaline phosphatase, U/L				.34		n = 182	<.001	.32
Median (IQR)	67 (59–79)	61.5 (53–67)	72 (50–92.5)		64 (55–77)	73.5 (60–91)		

Variable	<30 (n = 52), n (%)	IT by age, y 30 to <40 (n = 33), n (%)	40 (n = 22), n (%)	P age trend	IT (n = 107), n (%)	IA (n = 192), n (%)	P IT vs IA	P 40 IT vs IA
Total bilirubin, *mg/dL*		n = 32			n = 106	n = 188		
Median (IQR)	0.6 (0.4–1.0)	0.6 (0.4–0.9)	0.7 (0.6–0.9)	.38	0.6 (0.4–0.9)	0.6 (0.5–0.8)	.90	.15
Albumin, *g/dL*		n = 32	n = 20		n = 104	n = 182		
Median (IQR)	4.4 (4.2–4.6)	4.3 (4.2–4.5)	4.2 (3.9–4.3)	.02	4.3 (4.1–4.5)	4.2 (3.9–4.4)	.02	.34
Platelets, × $10^3/mm^3$	n = 48	n = 30	n = 15		n = 93	n = 167		
Median (IQR)	235 (205–266)	221 (172–252)	215 (171–266)	.11	228 (195–266)	202 (167–243)	.002	.46
APRI	n=48	n=30	n=15		n=93	n=165		
<0.5	46 (95.8)	28 (93.3)	13 (86.7)	0.27	87 (93.5)	55 (33.3)	<.001	<.001
0.5–1.5	1 (2.1)	2 (6.7)	2 (13.3)		5 (5.4)	83 (50.3)		
>1.5	1 (2.1)	0 (0.0)	0 (0.0)		1 (1.1)	27 (16.4)		
HBsAg (log10 IU/mL)	n = 47	n = 24	n = 15		n = 87	n = 163		
Median (IQR)	4.7 (4.5–4.9)	4.7 (4.4–5.0)	4.8 (4.6–5.0)	.34	4.8 (4.5–4.9)	4.3 (3.7–4.7)	<.001	.02
HBeAg, *log10 IU/mL*	n = 51	n = 31			n = 104	n = 176		
Median (IQR)	3.3 (3.2–3.4)	3.4 (3.2–3.5)	3.4 (3.1–3.5)	.43	3.3 (3.2–3.4)	2.9 (1.9–3.3)	<.001	<.001
HBV DNA, *log10 IU/mL*	n = 51	n = 31			n = 104	n = 187		
Median (IQR)	8.3 (8.1–8.5)	8.3 (8.1–8.6)	8.3 (8.1–8.4)	.84	8.3 (8.1–8.5)	8.0 (7.0–8.3)	<.001	.004
HBV genotype		n = 32	n = 21		n = 105	n = 187		
B	28 (53.8)	12 (37.5)	6 (28.6)	.052	46 (43.8)	54 (28.9)	<.001	.29
C	22 (42.3)	18 (56.3)	13 (61.9)		53 (50.5)	89 (47.6)		
Other^c	2 (3.8)	2 (6.3)	2 (9.5)		6 (5.7)	44 (23.5)		
PC mutation (G1896A)	n = 44	n = 29	n = 17		n = 90	n = 144		
Wild type	42 (95.5)	28 (96.6)	16 (94.1)	.99	86 (95.6)	131 (91.0)	.19	.66
Any mutation	2 (4.5)	1 (3.4)	1 (5.9)		4 (4.4)	13 (9.0)		
Any BCP mutation (A1762T or G1764A)	n = 42	n = 29	n = 15		n = 86	n = 135		
Wild type	35 (83.3)	23 (79.3)	13 (86.7)	.99	71 (82.6)	76 (56.3)	<.001	.02
Any mutation	7 (16.7)	6 (20.7)	2 (13.3)		15 (17.4)	59 (43.7)		

Abbreviations: ALT, Alanine transaminase; APRI, AST-platelet-ratio index; AST, aspartate aminotransferase; BCP, basal core promoter; BMI, body mass index; CHB, chronic hepatitis B virus; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HBRN, Hepatitis B Research Network; HBeAg, hepatitis B e antigen; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; IA, immune active; IQR, interquartile range; IT, immunotolerant; PC, pre-core; ULN, upper limit of normal.