CLINICAL LIVER

Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study)

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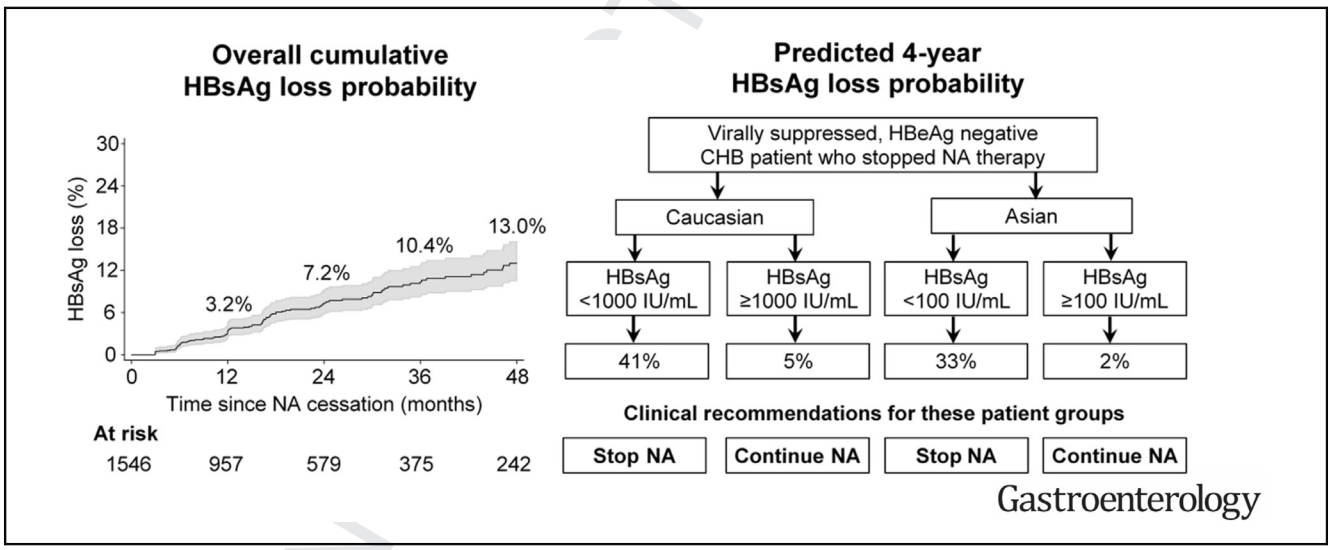

BACKGROUND AND AIMS: Functional cure, defined based on hepatitis B surface antigen (HBsAg) loss, is rare during nucleos(t)ide analogue (NA) therapy and guidelines on finite NA therapy have not been well established. We aim to analyze off-therapy outcomes after NA cessation in a large, international, multicenter, multiethnic cohort of patients with chronic hepatitis B (CHB). **METHODS:** This cohort study included patients with virally suppressed CHB who were hepatitis B e antigen (HBeAg)–negative and stopped NA therapy. Primary outcome was HBsAg loss after NA cessation, and secondary outcomes included virologic, biochemical, and clinical relapse, alanine aminotransferase flare, retreatment, and liver-related events after NA cessation. **RESULTS:** Among 1552 patients with CHB, cumulative probability of HBsAg loss was 3.2% at 12 months and 13.0% at 48 months of follow-up. HBsAg loss was higher among whites (vs Asians: subdistribution hazard ratio, 6.8; 95% confidence interval, 2.7–16.8; $P < .001$) and among patients with HBsAg levels <100 IU/mL at end of therapy (vs ≥100 IU/mL: subdistribution hazard ratio, 22.5; 95% confidence interval, 13.1–38.7; $P < .001$). At 48 months of follow-up, whites with HBsAg levels <1000 IU/mL and Asians with HBsAg levels <100 IU/mL at end of therapy had a high predicted probability of HBsAg loss (>30%). Incidence rate of hepatic decompensation and hepatocellular carcinoma

was 0.48 per 1000 person-years and 0.29 per 1000 person-years, respectively. Death occurred in 7/19 decompensated patients and 2/14 patients with hepatocellular carcinoma. **CONCLUSIONS:** The best candidates for NA withdrawal are virally suppressed, HBeAg- negative, noncirrhotic patients with CHB with low HBsAg levels, particularly whites with <1000 IU/mL and Asians with <100 IU/mL. However, strict surveillance is recommended to prevent deterioration.

Keywords: HBV; Discontinuation; Antiviral; HBsAg seroconversion.

Hepatitis B virus (HBV) infection remains a major public health concern with significant morbidity and mortality, affecting 292 million individuals globally.[1] Currently approved agents for management include (pegylated [PEG]-)interferon and nucleos(t)ide analogue (NA) therapies.[2–5] Despite the advent of effective oral antiviral agents with a good safety profile,[6,7] the majority of the patients with chronic hepatitis B (CHB) require long-term management and treatment. NAs have been shown to reduce progression toward cirrhosis, liver failure, and hepatocellular carcinoma (HCC),[8–11] however, even with sustained HBV DNA suppression, the risk of long-term complications, particularly HCC, remains.[12,13] Hepatitis B surface antigen (HBsAg) loss, which is considered the functional cure, is rare on NA therapy.[2,4,14–22] Long-term adherence, compliance, drug safety, and financial and emotional burdens for patients and caregivers present additional challenges.[23,24]

Finite NA therapy has been proposed as an alternative to long-term treatment. Because virologic relapse is nearly universal, even after prolonged viral suppression,[25] the rationale for stopping NAs is to ultimately induce a durable remission in the form of an inactive carrier state or, ideally a functional cure.[12] However, the occurrence of a combined virologic and biochemical relapse can range from mild alanine aminotransferase (ALT) elevations to clinically significant ALT flares, which may even result in hepatic decompensation.[17,26–31] Because such findings raise concerns on whether the current criteria for stopping NAs are applicable to all patients with CHB, the safe cessation of NA therapy remains one of the most controversial topics in the clinical management of CHB with discordance between guidelines.[2,4,19,32–34]

Existing studies included small, single-center cohorts with different study-specific endpoints. Based on the patient population and study design, studies on finite NA therapy have reported off-therapy HBsAg loss rates with wide variability ranging from 0%–55% over follow-up periods spanning 0.5–8 years.[17,35–42] Thus, a large cohort with individual patient-level data with sufficient statistical power to analyze the safety and efficacy of NA cessation in patients with CHB is required. The main objective of this study was to investigate factors associated with HBsAg loss, and describe virologic, biochemical, and clinical responses after cessation of NA therapy with the hope to improve current patient management and help in the design of prospective HBV cure studies.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Functional cure, or hepatitis B surface antigen loss is rare on nucleos(t)ide analogue therapy. Nucleos(t)ide analogue withdrawal as a therapeutic alternative remains elusive in clinical practice because current knowledge is mainly based on small and single-center studies.

NEW FINDINGS

In this global study of individual patient-level data on 1552 patients with chronic hepatitis B who stopped nucleos(t)ide analogue therapy, cumulative off-therapy hepatitis B surface antigen loss probability was 3.2% at 1 year, and 13.0% at 4 years (annual incidence: 2.9 per 1000 person-years). The predicted probability was >30% among whites with hepatitis B surface antigen <1000 IU/mL and Asians with hepatitis B surface antigen <100 IU/mL at nucleos(t)ide analogue withdrawal, while controlling for other factors.

LIMITATIONS

Some bias may persist due to heterogeneity across centers despite adjusting for potential confounders and accounting for differences in retreatment criteria.

IMPACT

These findings identify factors associated with off-therapy hepatitis B surface antigen loss that help in the selection of patients for nucleos(t)ide analogue withdrawal.

Methods

This is a large, global, multicenter, multiethnic cohort study of patients with CHB who stopped NA therapy between 2001 and 2020 from 13 participating centers across Asia, Europe, and North America (Figure 1, Supplementary Table 1).[17,21,38,41,43–45] A standardized case report form was used to capture data. All data cleaning, data quality assessments, and analyses were centralized at the Toronto Centre for Liver Disease (University Health Network, Canada). After anonymized and deidentified individual patient-level longitudinal data were received from the participating centers, meticulous data queries were sent to each center to ensure accuracy. According to local rules, the study was approved by the research ethics board of each participating center and performed in concordance with Good Clinical Practice guidelines and the Declaration of Helsinki 1964 as modified by the 59th WMA General Assembly, Seoul, South Korea, in October 2008, and the local national laws governing the conduct of clinical research studies.

Abbreviations used in this paper: **ALT, alanine aminotransferase; anti-HBs, hepatitis B surface antibody; CHB, chronic hepatitis B; CI, confidence interval; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analogue; PEG, pegylated; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.**

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Study Population and Variables

Adult patients (aged ≥18 years) with CHB (HBsAg positive >6 months) were included if they were virally suppressed and hepatitis B e antigen (HBeAg)–negative at the end of therapy (Figure 1). Stopping criteria and retreatment criteria varied by center location as listed in Supplementary Table 1. Patients who had previously been diagnosed with HCC, patients with coinfection (hepatitis C virus, hepatitis delta virus, and/or human immunodeficiency virus), and patients who received (PEG-)interferon treatment within 12 months prior to NA cessation were excluded from this study. NA therapy duration refers to the duration of continuous NA therapy including consolidation. Follow-up refers to time since NA cessation while the patient remained off-therapy. The patient was defined as being cirrhotic if cirrhosis had been diagnosed before cessation. Cirrhosis was diagnosed based on histologic findings or ultrasonographic evidence with or without splenomegaly. Hepatic decompensation was defined based on development of a serum total bilirubin level ≥2 mg/dL, an increased INR, appearance of clinical jaundice, onset of ascites, variceal bleeding, or hepatic encephalopathy.

Laboratory Assays

Quantitative or qualitative HBsAg, HBeAg, and HBV DNA was determined using in-house or commercially available assays as described in Supplementary Table 2. The upper limit of normal (ULN) for ALT values as defined by each participating center was used.

Off-Therapy Outcome Measures

The main outcome analyzed in this study was HBsAg loss after NA cessation, with or without seroconversion to hepatitis B surface antibody (anti-HBs).[32,46] Secondary outcomes after NA cessation included virologic, biochemical, and clinical relapse, ALT flare, retreatment, liver-related events including hepatic decompensation and HCC, and mortality. Virologic relapse was defined as a single elevation of HBV DNA ≥2000 IU/mL, biochemical relapse was defined as a single elevation of ALT ≥2x ULN, and clinical relapse was defined as elevations of HBV DNA ≥2000 IU/mL and ALT ≥2x ULN at the same visit. An ALT flare was defined as ALT ≥5x ULN with or without virologic relapse. Hepatic decompensation was considered related to NA cessation if diagnosed off-therapy or within 6 months of starting retreatment. HCC was only considered to have occurred off-therapy if diagnosed at least 6 months after NA cessation, and within 6 months of starting retreatment if retreated.

Statistical Analysis

Clinical and demographic characteristics of the study cohort were presented as frequencies and proportions for categorical variables, and mean ± standard deviation or median (range), as appropriate, for continuous variables. Cumulative probabilities were estimated using Kaplan–Meier analysis and compared between groups using the log-rank test. All outcomes were analyzed while the patient remained off-therapy. Patients were censored at the last recorded visit date, date lost-to-follow-up, or at retreatment if retreated. While analyzing retreatment as an outcome, patients were censored at the last recorded visit date, date lost-to-follow-up, or at HBsAg loss. Competing risks regression using the Fine-Gray subdistribution method was used to analyze factors associated with HBsAg loss, modeled with retreatment as a competing risk.[47] Variables were entered into the multivariable model a priori based on the hypothesized effect on the outcome and clinical relevance. To develop a clinically meaningful rule, the predicted probability of HBsAg loss in different patient subgroups was calculated. These probabilities are estimates calculated at the mean of all other covariates in the multivariable model. Incidence rates were calculated over an off-therapy follow-up period of 120 months for all outcomes except hepatic decompensation for which a follow-up period of 48 months was used. For Kaplan-Meir and competing risks regression analyses, the latest time under which patients were both under observation and at risk was 48 months. A two-tailed P value $< .05$ was considered statistically significant. Statistical analyses used STATA Version 15.1 (StataCorp, College Station, TX).

Results

Characteristics of the Study Cohort

Of 1726 patients with CHB who stopped NA therapy, 1552 met the inclusion and exclusion criteria for this study (Figure 1). Patient characteristics have been described in Table 1. Mean age at end of therapy was 52.9 ± 11.3 years, and 72.3% were male, 87.6% were Asian, and 11.3% were white. Genotype B (42.7%) was the most prevalent genotype followed by genotype C (11.0%); however, genotype was unavailable for 42.7% of the cohort due to low or undetectable levels of HBV DNA. Most patients received either entecavir (ETV; 63.2%) or tenofovir disoproxil fumarate (TDF; 27.1%) therapy before cessation. The median follow-up duration was 18.4 (range, 7.9–39.4) months. At end of therapy, 11.9% had been previously diagnosed with cirrhosis, mean HBsAg was 2.6 ± 0.8 $\log_{10}$ IU/mL, and median ALT × ULN was 0.6 (range, 0.4–0.8).

Outcomes After NA Cessation

HBsAg loss. Overall, 114 patients achieved HBsAg loss with an incidence rate of 2.9 per 1000 person-years. The cumulative probability of HBsAg loss increased from 1.3% (95% confidence interval [CI], 0.8%–2.1%) at 6 months to 3.2% (95% CI, 2.3%–4.4%) at 12 months and reached 13.0% (95% CI, 10.5%–16.0%) at 48 months of follow-up (Figure 2*A*). No HBsAg reversions were reported.

When stratified by baseline characteristics, there were statistically significant differences in the cumulative probability of HBsAg loss by age at end of therapy ($P = .03$), race/ethnicity ($P < .001$), NA type before cessation ($P = .01$), and HBsAg levels at end of therapy ($P < .001$) (Figure 3). At 48 months of follow-up, the cumulative probability of HBsAg loss was higher among patients aged ≥50 years at end of therapy (16.8%; 95% CI, 12.9%–21.7%) compared with those aged <50 years (8.7%; 95% CI, 6.0%–12.5%) (Figure 3*A*), among whites (36.5%; 95% CI, 26.0%–49.5%) compared with Asians (10.6%; 95% CI, 8.1%–13.7%) (Figure 3*C*), among patients treated with TDF before cessation (18.1%; 95% CI, 12.2%–26.5%) compared with ETV-treated patients (10.5%; 95% CI, 7.8%–14.2%)

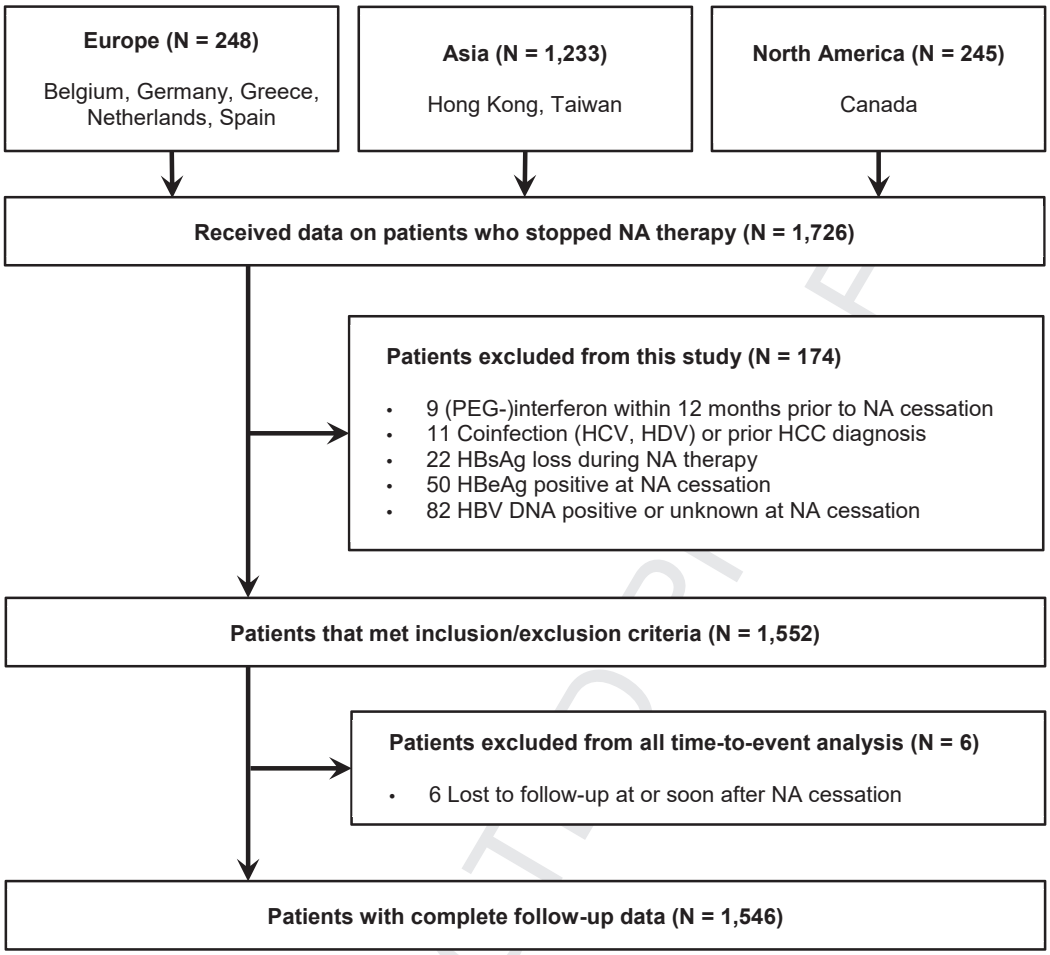

Figure 1. Flow diagram of patient inclusion and exclusion. HCV, hepatitis C virus.

(Figure 3*D*), and among patients with HBsAg <100 IU/mL at end of therapy (43.0%; 95% CI, 34.4–52.7%) compared with patients with HBsAg levels between 100–1000 IU/mL at end of therapy (7.4%; 95% CI, 4.6–11.7%) or HBsAg >1000 IU/mL at end of therapy (1.1%; 95% CI, 0.3–3.5%; Figure 3*F*).

Univariate competing risks regression yielded results similar to those of the Kaplan-Meir analysis. Rate of HBsAg loss was significantly higher among whites compared with Asians (subdistribution hazard ratio, 4.9; 95% CI, 3.2–7.4; $P < .001$) and patients treated with TDF before cessation compared with ETV-treated patients (subdistribution hazard ratio, 1.8; 95% CI, 1.1–2.7; $P = .01$) (Table 2). HBsAg levels at the end of therapy were strongly associated with HBsAg loss, and patients with HBsAg <100 IU/mL at the end of therapy had the highest rate of HBsAg loss. Longer NA duration and prior (PEG-)interferon treatment were also significantly associated with HBsAg loss (Table 2). On adjusted multivariable competing risks regression, rate of HBsAg loss was 6.8 times higher (95% CI, 2.7–16.8; $P < .001$) among whites compared with Asians, and 22.5 times higher (95% CI, 13.1– 38.7; $P < .001$) among patients with HBsAg levels <100 IU/mL at the end of therapy compared with patients with HBsAg levels ≥100 IU/mL at the end of therapy. Start of therapy HBeAg status was not significant on univariate or multivariable analyses. There were no interactions included in the multivariable model presented in Table 2.

When exploring interactions between race and HBsAg levels at the end of therapy, we analyzed 3 thresholds for HBsAg levels: 10 IU/mL (1 $\log_{10}$), 100 IU/mL (2 $\log_{10}$), and 1000 IU/mL (3 $\log_{10}$) (Figure 4). In this cohort, the average predicted probabilities of HBsAg loss at 48 months of follow-up among patients with low HBsAg levels of <10 IU/mL at the end of therapy were comparable and >75% among whites and Asians (P = not significant [NS]; Q17 Figure 4*A*); however, the predicted probabilities of HBsAg loss were considerably higher among whites with HBsAg levels <100 IU/mL (84.1%; Figure 4*B*) or <1000 IU/mL (40.9%; Figure 4*C*) at end of therapy compared with Asians using the same cut-points (<100 IU/mL: 32.5%; <1000 IU/mL: 9.7%) ($P < .01$ for both comparisons). Patient characteristics based on race/ethnicity have also been described in Supplementary Table 3.

Virologic and biochemical responses. Virologic relapse occurred in 1207 patients, and cumulative probabilities increased from 47.8% (95% CI, 45.3%–50.3%) at 6 months to 68.9% (95% CI, 66.5%–71.2%) at 12 months and reached 83.4% (95% CI, 81.2%–85.5%) at 48 months of follow-up (Figure 2*B*). Biochemical relapse occurred in 757

patients, and cumulative probabilities increased from 22.3% (95% CI, 20.2%–24.5%) at 6 months to 38.1% (95% CI, 35.5%–40.7%) at 12 months of follow-up and reached 61.1% (95% CI, 58.0%–64.2%) at 48 months (Figure 2*C*). Clinical relapse occurred in 658 patients, and cumulative probabilities increased from 17.2% (95% CI, 15.4%–19.3%) at 6 months to 31.9% (95% CI, 29.4%–34.4%) at 12 months of follow-up and reached 54.6% (95% CI, 51.5%–57.7%) at 48 months (Figure 2*D*). An ALT flare occurred in 359 patients, and cumulative probabilities increased from 10.5% (95% CI, 9.0%–12.2%) at 6 months to 18.6% (95% CI, 16.6%–20.8%) at 12 months of follow-up and reached 30.8% (95% CI, 27.9%–33.9%) at 48 months (Figure 2*E*).

Retreatment. After NA cessation, 729 patients were retreated, and the cumulative probability of retreatment increased from 16.2% (95% CI, 14.4%-18.2%) at 6 months to 29.8% (95% CI, 27.5%–32.2%) at 12 months of follow-up and reached 54.7% (95% CI, 51.7%-57.7%) at 48 months (Figure 2*F*). There were statistically significant differences in the cumulative probability of retreatment by age group ($P < .001$), start of therapy HBeAg status ($P = .02$), and HBsAg levels at end of therapy ($P < .001$) (Supplementary Figure 1).

Liver-related events and mortality. There were 19 patients who developed hepatic decompensation after NA cessation (8/184 [4.3%] patients with cirrhosis vs 11/1368 [0.8%] patients without cirrhosis; $P < .001$) with an incidence rate of 0.48 per 1000 person-years. No decompensating events occurred after 48 months of follow-up. Among patients who developed hepatic decompensation, 1/19 (5.3%) had subsequent HBsAg loss, and 16/19 (84.2%) started retreatment. Death occurred in 7 (36.8%) of the 19 decompensated patients, of whom 6 died after starting retreatment. In 4/7 (57.1%), death was reported to be related to a hepatitis B–associated flare. Among the other 3/7 (42.9%) deaths, 1 patient died due septic shock caused by urosepsis, 1 died due to lymphoma, and 1 died due to cholangiocarcinoma.

Table 1. Characteristics of the Patients Who Stopped NA Therapy

Total, N	1552
Age at end of therapy, *y*, mean ± SD	52.9 ± 11.2
Male sex, n (%)	1122 (72.3)
Race/ethnicity: white/Asian/black/other, n (%)	175 (11.3)/1359 (87.6)/13 (0.8)/5 (0.3)
HBV genotype: A/B/C/D/other/missing, n (%)	9 (0.6)/662 (42.7)/170 (11.0)/45 (2.9)/4 (0.3)/662 (42.7)
Prior (PEG-)interferon, n (%)	133 (8.6)
NA-naïve, n (%)	1292 (83.3)
NA type before cessation: ETV/TDF/other, n (%)	981 (63.2)/421 (27.1)/150 (9.7)
Minimum consolidation, *y*: <1/1–2/≥3	83 (5.4)/1129 (72.7)/340 (21.9)
NA duration,[a] *y*, median (range)	3.0 (3.0–4.0)
Number of follow-up visits, median (range)	6 (3–9)
Follow-up duration between visits, *months*, median (range)	2.8 (2.0–5.0)
Total follow-up duration, *months*, median (range)	18.4 (7.9–39.4)
At start of therapy[b]	
HBeAg-negative, n (%)	1306 (84.2)
HBV DNA, log10 IU/mL, mean ± SD	5.9 ± 1.6
ALT x ULN, median (range)	3.0 (1.9–7.3)
At end of therapy (NA cessation)[c]	
HBsAg, log10 IU/mL, mean ± SD	2.6 ± 0.8
HBsAg, IU/mL: <100/100–1000/>1000, n (%)	225 (14.5)/682 (43.9)/463 (29.8)
Cirrhosis,[d] n (%)	184 (11.9)
ALT x ULN, median (range)	0.6 (0.4–0.8)

[a]NA duration was unknown for 15 (1%) patients.
[b]At start of therapy, HBeAg status was unavailable for 11 (0.7%), HBV DNA levels were unavailable for 190 (12%), and ALT levels were unavailable for 376 (24%) patients.
[c]At end of therapy, HBsAg levels were unavailable for 182 (12%), and ALT levels were unavailable for 47 (3%) patients.
[d]Patient was defined as cirrhotic at end of therapy if cirrhosis had been diagnosed at any time before NA cessation.

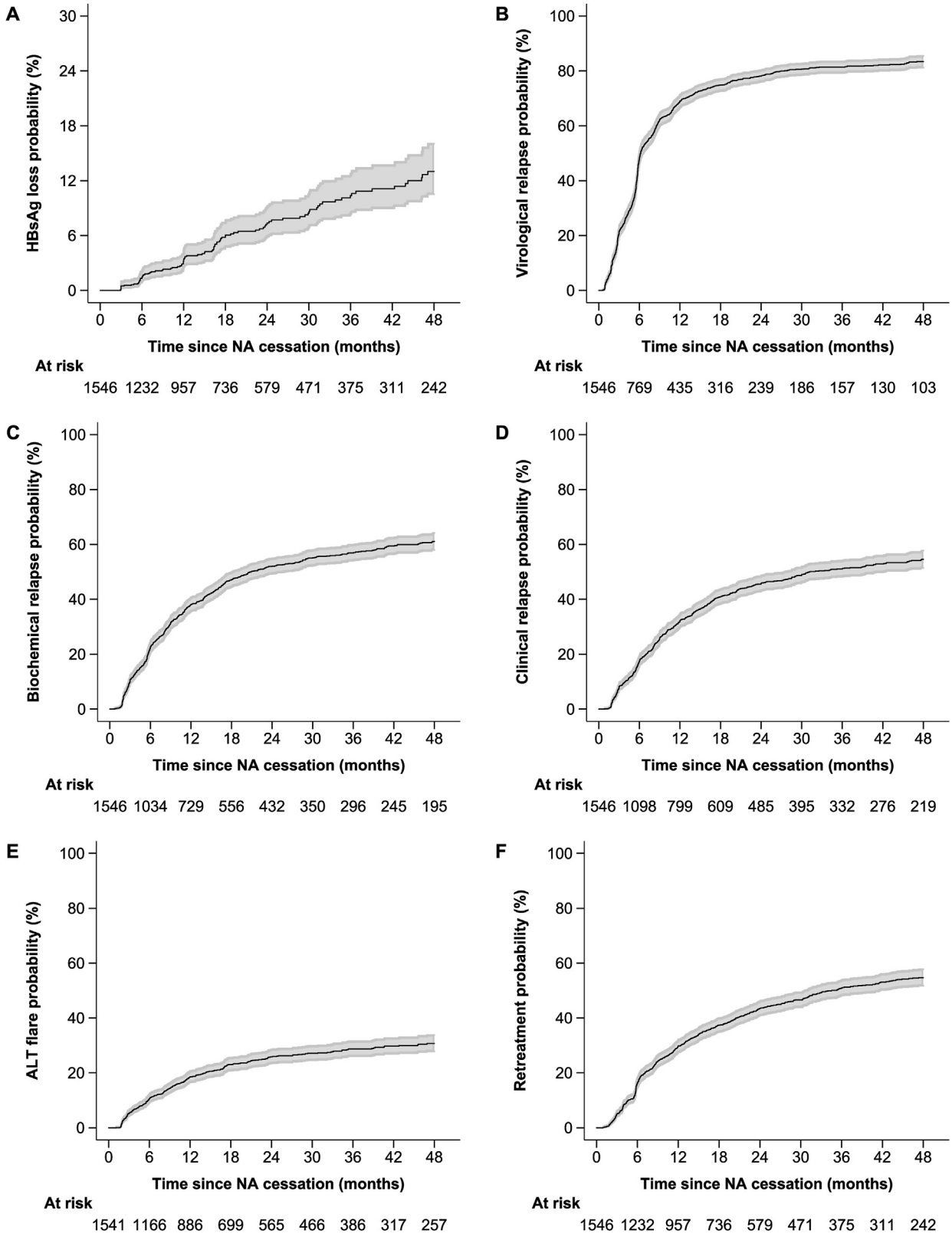

Figure 2. Cumulative probability of outcomes during off-therapy follow-up: (*A*) HBsAg loss, (*B*) virologic relapse (HBV DNA ≥2000 IU/mL), (*C*) biochemical relapse (ALT ≥2x ULN), (*D*) clinical relapse (HBV DNA ≥2000 IU/mL and ALT ≥2x ULN), (*E*) ALT flare (ALT ≥5x ULN), and (*F*) retreatment.

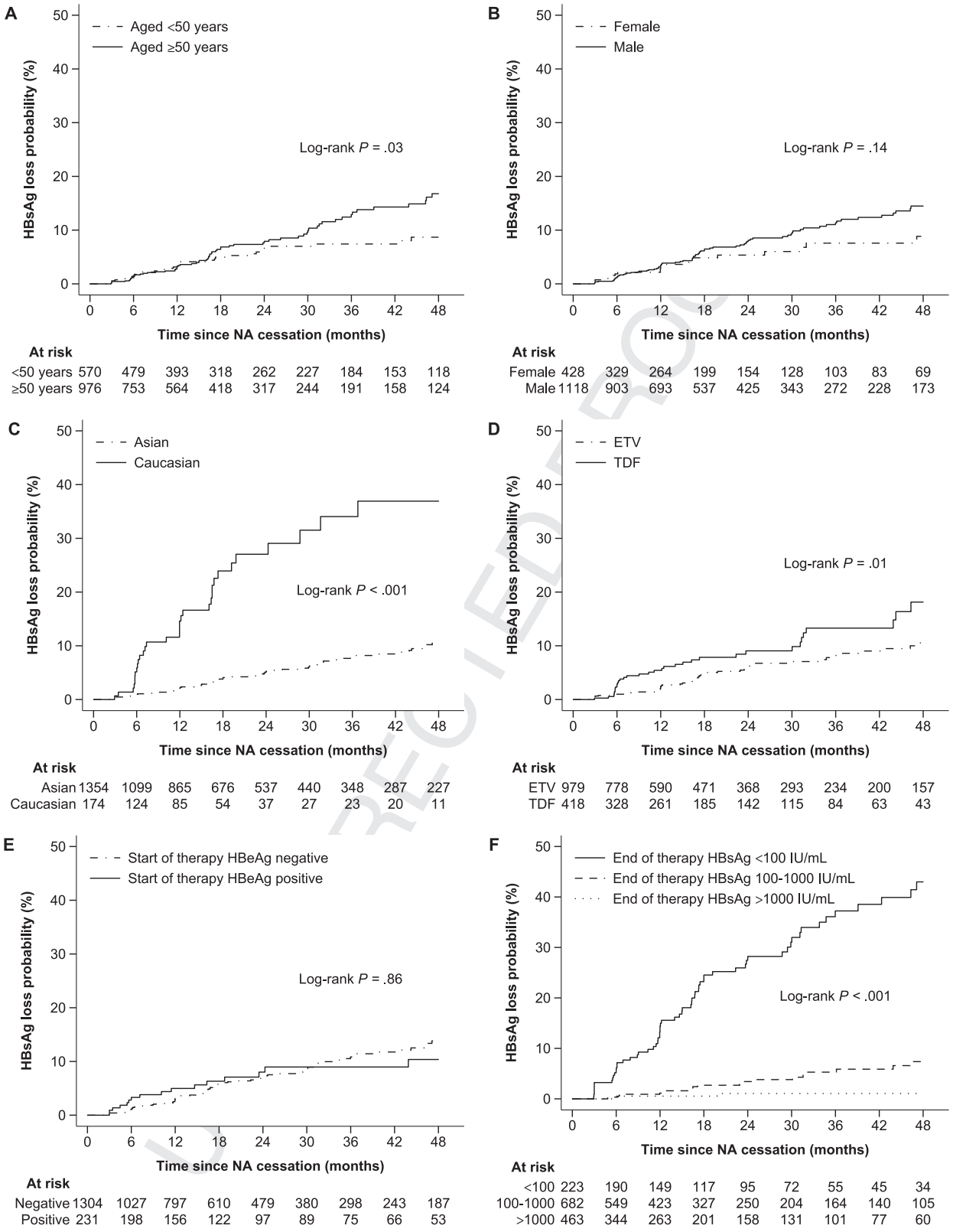

Figure 3. Cumulative probability of HBsAg loss by patient characteristics: (*A*) age at NA cessation, (*B*) sex, (*C*) race/ethnicity, (*D*) NA type before cessation, (*E*) start of therapy HBeAg status, and (*F*) end of therapy HBsAg levels.

There were 14 patients who developed HCC at least 6 months after NA cessation (4/184 [2.2%] patients with cirrhosis vs 10/1368 [0.7%] patients without cirrhosis; $P =$ NS) with an incidence rate of 0.29 per 1000 person-years. Among patients who developed HCC, 1/14 (7.1%) had subsequent HBsAg loss whereas 1/14 (7.1%) had HBsAg loss before HCC diagnosis, and 6/14 (42.9%) started retreatment. Death occurred in 2 (14.3%) of the 14 patients with HCC, of whom 1 died after starting retreatment. Two additional cases of HCC were reported off-therapy within 6 months after cessation.

No patients included in this study developed both hepatic decompensation and HCC. There were 5 other deaths among patients who did not develop liver-related complications off-therapy, of whom 3 died after starting retreatment.

Discussion

In this study of 1552 patients with CHB who stopped NA therapy, the cumulative probability of HBsAg loss at year 1 of follow-up was 3.2%, which more than quadrupled to 13.0% by year 4. As would be expected, by year 4 of follow-up, most of the cohort had virologic relapse (83.4%) while the rates of clinical relapse were lower (54.6%), and 54.7% of the cohort had started retreatment. This study is unique in that, to our knowledge, it is the first study to use individual patient-level data to analyze outcomes after cessation

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Table 2. Fine-Gray Competing Risks Regression Models for HBsAg Loss

	Univariate		Multivariable	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Age at end of therapy, *y*	1.01 (0.99–1.02)	.55	0.99 (0.97–1.01)	.24
Age at end of therapy, *y*				
<50 y	1.00 (reference)			
≥50 y	1.28 (0.83–1.96)	.26		
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.45 (0.88–2.37)	.14	0.98 (0.57–1.70)	.96
Race/ethnicity				
Asian	1.00 (reference)		1.00 (reference)	
White	4.86 (3.19–7.41)	<.001	6.80 (2.75–16.8)	<.001
Prior (PEG-)interferon				
No	1.00 (reference)			
Yes	2.18 (1.28–3.73)	.004		
NA type				
ETV	1.00 (reference)		1.00 (reference)	
TDF	1.76 (1.14–2.73)	.01	1.29 (0.81–2.05)	.29
Other	2.02 (1.13–3.59)	.02	0.48 (0.17–1.36)	.17
NA duration, *y*	1.16 (1.10–1.23)	<.001	1.05 (0.96–1.16)	.29
HBeAg at start of therapy				
Negative	1.00 (reference)		1.00 (reference)	
Positive	1.07 (0.62–1.84)	.81	1.57 (0.69–3.57)	.28
HBsAg levels at end of therapy, $\log_{10}$ IU/mL	0.24 (0.19–0.30)	<.001		
HBsAg level at end of therapy				
≥100 IU/mL	1.00 (reference)		1.00 (reference)	
<100 IU/mL	15.6 (9.75–25.0)	<.001	22.5 (13.1–38.7)	<.001
HBsAg level at end of therapy				
>1000 IU/mL	1.00 (reference)			
100–1000 IU/mL	4.74 (1.41–15.9)	.01		
<100 IU/mL	50.4 (15.7–161)	<.001		
Cirrhosis at end of therapy				
Noncirrhotic	1.00 (reference)			
Cirrhotic	1.01 (0.56–1.84)	.96		
ALT x ULN at end of therapy $\log_{10}$ ULN	1.28 (0.58–2.82)	.54		

SHR, subdistribution hazard ratio.

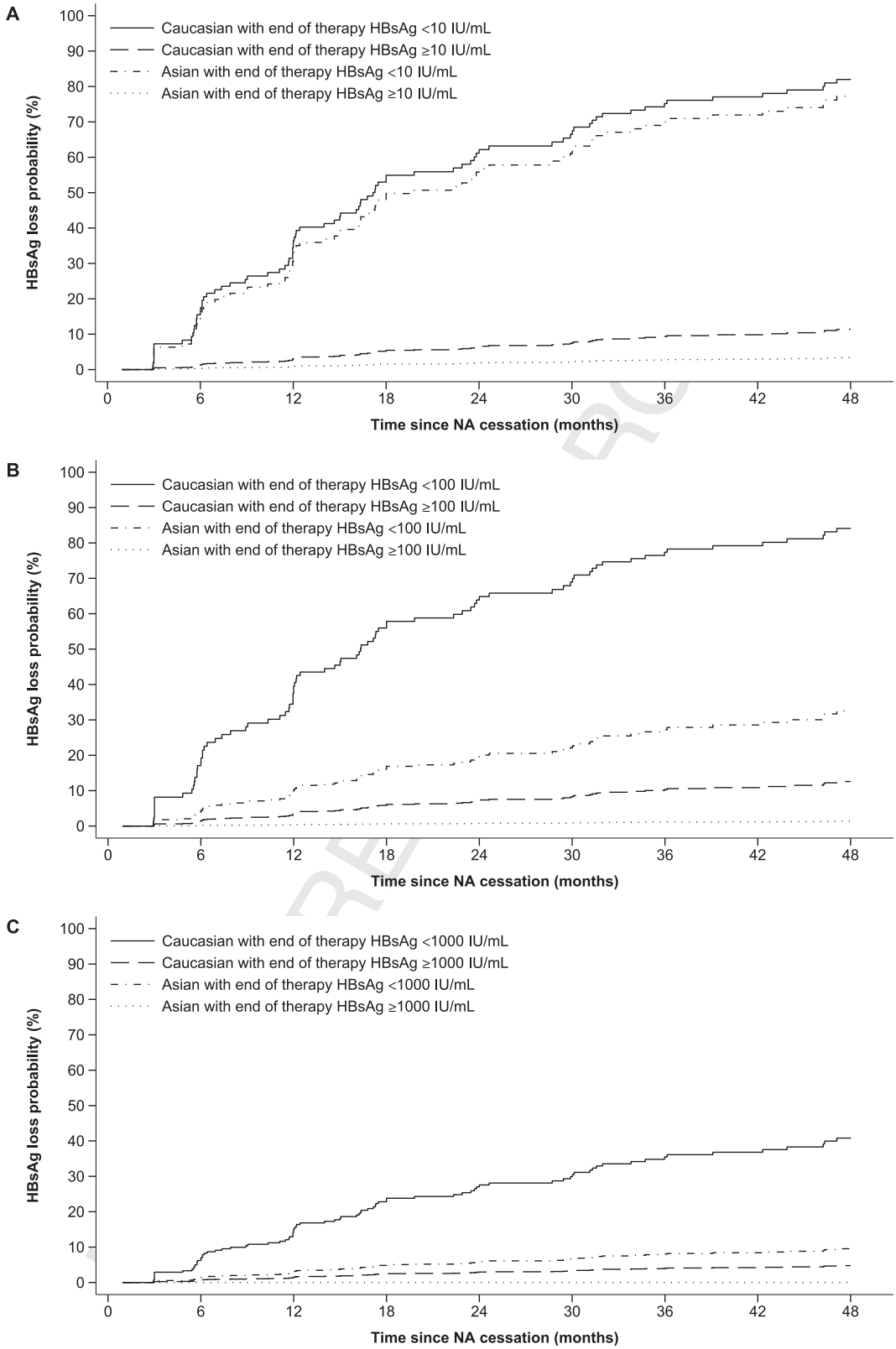

Figure 4. Predicted probability of HBsAg loss after multivariable competing risks regression by race for 3 thresholds of HBsAg levels at end of therapy: (*A*) 10 IU/mL (1 $\log_{10}$), (*B*) 100 IU/mL (2 $\log_{10}$), and (*C*) 1000 IU/mL (3 $\log_{10}$).

of NA therapy in a large, ethnically diverse, global cohort of patients with CHB. Although there remains heterogeneity between participating centers, individual patient-level data provide robust estimates with the ability to adjust for potential confounders ,which was not possible in any of the prior studies.[35,48,49] Modeling retreatment as a competing risk accounts for differences in stopping and retreatment criteria by center location and policies.

This study affirms the favorable outcomes associated with lower HBsAg levels at the time of NA cessation.[14,17,22,33,40,48,50] This may be associated with patient status with respect to rates of viral replication at the time of NA cessation.[2,12,35,51,52] These data reiterate the importance of HBsAg quantification during regular clinical follow-up.[53] Comparison of results from different prior studies have suggested that HBsAg loss is typically higher among whites compared with Asians.[17,20,41,45,54] Nevertheless, most of these studies were rather small and were single-center studies in populations that were predominantly one race. In this study, although whites had relatively higher rates even when adjusted for potential confounders, off-therapy HBsAg loss among Asians was also considerably higher than known on-therapy rates.[36,55] Thus, contrary to speculations in prior studies, Asians may also benefit from stopping NA therapy. The disparities by race and age at end of therapy may stem from differences in confounding variables such as HBV genotype, mode of transmission, and duration of infection.[56–58]

Virologic and biochemical responses are typically used to define retreatment criteria (Supplementary Table 1), and thus retreatment can be thought of as a composite outcome with respect to relapse and flares. In a systematic review, Papatheodoridis et al[59] reported no significant differences in virologic response between groups by start of therapy HBeAg status and numerically higher durable biochemical response rates in start of therapy HBeAg-positive cases, however, retreatment rates were not evaluated in their study. Other studies have reported conflicting results pertaining to rates of retreatment by start of therapy HBeAg status.[20–22,33,59–61] In our cohort, there were no significant differences in HBsAg loss by start of therapy HBeAg status, however, it affected the magnitude of associations in the competing risks multivariable model, which may be attributable to the lack of standardized definitions and criteria in the current guidelines.[2–4] Contrary to findings by Jeng et al,[17] HBsAg loss appeared higher among patients treated with TDF prior to NA cessation compared with ETV-treated patients. Nevertheless, similar to their study, there were no significant differences between the 2 groups in the multivariable model. With respect to virological relapse, our results are comparable to other studies in that the TDF-treated patients experienced earlier and higher rates of relapse compared with ETV-treated patients.[62–64]

This study highlights that even though all patients with low HBsAg levels would benefit from NA withdrawal with respect to HBsAg loss, the HBsAg level cut-point at NA withdrawal for beneficial outcomes vary by race/ethnicity (Figures 4, 5). We arbitrarily chose those with a predicted probability of HBsAg loss of at least 30% to be good candidates for NA withdrawal. Thus, we recommend NA withdrawal in Caucasian patients with HBsAg levels <1000 IU/mL and Asian patients with HBsAg levels <100 IU/mL (Figure 5). These results also agree with the recommendations provided by Berg et al.[34]

The results from our study suggest that higher rates of HBsAg loss can be achieved during shorter follow-up periods with finite NA therapy. To date, there have been three randomized controlled trials comparing HBsAg loss on- and off-NA therapy.[20–22] The trials showed minimal to absent HBsAg loss in those who continued NA therapy, and they also suggested that NA withdrawal is more effective among whites compared with Asians. In our study, one could question whether a control group of patients who continued NA therapy would solidify the proven efficacy of NA withdrawal. However, considering the complexity of such an approach at multiple sites across the globe, and given the ample evidence in the literature showing that HBsAg loss on NA is extremely low, we did not pursue such a study design. Results from a prospective cohort study by Jeng et al[17] showed a 1.78% annual HBsAg loss rate for those who stopped NA therapy versus 0.15% among those who continued. Chan et al[65] recently reported approximately 1% HBsAg loss at 5 years among 1248 patients treated with tenofovir alafenamide or TDF followed by tenofovir alafenamide in prospective registration randomized controlled trials. Comparing on- and off-NA therapy rates of HBsAg loss across cohort studies, such as the current study, will not yield meaningful information due to differences in the included patient population and baseline criteria. Larger prospective randomized controlled trials with a diverse patient population are necessary to fully determine the differences in outcomes between those who stopped and continued NA therapy.

Although we may be able to discern which patient is more likely to achieve functional cure based on end of therapy profiles, it is still unclear what, and when, preemptive measures need to be taken to prevent severe hepatic flares, which often lead to severe or even fatal outcomes. Distinguishing between beneficial and detrimental flares in clinical practice at the time of occurrence is challenging.[66–68] The cumulative probability of patients who developed hepatic decompensation reached 1.7% with significant mortality, and 1.5% developed HCC by year 4 of follow-up.[69] It is unclear whether HCC incidence was related to treatment cessation in this cohort. None of the patients decompensated after HBsAg loss, and only 1 patient developed HCC. Thus, HBsAg loss remains the most important endpoint,[19,70] however, it is difficult to predict patient outcome after a relapse, and hepatic decompensation remains a threat to patient safety. The cumulative probability of HBsAg loss continued to increase over time regardless of the type of relapse, however, there were no statistically significant differences in rates of HBsAg loss between patients who had biochemical relapse and those who did not (data not shown). Moreover, the majority of the patients was retreated soon after the occurrence of either relapse and, thus, it is hard to ascertain whether these patients would have had subsequent HBsAg loss or hepatic

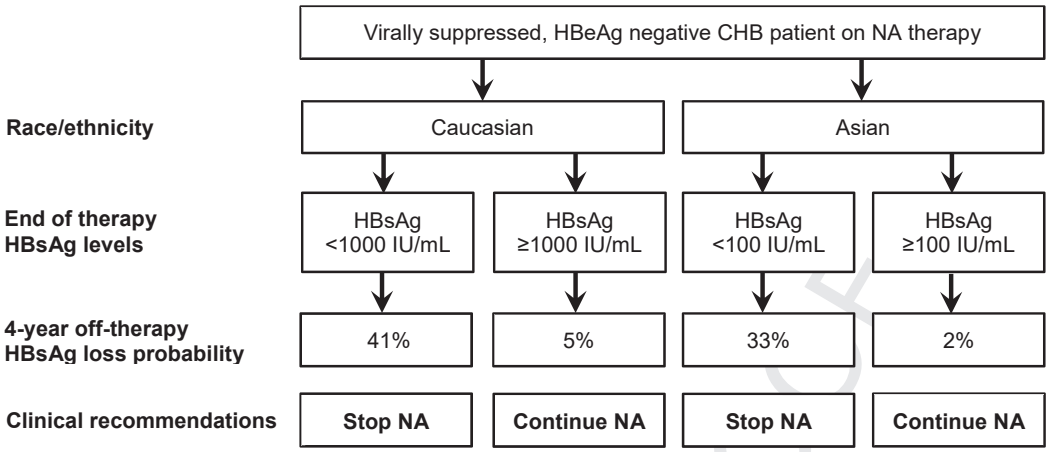

Figure 5. Clinical recommendations on NA withdrawal based on the predicted 4-year HBsAg loss probability by patient groups. These predicted probabilities are estimates calculated for a patient of average age irrespective of sex, NA type before cessation, and start of therapy HBeAg status.

decompensation. Ghany et al[71] and Liaw et al[66] suggested that early retreatment may lower the probability of HBsAg loss by dampening the host immune response, and, provided that virologic relapse is almost certain in the majority of the patients, it may not be a suitable criterion for retreatment.[72] Although this study may not provide strong evidence for or against certain retreatment criteria, these results emphasize the need for standardization of retreatment criteria and monitoring frequency after cessation.[42] Prior studies seem to agree on restarting NA therapy in cases of persistent clinical relapse, ALT flares, progression of fibrosis, or signs of decompensation.[19–21,66] In current clinical practice, the final decision on whether to retreat is typically left to the discretion of the treating physician.

Most guidelines recommend continued NA therapy in cirrhotic patients in the absence of HBsAg loss,[2–4,20] however, the exclusion of finite therapy as an option for cirrhotic patients alone may not be sufficient. In this study, cirrhosis status before NA cessation did not appear to be associated with off-therapy HBsAg loss, but patients with a cirrhosis diagnosis had higher rates of liver-related complications, and more specifically, hepatic decompensation. Thus, our results support the current guidelines in that patients with documented cirrhosis should continue NA therapy. An in-depth analysis of predictors of hepatic decompensation and HCC after cessation is necessary to understand the role of cirrhosis, while accounting for differences in the diagnostic methods used to define cirrhosis. Comparative studies analyzing on- and off-therapy rates of hepatic decompensation are sparse. Of the few published studies analyzing rates among cirrhotic patients, some report no difference,[73] some report low rates of hepatic decompensation after NA cessation,[59,74] whereas others report fatal outcomes.[17,43,75,76] With respect to HCC in HBeAg-negative patients with CHB, most studies concluded that there was no difference between on- and off-therapy rates of HCC but higher rates among cirrhotics.[17,26,36] One major limitation of comparing on- and off-therapy rates of hepatic decompensation and HCC is the differences in patient profile at baseline because those who stop usually have milder disease.

Given that potent NAs are highly effective, affordable, well-tolerated with proven safety, and shown to improve long-term prognosis, the costs associated with more frequent postcessation monitoring, increased laboratory testing, and the development of liver-related complications may attribute to higher patient burden compared with continued therapy and should be taken into consideration where appropriate. Nonadherence and issues with compliance persist on- as well as off-therapy whereas the risk of potentially fatal outcomes is higher with finite therapy. Therefore, strict long-term postcessation surveillance is critical if stopping NA therapy is pursued to aim for HBsAg loss or necessary due to socioeconomic concerns or local policies.

This study has limitations. First, the frequency of follow-up visits and length of follow-up varied by center. Nonetheless, the median time between visits was short (2.8 months) in this cohort and the majority of patients started retreatment before the end of follow-up at centers with shorter follow-up durations. Second, there may have been misclassification bias, for cirrhosis and HCC in particular, based on the center-specific monitoring and surveillance policies. Because there were no biopsies performed at NA withdrawal, patients who were considered noncirrhotic and who developed complications may have had undiagnosed underlying cirrhosis. Third, a small minority of this cohort had been previously treated with (PEG-)interferon, however, it was discontinued at least 12 months before NA cessation and, therefore, the likelihood of an on-going effect would be low.[77] Prior (PEG-)interferon use was not a significant predictor in the multivariable model and, hence, it was excluded to avoid overfitting.[78] Lastly, HBV genotyping could not be performed for many patients because of viral suppression before NA cessation.

In conclusion, the findings from this study in a large cohort of patients with CHB suggest that stopping NA therapy may be beneficial to achieve functional cure in

virally suppressed, HBeAg-negative, noncirrhotic patients with low HBsAg levels provided that close and frequent postcessation monitoring is feasible. NA withdrawal may be particularly effective among white patients with HBsAg levels <1000 IU/mL and among Asian patients with HBsAg levels <100 IU/mL regardless of their start of therapy HBeAg status. These results have important implications not only in aiding decision making for regular clinical practice and providing evidence to promote uniformity across guidelines, but also in the design of prospective studies and randomized trials analyzing novel treatment options and biomarkers focused on a HBV cure.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.11.002.

References

1. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018;3:383–403.
2. Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
3. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560–1599.
4. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98.
5. Campenhout MJH, Brouwer WP, Xie Q, et al. Long-term follow-up of patients treated with entecavir and peginterferon add-on therapy for HBeAg-positive chronic hepatitis B infection: ARES long-term follow-up. J Viral Hepat 2019;26:109–117.
6. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci 2015; 60:1457–1464.
7. Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. J Hepatol 2018;68:1129–1136.
8. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886–893.
9. Lai CL, Yuen MF. Prevention of hepatitis B virus-related hepatocellular carcinoma with antiviral therapy. Hepatology 2013;57:399–408.
10. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468–475.
11. Liu K, Choi J, Le A, et al. Tenofovir disoproxil fumarate reduces hepatocellular carcinoma, decompensation and death in chronic hepatitis B patients with cirrhosis. Aliment Pharmacol Ther 2019;50:1037–1048.
12. Lok ASF. Hepatitis B treatment: what we know now and what remains to be researched. Hepatol Commun 2019; 3:8–19.
13. Dusheiko G, Wang B, Carey I. HBsAg loss in chronic hepatitis B: pointers to the benefits of curative therapy. Hepatol Int 2016;10:727–729.
14. Yeo YH, Ho HJ, Yang HI, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology 2019;156:635–646.e9.
15. Kim GA, Lim YS, An J, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014; 63:1325–1332.
16. Cornberg M, Siederdissen CH. HBsAg seroclearance with NUCs: rare but important. Gut 2014; 63:1208–1209.
17. Jeng WJ, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen–negative chronic hepatitis B. Hepatology 2018;68:425–434.
18. Yip TCF, Wong GLH, Chan HLY, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. J Hepatol 2019;70:361–370.
19. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD Guidelines for Treatment of Chronic Hepatitis B. Hepatology 2016;63:261–283.
20. Berg T, Simon KG, Mauss S, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients – FINITE study. J Hepatol 2017;67:918–924.
21. Liem KS, Fung S, Wong DK, et al. Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study). Gut 2019; 68:2206–2213.
22. van Bömmel F, Stein K, Heyne R, et al. Response to discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg negative patients: results of the Stop-NUC trial. J Hepatol 2020;73:S118–S119.
23. Ford N, Scourse R, Lemoine M, et al. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis B infection: a systematic review and meta-analysis. Hepatol Commun 2018;2:1160–1167.
24. **Shin JW, Jung SW**, Lee SB, et al. Medication non-adherence increases hepatocellular carcinoma, cirrhotic complications, and mortality in chronic hepatitis B patients treated with entecavir. Am J Gastroenterol 2018; 113:998–1008.
25. Lampertico P, Berg T. Less can be more: a finite treatment approach for HBeAg-negative chronic hepatitis B. Hepatology 2018;68:397–400.
26. Chen YC, Peng CY, Jeng WJ, Chien RN, Liaw YF. Clinical outcomes after interruption of entecavir therapy in

HBeAg-negative chronic hepatitis B patients with compensated cirrhosis. Aliment Pharmacol Ther 2015; 42:1182–1191.
27. Chen CH, Hung CH, Hu TH, et al. Association between level of hepatitis B surface antigen and relapse after entecavir therapy for chronic hepatitis B virus infection. Clin Gastroenterol Hepatol 2015;13:1984–1992.e1.
28. Chen CH, Hung CH, Wang JH, Lu SN, Hu TH, Lee CM. Long-term incidence and predictors of hepatitis B surface antigen loss after discontinuing nucleoside analogues in noncirrhotic chronic hepatitis B patients. Clin Microbiol Infect 2018;24:997–1003.
29. Chen CH, Hsu YC, Lu SN, et al. The incidence and predictors of HBV relapse after cessation of tenofovir therapy in chronic hepatitis B patients. J Viral Hepat 2018;25:590–597.
30. Jeng WJ, Chen YC, Sheen IS, et al. Clinical relapse after cessation of tenofovir therapy in hepatitis B e antigen-negative patients. Clin Gastroenterol Hepatol 2016; 14:1813–1820.e1.
31. Jeng WJ, Sheen IS, Chen YC, et al. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. Hepatology 2013; 58:1888–1896.
32. Cornberg M, Lok ASF, Terrault NA, et al. Guidance for design and endpoints of clinical trials in chronic hepatitis B - report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. J Hepatol 2020; 72:539–557.
33. Papatheodoridi M, Papatheodoridis GV. Emerging diagnostic tools to decide when to discontinue nucleos(t)ide analogues in chronic hepatitis B. Cells 2020; 9:493.
34. Berg T, Lampertico P. The times they are a-changing – a refined proposal for finite HBV nucleos(t)ide analogue therapy. J Hepatol Published online 2021.
35. Liem KS, Gehring AJ, Feld JJ, Janssen HLA. Challenges with stopping long-term nucleos(t)ide analogue therapy in patients with chronic hepatitis B. Gastroenterology 2020;158:1185–1190.
36. Hung CH, Wang JH, Lu SN, Hu TH, Lee CM, Chen CH. Hepatitis B surface antigen loss and clinical outcomes between HBeAg-negative cirrhosis patients who discontinued or continued nucleoside analogue therapy. J Viral Hepat 2017;24:599–607.
37. Ge GH, Ye Y, Zhou XB, et al. Hepatitis B surface antigen levels of cessation of nucleos(t)ide analogs associated with virological relapse in hepatitis B surface antigen-negative chronic hepatitis B patients. World J Gastroenterol 2015;21:8653–8659.
38. Seto WK, Hui AJ, Wong VWS, et al. Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study. Gut 2015;64:667–672.
39. Yao CC, Hung CH, Hu TH, et al. Incidence and predictors of HBV relapse after cessation of nucleoside analogues in HBeAg-negative patients with HBsAg $\leq$ 200 IU/mL. Sci Rep 2017;7:1–10.
40. Hadziyannis SJ, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 2012;143:629–636.e1.
41. Papatheodoridis GV, Rigopoulou EI, Papatheodoridi M, et al. Daring-B: discontinuation of effective entecavir or tenofovir disoproxil fumarate long-term therapy before HBsAg loss in non-cirrhotic HBeAg-negative chronic hepatitis B. Antivir Ther 2018;23:677–685.
42. **Höner Zu Siederdissen C, Rinker F**, Maasoumy B, et al. Viral and host responses after stopping long-term nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B. J Infect Dis 2016;214:1492–1497.
43. Van Hees S, Bourgeois S, Van Vlierberghe H, et al. Stopping nucleos(t)ide analogue treatment in Caucasian hepatitis B patients after HBeAg seroconversion is associated with high relapse rates and fatal outcomes. Aliment Pharmacol Ther 2018;47:1170–1180.
44. Chi H, Hansen BE, Yim C, et al. Reduced risk of relapse after long-term nucleos(t)ide analogue consolidation therapy for chronic hepatitis B. Aliment Pharmacol Ther 2015;41:867–876.
45. Hsu YC, Nguyen MH, Mo LR, et al. Combining hepatitis B core-related and surface antigens at end of nucleos(t)ide analogue treatment to predict off-therapy relapse risk. Aliment Pharmacol Ther 2018;49:1–9.
46. Lok AS, Zoulim F, Dusheiko G, et al. Durability of hepatitis B surface antigen loss with nucleotide analogue and peginterferon therapy in patients with chronic hepatitis B. Hepatol Commun 2020;4:8–20.
47. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
48. Liu J, Li T, Zhang L, Xu A. The role of hepatitis B surface antigen in nucleos(t)ide analogues cessation among asian patients with chronic hepatitis B: a systematic review. Hepatology 2019;70:1045–1055.
49. van Bömmel F, Berg T. Stopping long-term treatment with nucleos(t)ide analogues is a favourable option for selected patients with HBeAg-negative chronic hepatitis B. Liver Int 2018;38:90–96.
50. Matsumoto A, Tanaka E, Minami M, et al. Low serum level of hepatitis B core-related antigen indicates unlikely reactivation of hepatitis after cessation of lamivudine therapy. Hepatol Res 2007;37:661–666.
51. Pfefferkorn M, Böhm S, Schott T, et al. Quantification of large and middle proteins of hepatitis B virus surface antigen (HBsAg) as a novel tool for the identification of inactive HBV carriers. Gut 2018;67:2045–2053.
52. Cornberg M, Wong VWS, Locarnini S, Brunetto M, Janssen HLA, Chan HLY. The role of quantitative hepatitis B surface antigen revisited. J Hepatol 2017; 66:398–411.
53. Tseng TC, Liu CJ, Chen CL, et al. Risk stratification of hepatocellular carcinoma in hepatitis B virus e antigen-negative carriers by combining viral biomarkers. J Infect Dis 2013;208:584–593.
54. Van Hees S, Chi H, Hansen B, et al. Caucasian ethnicity, but not treatment cessation is associated with hbsag loss following nucleos(T)ide analogue-induced HBeAg seroconversion. Viruses 2019;11:1–10.

55. Chen CH, Hu TH, Wang JH, et al. Comparison of HBsAg changes between HBeAg-negative patients who discontinued or maintained entecavir therapy. Hepatol Int 2020;14:317–325.
56. Tu T, Budzinska MA, Shackel NA, Urban S. HBV DNA integration: molecular mechanisms and clinical implications. Viruses 2017;9.
57. Podlaha O, Wu G, Downie B, et al. Genomic modeling of hepatitis B virus integration frequency in the human genome. PLoS One 2019;14:1–9.
58. **Zhao LH, Liu X, Yan HX, Li WY, Zeng X, Yang Y**, et al. Genomic and oncogenic preference of HBV integration in hepatocellular carcinoma. Nat Commun 2016;7:1–10.
59. Papatheodoridis GV, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systematic review. Hepatology 2016;63:1481–1492.
60. Papatheodoridis GV, Manolakopoulos S, Su TH, et al. Significance of definitions of relapse after discontinuation of oral antivirals in HBeAg-negative chronic hepatitis B. Hepatology 2018;68:415–424.
61. **García-López M, Lens S**, Pallett LJ, et al. Viral and immune factors associated with successful treatment withdrawal in HBeAg-negative chronic hepatitis B patients. J Hepatol 2020:1–11.
62. Su TH, Yang HC, Tseng TC, et al. Distinct relapse rates and risk predictors after discontinuing tenofovir and entecavir therapy. J Infect Dis 2018;217:1193–1201.
63. Höner Zu Siederdissen C, Hui AJ, Sukeepaisarnjaroen W, et al. Contrasting timing of virological relapse after discontinuation of tenofovir or entecavir in hepatitis B e antigen-negative patients. J Infect Dis 2018;218:1–26.
64. Choi HSJ, Hirode G, Chen C, et al. Earlier and more frequent virological and clinical relapse after cessation of tenofovir disoproxil fumarate versus entecavir therapy: results from a global, multi-ethnic cohort of patients with chronic hepatitis B virus infection (RETRACT-B Study). J Hepatol 2021;75:S751–S752.
65. Chan HLY, Ferret MAB, Agarwal K, et al. Maintenance of high levels of viral suppression and improved safety profile of tenofovir alafenamide (TAF) relative to tenofovir disoproxil fumarate (TDF) in chronic hepatitis B patients treated for 5 years in 2 ongoing phase 3 studies. Hepatology 2020;72(1 Suppl):490A.
66. Liaw YF, Jeng WJ, Chang ML. HBsAg kinetics in retreatment decision for off-therapy hepatitis B flare in HBeAg-negative patients. Gastroenterology 2018;154:2280–2281.
67. Liaw YF. Hepatitis B flare after cessation of nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B: to retreat or not to retreat. Hepatology 2021;73:843–852.
68. Liaw YF, Jeng WJ. Benefit of stopping finite nucleos(t)ide analogues therapy in chronic hepatitis B patients. Gut 2020;69:1898–1899.
69. Hirode G, Hansen B, Chen C-H, et al. Hepatic decompensation and hepatocellular carcinoma after stopping nucleos (t)ide analogue therapy: results from a large, global, multi-ethnic cohort of patients with chronic hepatitis B (RETRACT-B study). J Hepatol 2021; 75:S749–S750.
70. **Anderson RT, Choi HSJ**, Lenz O, et al. Association between seroclearance of hepatitis B surface antigen and long-term clinical outcomes of patients with chronic hepatitis B virus infection: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2021;19:463–472.
71. Ghany MG, Feld JJ, Chang KM, et al. Serum alanine aminotransferase flares in chronic hepatitis B infection: the good and the bad. Lancet Gastroenterol Hepatol 2020;5:406–417.
72. Chen CJ, Iloeje UH, Yang HI. Long-Term outcomes in hepatitis B: the REVEAL-HBV Study. Clin Liver Dis 2007; 11:797–816.
73. Liaw YF. Finite nucleos(t)ide analog therapy in HBeAg-negative chronic hepatitis B: an emerging paradigm shift. Hepatol Int 2019;13:665–673.
74. Chang ML, Liaw YF, Hadziyannis SJ. Systematic review: cessation of long-term nucleos(t)ide analogue therapy in patients with hepatitis B e antigen-negative chronic hepatitis B. Aliment Pharmacol Ther 2015;42:243–257.
75. **Zhang H, Giang E**, Bao F, et al. Virus reactivation in a non-cirrhotic HBV patient requiring liver transplantation after cessation of nucleoside analogue therapy. Hepatology 2020;72:522A.
76. Lim SG, Wai CT, Rajnakova A, Kajiji T, Guan R. Fatal hepatitis B reactivation following discontinuation of nucleoside analogues for chronic hepatitis B. Gut 2002; 51:597–599.
77. Choi HSJ, van Campenhout MJH, van Vuuren AJ, et al. Ultra-long-term follow-up of interferon alfa treatment for HBeAg-positive chronic hepatitis B virus infection. Clin Gastroenterol Hepatol 2021;19:1933–1940.e1.
78. Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. 2nd ed. Springer International Publishing, 2015. Q20 Q21 Q22

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Conflicts of interest

Tung-Hung Su receives research grants from Gilead Sciences, and was on the speaker's bureaus for Abbvie, Bayer, Bristol Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, and Takeda. Wai-Kay Seto received speaker's fees from AstraZeneca and Mylan, is an advisory board member of CSL Behring, is an advisory board member and received speaker's fees from AbbVie, and is an advisory board member and received speaker's fees and researching funding from Gilead Sciences. Sabela Lens received speaker and advisor fees from Abbvie and Gilead Sciences and grant support from Gilead Sciences. Grace Wong receives research support from AbbVie and Gilead Sciences, is an advisory board member or consultant for Gilead Sciences and Janssen, and is a speaker for Abbott, AbbVie, Bristol Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche. Jordan Feld receives research grants from Abbvie, Gilead, Janssen, Enanta, and Eiger, and is a consultant for Abbvie, Gilead, Finch, Arbutus, and GlaxoSmithKline. Milan Sonneveld receives speaker's fees and research support from Roche, Bristol Myers Squibb, Gilead Sciences, and Fujirebio. Henry L.Y. Chan is a consultant for AbbVie, Aligos, Arbutus, Hepion, Janssen, Glaxo-Smith-Kline, Gilead Sciences, Merck, Roche, Vaccitech, VenatoRx, and Vir Biotechnology, and has received an honorarium for lectures for Gilead Sciences, Mylan, and Roche. Xavier Forns is an advisor for Abbvie and Gilead Sciences. George V. Papatheodoridis is an advisor/lecturer for Abbvie, Dicerna, Gilead Sciences, GlaxoSmithKline, Ipsen, Janssen, Merck Sharp and Dohme, Roche, Spring Bank, and Takeda, and has received research grants from Abbvie and Gilead Sciences. Thomas Vanwolleghem has received grants from Gilead Sciences, Roche, and Bristol Myers Squibb, is a consultant for Janssen Pharmaceuticals, Gilead Sciences, Abbvie, and Bristol Myers Squibb, and is a sponsored lecturer for W.L. Gore, Gilead Sciences, and Bristol Myers Squibb. Man-Fung Yuen serves as advisor/consultant for AbbVie, Aligos Therapeutics, Arbutus Biopharma, Bristol Myers Squibb, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals, and Roche and receives grant/research supports from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myers Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Springbank Pharmaceuticals, Sysmex Corporation, and Roche. Yao-Chun Hsu has served as an Advisory Committee member for Gilead and as a speaker for Abbvie, Bristol Myers Squibb, Roche, Novartis, and Gilead. Jia-Horng Kao is a consultant for or on the advisory board of Abbvie, Roche, and Gilead Sciences, and is a speaker for Abbvie, Fujirebio, and Gilead Sciences. Markus Cornberg reports personal fees for lectures and/or consulting from Abbvie, Gilead Sciences, Merck Sharp and Dohme, GlaxoSmithKline, Janssen-Cilag, Spring Bank Pharmaceuticals, Novartis, Swedish Orphan Biovitrum, and Falk Foundation, and grants and personal fees from Roche, outside of the submitted work. Bettina E. Hansen has received grants from Intercept, CymaBay, Albireo, Mirum, Calliditas, and Gliad and is a consultant for Intercept, CymaBay, Albireo, Mirum, Genfit, Calliditas, Eiger, and ChemomAb. Harry L.A. Janssen has received grants from AbbVie, Gilead Sciences, Janssen, and Roche, and is a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Merck, Roche, Arbutus, and Vir Biotechnology Inc.. All other authors disclose no conflicts.

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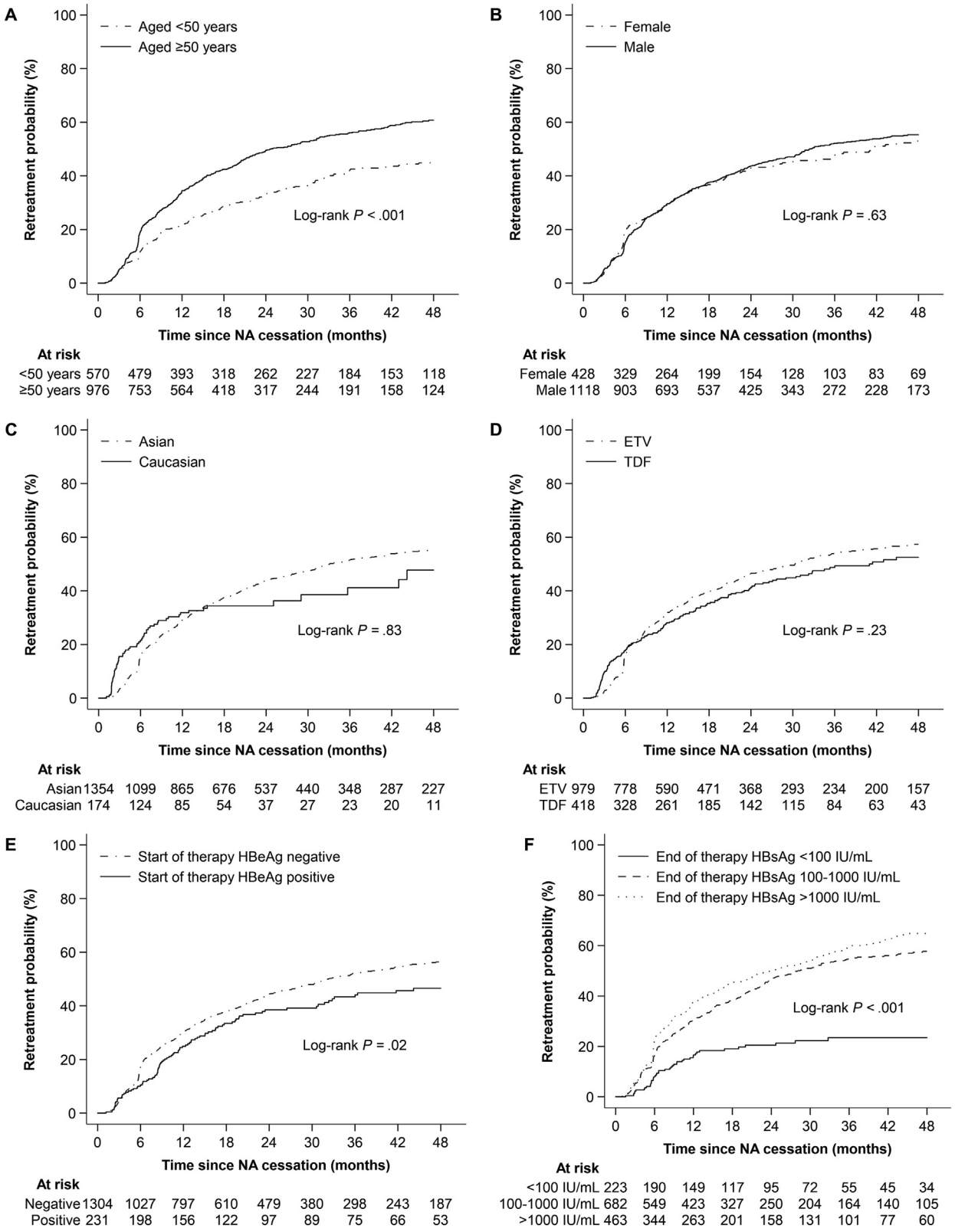

Supplementary Figure 1. Cumulative probability of retreatment by patient characteristics: (*A*) age at NA cessation, (*B*) sex, (*C*) race/ethnicity, (*D*) NA type before cessation, (*E*) start of therapy HBeAg status, and (*F*) end of therapy HBsAg levels.

Supplementary Table 1. Stopping and Retreatment Criteria for Subjects Included in the Study

Center country	Number of centers	Study design	NA stopping criteria	Retreatment criteria
Belgium	1[a]	Cohort	HBeAg-negative for at least 6 mo, at the discretion of the treating physician, patient's own initiative	Belgian reimbursement criteria, at the discretion of the treating physician
Germany	1	Cohort, trial	HBeAg-negative with at least 42 mo of undetectable HBV DNA	At the discretion of the treating physician
Greece	1	Trial	HBeAg-negative with at least 36 mo of undetectable HBV DNA	Virologic relapse, combined relapse, ALT >10× ULN, ALT >3× ULN, and HBV DNA >100,000 IU/mL at the same visit, ALT >ULN and HBV DNA >2000 IU/mL on 3 sequential visits, patients' and physicians' decisions in case of HBV DNA >20,000 IU/mL
Netherlands	1	Cohort, trial	HBeAg-negative with at least 12 mo of undetectable HBV DNA, patient's own initiative	At the discretion of the treating physician, Patient's own initiative
Spain	1	Cohort, trial	HBeAg-negative with at least 36 mo of undetectable HBV DNA	At the discretion of the treating physician
Hong Kong	3	Cohort, trial	APASL guidelines	Virologic relapse regardless of ALT level
Taiwan	4	Cohort, trial	APASL guidelines, Taiwan's national health plan, patient's own initiative	Taiwan's national health plan, hyperbilirubinemia (serum total bilirubin >2 mg/dL), coagulopathy (prothrombin time prolongation >3 s), combined relapse, at the discretion of the treating physician, patient's own initiative
Canada	1	Cohort, trial	HBeAg-negative with at least 12 mo of undetectable HBV DNA	HBeAg seroreversion, HBV DNA >2000 IU/mL and ALT >600 IU/mL at any visit, HBV DNA >2000 IU/mL and ALT >5× ULN on 2 consecutive visits, HBV DNA >2000 IU/mL and ALT >200 IU/mL but <600 IU/mL for >6–8 weeks, HBV DNA >20 000 IU/mL on 2 consecutive visits at least 4 weeks apart, at the discretion of the treating physician

APASL, Asia-Pacific Association for the Study of the Liver.
[a]Data was centralized at 1 center, however, it was collected from 18 centers across Belgium.

Supplementary Table 2. Laboratory Methods and Tests Used

Site country	Qualitative HBeAg assay	HBsAg assay (quantification limit)	HBV DNA assay (quantification limit)	ALT ULN (U/L)
Belgium	ELISA kit, Chemiluminescent microparticle immunoassay kit	ELISA kit, chemiluminescent microparticle immunoassay kit	PCR (12 IU/mL)	49
Germany	ELISA kit	ELISA kit (0.22 IU/mL)	PCR (10 IU/mL)	34 (female) and 45 (male)
Greece	NA	Roche Elecsys HBsAg II Quant reagent kit (0.05 IU/mL)	PCR (50 IU/mL)	40
Netherlands	CLIA-K	CLIA-K (0.05 IU/mL)	Roche Cobas AmpliPrep/ Cobas TaqMan (20 IU/mL)	34 (female) and 45 (male)
Spain	Siemens Advia Centaur system	Abbott Laboratories Architect HBsAg QT (0.05 IU/ mL)	Roche Cobas 6800 system (13 IU/ mL)	40
Hong Kong	Abbott Diagnostics enzyme immunoassay kit	Roche Elecsys HBsAg II Quant reagent kit (0.05 IU/mL)	Roche Cobas TaqMan HBV test (20 IU/mL), TaqMan RT-PCR (NA)	36 (female) and 58 (male), 47 (female) and 53 (male)
Taiwan	Abbott Diagnostics enzyme immunoassay kit, Chemiluminescent microparticle immunoassay kit	Roche Elecsys HBsAg II Quant reagent kit (0.05 IU/mL), Abbott Laboratories Architect i2000 HBsAg QT (0.05 IU/mL), Chemiluminescent microparticle immunoassay kit (0.05 IU/ mL)	Roche Cobas AmpliPrep/ Cobas TaqMan (20 IU/mL), Roche Cobas 6800 system (10 IU/ mL), Abbott RealTime HBV assay (20 IU/mL)	36, 40, 41
Canada	Abbott Laboratories Architect, commercial enzyme immunoassay kit	Abbott Laboratories Architect HBsAg QT (0.05 IU/ mL), LIAISON XL (0.05 IU/mL)	Roche Cobas TaqMan 48 PCR (20 IU/mL), RT-PCR (NA)	40, 30 (female) and (male)

CLIA-K, chemiluminescent immunoassay kit; ELISA, enzyme-linked immunosorbent assay; NA, not available; PCR, polymerase chain reaction; RT, reverse transcription.

Supplementary Table 3. Characteristics of Included Asian and White Patients

	Asian (N = 1359)	White (N = 175)	*P*
Age at end of therapy, *y*, mean ± SD	52.9 ± 11.2	54.2 ± 11.4	.16
Male sex, n (%)	988 (72.7)	123 (70.3)	.50
HBV genotype: A/B/C/D/other/missing, n (%)	0 (0)/660 (48.6)/168 (12.4)/3 (0.2)/0 (0)/528 (38.9)	6 (3.4)/1 (0.6)/1 (0.6)/39 (22.3)/3 (1.7)/125 (71.4)	<.001
Prior (PEG-)interferon, n (%)	88 (6.5)	44 (25.1)	<.001
NA-naïve, n (%)	1170 (86.1)	107 (61.1)	<.001
NA type before cessation: ETV/TDF/other, n (%)	921 (67.8)/342 (25.2)/96 (7.1)	52 (29.7)/70 (40.0)/53 (30.3)	<.001
Minimum consolidation, *y*: <1/1–2/≥3	63 (4.6)/1113 (81.9)/183 (13.5)	14 (8.0)/15 (8.6)/146 (83.4)	<.001
NA duration, *y*, median (IQR)	3.0 (3.0–3.4)	7.4 (4.8–10.5)	<.001
Number of follow-up visits, median (IQR)	6 (3–9)	7 (3–8)	.51
Follow-up duration between visits, *mo*, median (IQR)	2.8 (2.0–5.2)	2.4 (1.4–3.7)	<.001
Total follow-up duration, *mo*, median (IQR)	17.8 (8.0–36.5)	12.0 (5.5–20.5)	<.001
At start of therapy			
HBeAg-negative, n (%)	1150 (84.9)	143 (85.1)	.93
HBV DNA, $\log_{10}$ IU/mL, mean ± SD	5.9 ± 1.6	5.7 ± 2.0	.23
ALT × ULN, median (IQR)	3.1 (1.9–8.0)	2.4 (1.4–4.1)	<.001
At end of therapy (NA cessation)			
HBsAg, $\log_{10}$ IU/mL, mean ± SD	2.6 ± 0.8	2.8 ± 0.9	<.001
HBsAg, IU/mL: <10/≥10, n (%)	53 (3.9)/1172 (86.2)	6 (3.4)/133 (76.0)	1.00
HBsAg, IU/mL: <100/≥100, n (%)	207 (15.2)/1018 (74.9)	18 (10.3)/121 (69.1)	.24
HBsAg, IU/mL: <1000/≥1000, n (%)	842 (62.0)/383 (28.2)	63 (36.0)/76 (43.4)	<.001
Cirrhosis, n (%)	169 (12.4)	10 (5.9)	.01
ALT × ULN, median (IQR)	0.6 (0.4–0.8)	0.6 (0.4–0.7)	.79

IQR, interquartile range.