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This item is the archived peer-reviewed author-version of:

Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B : an international, multi-center, multi-ethnic cohort (RETRACT-B study)

Reference:
Hirode Grishma, Choi Hannah S.J., Chen Chien-Hung, Su Tung-Hung, Seto Wai-Kay, Van Hees Stijn, Papatheodoridi Margarita, Lens Sabela, Wong Grace, Brakenhoff Sylvia M., ...- Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B : an international, multi-center, multi-ethnic cohort (RETRACT-B study)
Gastroenterology - ISSN 1528-0012 - 162:3(2022), p. 757-771.e4
Full text (Publisher's DOI): https://doi.org/10.1053/J.GASTRO.2021.11.002
To cite this reference: https://hdl.handle.net/10067/1887860151162165141

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What You Need to Know

Background and Context: Functional cure, or HBsAg loss is rare on NA therapy. NA withdrawal as a therapeutic alternative remains elusive in clinical practice as current knowledge is mainly based on small and single-center studies.

New findings: In this global study of individual patient-level data on 1,552 CHB patients who stopped NA therapy, cumulative off-therapy HBsAg 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 Caucasians with HBsAg <1000 IU/mL and Asians with HBsAg <100 IU/mL at NA 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 HBsAg loss which help in the selection of patients for NA withdrawal.

Lay Summary

NA withdrawal with close follow-up monitoring is beneficial to achieve functional cure among virally suppressed CHB patients who are HBeAg negative with low HBsAg levels and without advanced liver disease.

Title: Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B: An international, multi-center, multi-ethnic cohort (RETRACT-B study)

Short title: Finite NA therapy is effective for HBsAg loss

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Date of re-submission: 28 October 2021

Manuscript word count: 6,623 words

Conflict of interest disclosures:

Tung-Hung Su receives research grants from Gilead Sciences, and was on 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, 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, Eiger, and is a consultant for Abbvie, Gilead, Finch, Arbutus and GlaxoSmithKline.

Milan Sonneveld receives speakers' fees and research support from Roche, Bristol Myers Squibb, Gilead Sciences, and Fujirebio.

Henry LY Chan is a consultant for AbbVie, Aligos, Arbutus, Hepion, Janssen, Glaxo-Smith-Kline, Gilead Sciences, Merck, Roche, Vaccitech, VenatoRx, and Vir Biotechnology, 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, Takeda, and has received research grants from Abbvie, Gilead Sciences.

Thomas Vanwolleghem has received grants from Gilead Sciences, Roche, Bristol Myers Squibb, is a consultant for Janssen Pharmaceuticals, Gilead Sciences, Abbvie, Bristol Myers Squibb, and a sponsored lecturer for W.L. Gore, Gilead Sciences, Bristol Myers Squibb.

Man-Fung Yuen serves as advisor/consultant for AbbVie, Aligos Therarpeutics, Arbutus Biopharma, Bristol Myers Squibb, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals, 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, 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, Gilead Sciences, and 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, Falk Foundation, 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 LA 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, Vir Biotechnology Inc.

No other disclosures were reported.

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Data acquisition: All authors

Data analysis and interpretation: GH, BEH

Drafting of the manuscript: GH

Critical revision of the manuscript for important intellectual content: All authors

Funding and supervision: HLAJ

Acknowledgements

We would like to thank all the participating centers, investigators, and research staff for their time and effort.

List of abbreviations

ALT – Alanine aminotransferase

Anti-HBs – Hepatitis B surface antibody

CHB – Chronic hepatitis B

CI – Confidence interval

DNA – Deoxyribonucleic acid

ETV – Entecavir

HBeAg – Hepatitis B e antigen

HBsAg – Hepatitis B surface antigen

HBV – Hepatitis B virus

HCC – Hepatocellular carcinoma

HCV – Hepatitis C virus

HDV – Hepatitis delta virus

HIV – Human immunodeficiency virus

HR – Hazard ratio

NA – Nucleos(t)ide analogue

PEG - Pegylated

SHR – Subdistribution hazard ratio

TDF – Tenofovir disoproxil fumarate

ULN – Upper limit of normal

Abstract

Background and Aims: Functional cure, defined by 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 following NA cessation in a large, international, multi-center, multi-ethnic cohort of chronic hepatitis B (CHB) patients.

Methods: This cohort study included virally suppressed CHB patients who were hepatitis B e antigen (HBeAg) negative and stopped NA therapy. Primary outcome was HBsAg loss after NA cessation, and secondary outcomes included virological, biochemical, and clinical relapse, ALT flare, retreatment, and liver-related events after NA cessation.

Results: Among 1,552 CHB patients, 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 Caucasians (vs. Asians: SHR 6.8; 95% CI 2.7–16.8; $P < .001$), and among patients with HBsAg levels <100 IU/mL at end of therapy (vs. ≥100 IU/mL: SHR 22.5; 95% CI 13.1–38.7; $P < .001$). At 48 months of follow-up, Caucasians 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 (HCC) 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 HCC.

Conclusion: The best candidates for NA withdrawal are virally suppressed, HBeAg negative, non-cirrhotic CHB patients with low HBsAg levels, particularly Caucasians with <1000 IU/mL and Asians with <100 IU/mL. However, strict surveillance is recommended to prevent deterioration.

Keywords: HBV, discontinuation, antiviral, HBsAg seroconversion

Abstract word count: 261 words

Introduction

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 (NAs) therapies.[2–5] Despite the advent of effective oral antiviral agents with a good safety profile,[6,7] the majority of the chronic hepatitis B (CHB) patients require long-term management and treatment. NAs have been shown to reduce progression towards 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 the financial and emotional burden for patients and caregivers present additional challenges.[23,24]

Finite NA therapy has been proposed as an alternative to long-term treatment. Since virological 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 virological 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] Since such findings raise concerns on whether the current criteria for stopping NAs are applicable to all CHB patients, 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% to 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 CHB patients is required. The main objective of this study was to investigate factors associated with HBsAg loss, and describe virological, biochemical, and clinical responses following cessation of NA therapy with the hope to improve current patient management and help in the design of prospective HBV cure studies.

Methods

This is a large, global, multi-center, multi-ethnic cohort study of CHB patients 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 de-identified 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

252 Helsinki 1964 as modified by the 59th WMA General Assembly, Seoul, South Korea October
253 2008, and the local national laws governing the conduct of clinical research studies.
254
255 Study population and variables
256
257 Adult patients (aged ≥18 years) with CHB (HBsAg positive >6 months) were included if they
258 were virally suppressed and hepatitis B e antigen (HBeAg) negative at end of therapy (Figure 1).
259 Stopping criteria and retreatment criteria varied by center location as listed in Supplementary
260 Table 1. Patients who had previously been diagnosed with HCC, patients with coinfection
261 (hepatitis C virus [HCV], hepatitis delta virus [HDV], and/or [HIV]), and patients who received
262 (PEG-)interferon treatment within 12 months prior to NA cessation were excluded from this
263 study. NA therapy duration refers to the duration of continuous NA therapy including
264 consolidation. Follow-up refers to time since NA cessation while the patient remained off-
265 therapy. Patient was defined as cirrhotic if cirrhosis had been diagnosed prior to cessation.
266 Cirrhosis was diagnosed based on histological findings or ultrasonographic evidence with or
267 without splenomegaly. Hepatic decompensation was defined based on development of a serum
268 total bilirubin level ≥2 mg/dL, an increased INR, appearance of clinical jaundice, onset of
269 ascites, variceal bleeding, or hepatic encephalopathy.
270
271 Laboratory assays
272

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 were 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 virological, biochemical, and clinical relapse, ALT flare, retreatment, liver-related events including hepatic decompensation and HCC, and mortality. Virological 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 virological 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 ± SD or median (range), as appropriate, for continuous variables. Cumulative probabilities were estimated by 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 utilized STATA Version 15.1 (StataCorp, College Station, TX).

Results

Characteristics of the study cohort

Of 1,726 CHB patients who stopped NA therapy, 1,552 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

Caucasian. 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 prior to 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 x 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% 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 prior to 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 to those aged <50 years (8.7% [95% CI 6.0-12.5%]) (Figure 3*A*), among Caucasians (36.5% [95%

CI 26.0-49.5%]) compared to Asians (10.6% [95% CI 8.1-13.7%]) (Figure 3*C*), among patients treated with TDF prior to cessation (18.1% [95% CI 12.2-26.5%]) compared to ETV-treated patients (10.5% [95% CI 7.8-14.2%]) (Figure 3*D*), and among patients with HBsAg <100 IU/mL at end of therapy (43.0% [95% CI 34.4-52.7%]) compared to 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 Caucasians compared to Asians (SHR 4.9; 95% CI 3.2–7.4; $P < .001$), and patients treated with TDF prior to cessation compared to ETV-treated patients (SHR 1.8; 95% CI 1.1–2.7; $P = .01$) (Table 2). HBsAg levels at end of therapy were strongly associated with HBsAg loss, and patients with HBsAg <100 IU/mL at 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 Caucasians compared to Asians, and 22.5 times higher (95% CI 13.1–38.7; $P < .001$) among patients with HBsAg levels <100 IU/mL at end of therapy compared to patients with HBsAg levels ≥100 IU/mL at 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 end of therapy, we analyzed three 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 end of therapy were comparable and >75% among Caucasians and Asians (*P* = NS) (Figure 4*A*) however, the predicted probabilities of HBsAg loss were considerably higher among Caucasians 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 to Asians using the same cut-points (<100 IU/mL: 32.5%; <1000 IU/mL: 9.7%) (*P* < .01 for both comparisons). Patient characteristics by race/ethnicity have also been described in Supplementary Table 3.

Virological and biochemical responses

Virological relapse occurred in 1,207 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*).

388 *Retreatment*

389

390 After NA cessation, 729 patients were retreated, and the cumulative probability of retreatment
391 increased from 16.2% (95% CI 14.4-18.2%) at 6 months to 29.8% (95% CI 27.5–32.2%) at 12
392 months of follow-up and reached 54.7% (95% CI 51.7-57.7%) at 48 months (Figure 2*F*). There
393 were statistically significant differences in the cumulative probability of retreatment by age
394 group ($P < .001$), start of therapy HBeAg status ($P = .02$), and HBsAg levels at end of therapy (P
395 $< .001$) (Supplementary Figure 1).

396

397 *Liver-related events and mortality*

398

399 There were 19 patients who developed hepatic decompensation after NA cessation (8/184 [4.3%]
400 of patients with cirrhosis vs. 11/1,368 [0.8%] of patients without cirrhosis, $P < .001$) with an
401 incidence rate of 0.48 per 1000 person-years. No decompensating events occurred after 48
402 months of follow-up. Among patients who developed hepatic decompensation, 1/19 (5.3%) had
403 subsequent HBsAg loss, and 16/19 (84.2%) started retreatment. Death occurred in 7 (36.8%) of
404 the 19 decompensated patients of which 6 died after starting retreatment. In 4/7 (57.1%), death
405 was reported to be related to a hepatitis B-associated flare. Among the other 3/7 (42.9%) deaths,
406 one patient died due septic shock caused by urosepsis, one died due to lymphoma, and one died
407 due to cholangiocarcinoma.

408

409 There were 14 patients who developed HCC at least 6 months after NA cessation (4/184 [2.2%]
410 of patients with cirrhosis vs. 10/1,368 [0.7%] of 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 while 1/14 (7.1%) had HBsAg loss prior to HCC diagnosis, and 6/14 (42.9%) started retreatment. Death occurred in 2 (14.3%) of the 14 patients with HCC of which 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 which 3 died after starting retreatment.

Discussion

In this study of 1,552 CHB patients 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 virological 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 following cessation of NA therapy in a large, ethnically diverse, global cohort of CHB patients. While 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 Caucasians compared to Asians.[17,20,41,45,54] Nevertheless, most of these studies were rather small, and single-center studies in populations that were predominantly one race. In this study, although Caucasians 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]

Virological 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 virological 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 to ETV-treated patients. Nevertheless, similar to their study, there were no significant differences between the two 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 to 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 Caucasians compared to 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 1,248 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.

While 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 one 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 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 virological relapse is almost certain in the majority of the patients, it may not be a suitable criterion for retreatment.[72] While 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 prior to 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 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

526 decompensation are sparse. Of the few published studies analyzing rates among cirrhotic
527 patients, some report no difference,[73] some report low rates of hepatic decompensation after NA
528 cessation,[59,74] while others report fatal outcomes.[17,43,75,76] With respect to HCC in HBeAg
529 negative CHB patients, most studies concluded that there was no difference between on- and off-
530 therapy rates of HCC but higher rates among cirrhotics.[17,26,36] One major limitation of comparing
531 on- and off-therapy rates of hepatic decompensation and HCC is the differences in patient profile
532 at baseline, as those who stop usually have milder disease.
533
534 Given that potent NAs are highly effective, affordable, well-tolerated with proven safety, and
535 shown to improve long-term prognosis, the costs associated with more frequent post-cessation
536 monitoring, increased laboratory testing, and the development of liver-related complications may
537 attribute to higher patient burden compared to continued therapy and should be taken into
538 consideration where appropriate. Non-adherence and issues with compliance persist on- as well
539 as off-therapy while the risk of potentially fatal outcomes is higher with finite therapy.
540 Therefore, strict long-term post-cessation surveillance is critical if stopping NA therapy is
541 pursued to aim for HBsAg loss, or necessary due to socioeconomic concerns or local policies.
542
543 This study has limitations. First, the frequency of follow-up visits, and length of follow-up varied
544 by center. Nonetheless, median time between visits was short (2.8 months) in this cohort and
545 majority of patients started retreatment before the end of follow-up at centers with shorter
546 follow-up durations. Second, there may have been misclassification bias; for cirrhosis and HCC
547 in particular, based on the center-specific monitoring and surveillance policies. Since there were
548 no biopsies performed at NA withdrawal, patients who were considered non-cirrhotic and who

549 developed complications may have had undiagnosed underlying cirrhosis. Third, a small
550 minority of this cohort had been previously treated with (PEG-)interferon however, it was
551 discontinued at least 12 months prior to NA cessation and therefore the likelihood of an on-going
552 effect would be low.[77] Prior (PEG-)interferon use was not a significant predictor in the
553 multivariable model and hence, it was excluded to avoid overfitting.[78] Lastly, HBV genotyping
554 could not be performed for many patients because of viral suppression prior to NA cessation.
555
556 In conclusion, the findings from this study in a large cohort of CHB patients suggest that
557 stopping NA therapy may be beneficial to achieve functional cure in virally suppressed, HBeAg
558 negative, non-cirrhotic patients with low HBsAg levels provided that close and frequent post-
559 cessation monitoring is feasible. NA withdrawal may be particularly effective among Caucasian
560 patients with HBsAg levels <1000 IU/mL and among Asian patients with HBsAg levels <100
561 IU/mL regardless of their start of therapy HBeAg status. These results have important
562 implications not only in aiding decision-making for regular clinical practice and providing
563 evidence to promote uniformity across guidelines, but also in the design of prospective studies
564 and randomized trials analyzing novel treatment options and biomarkers focused on HBV cure.

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Figure Legends

Figure 1. **Flow diagram of patient inclusion and exclusion**. HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HDV, Hepatitis delta virus; NA, Nucleos(t)ide analogue; PEG, Pegylated.

Figure 2. Cumulative probability of outcomes during off-therapy follow-up: **A). HBsAg loss, B). Virological 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.** ALT, Alanine aminotransferase; HBV, Hepatitis B virus; ULN, Upper limit of normal.

Figure 3. Cumulative probability of HBsAg loss by patient characteristics: A). Age at NA cessation, B). Sex, C). Race/ethnicity, D). NA type prior to cessation, E). Start of therapy HBeAg status, and F). End of therapy HBsAg levels. ETV, Entecavir; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

Figure 4. Predicted probability of HBsAg loss after multivariable competing risks regression by race for three 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 $\log_{10}$). HBsAg, Hepatitis B surface antigen.

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 prior to cessation, and start of therapy HBeAg status. CHB, Chronic hepatitis B; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue.

Table 1. Characteristics of the patients who stopped NA therapy

Total, N	**1552**
Age at end of therapy, years, mean ± SD	52.9 ± 11.2
Male sex, n (%)	1122 (72.3)
Race/ethnicity: Caucasian / 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 prior to cessation: ETV / TDF / Other, n (%)	981 (63.2) / 421 (27.1) / 150 (9.7)
Minimum consolidation, years: <1 / 1-2 / ≥3	83 (5.4) / 1129 (72.7) / 340 (21.9)
NA duration [*], years, 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 [†]	
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) [‡]	
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 [§], n (%)	184 (11.9)
ALT x ULN, median (range)	0.6 (0.4 – 0.8)

[*] NA duration was unknown for 15 (1%) patients.

[†] 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.

[‡] At end of therapy, HBsAg levels were unavailable for 182 (12%), and ALT levels were unavailable for 47 (3%) patients.

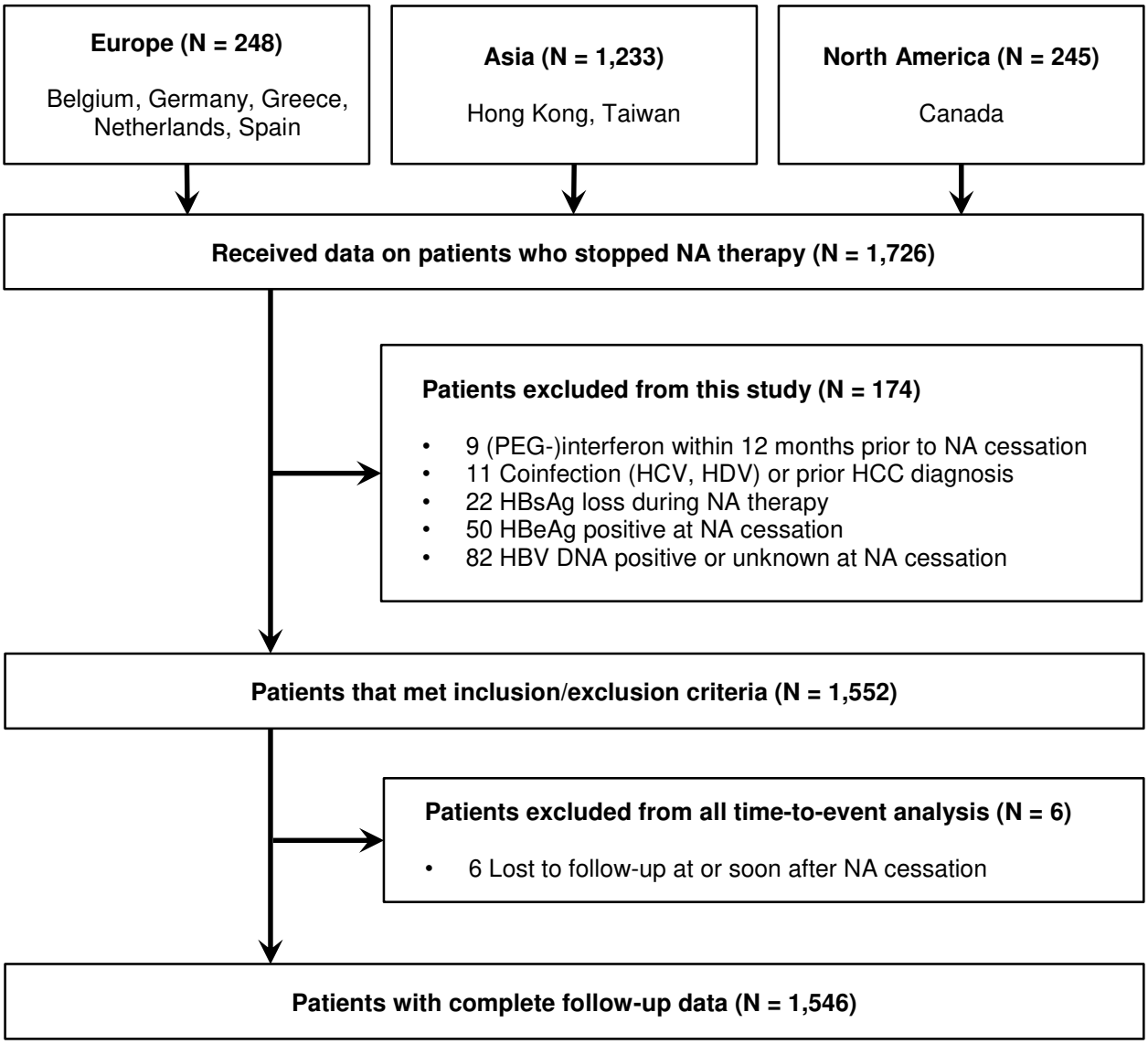
[§] Patient was defined as cirrhotic at end of therapy if cirrhosis had been diagnosed at any time prior to NA cessation.

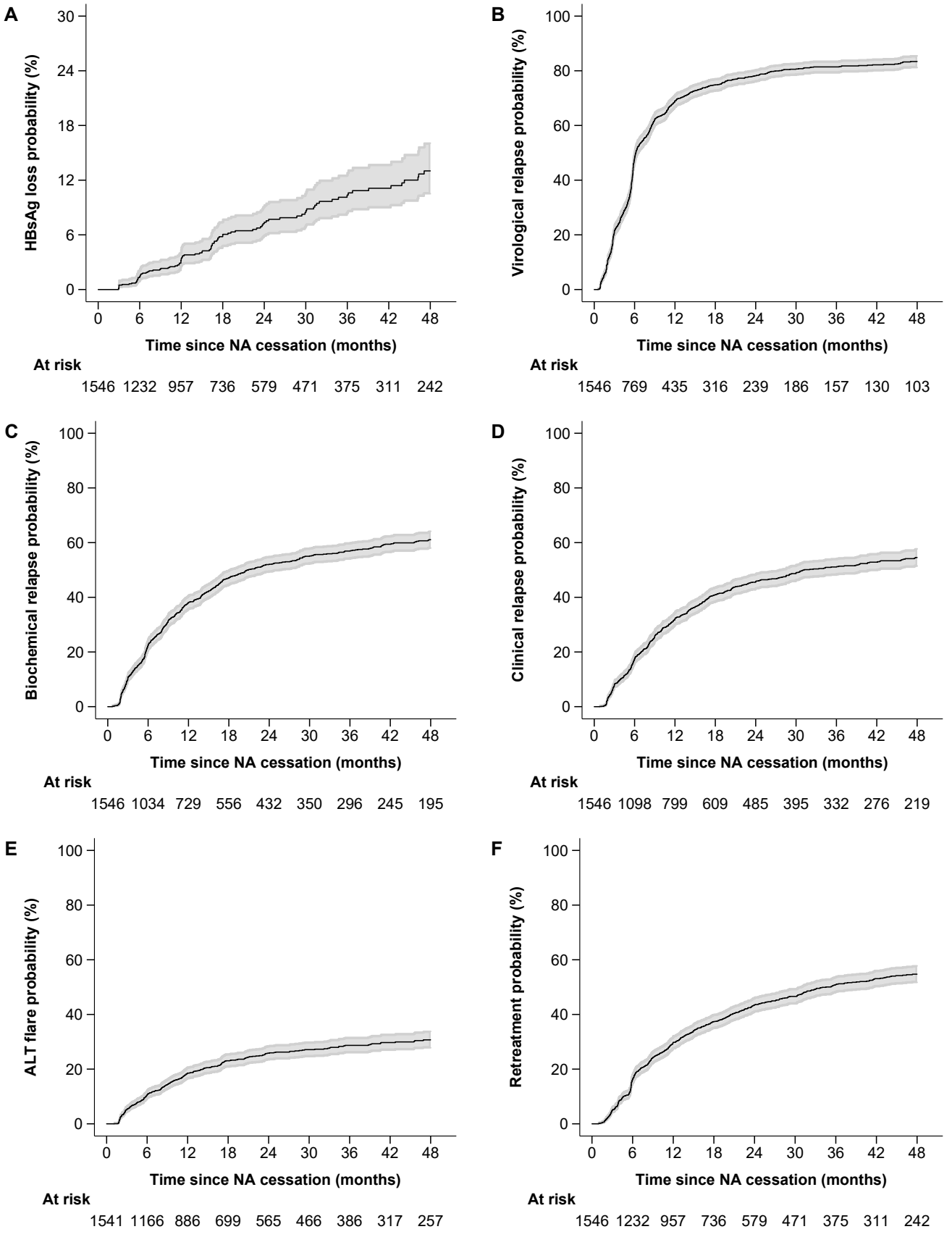
ALT, Alanine aminotransferase; ETV, Entecavir; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; NA, Nucleos(t)ide analogue; PEG, Pegylated; TDF, Tenofovir disoproxil fumarate; ULN, Upper limit of normal.

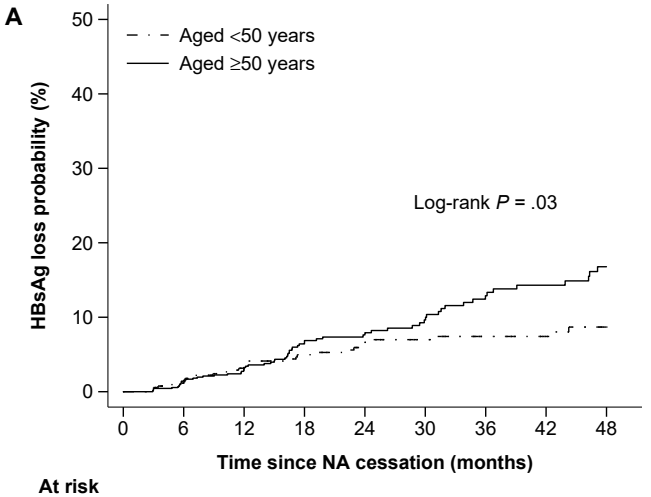
Table 2. Fine-Gray competing risks regression models for HBsAg loss

		Univariate SHR (95% CI)	*P*	Multivariable SHR (95% CI)	*P*
Age at end of therapy, years		1.01 (0.99 – 1.02)	.55	0.99 (0.97 – 1.01)	.24
Age at end of therapy, years					
	<50 years	1.00 (reference)			
	≥50 years	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)	
	Caucasian	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, years		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					
	Non-cirrhotic	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		

ALT, Alanine aminotransferase; CI, Confidence interval; ETV, Entecavir; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue; PEG, Pegylated; SHR, Subdistribution hazard ratio; TDF, Tenofovir disoproxil fumarate; ULN, Upper limit of normal.

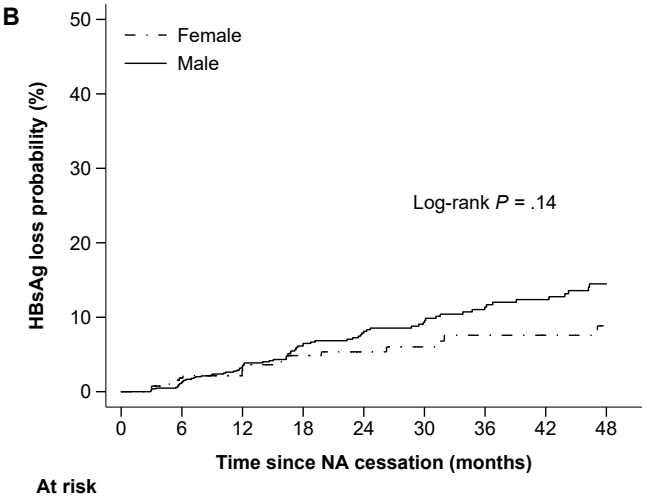

Europe (N = 248)
Belgium, Germany, Greece, Netherlands, Spain
Asia (N = 1,233)
Hong Kong, Taiwan
North America (N = 245)
Canada
Received data on patients who stopped NA therapy (N = 1,726)
Patients excluded from this study (N = 174)
• 9 (PEG-)interferon within 12 months prior to NA cessation
• 11 Coinfection (HCV, HDV) or prior HCC diagnosis
• 22 HBsAg loss during NA therapy
• 50 HBeAg positive at NA cessation
• 82 HBV DNA positive or unknown at NA cessation
Patients that met inclusion/exclusion criteria (N = 1,552)
Patients excluded from all time-to-event analysis (N = 6)
• 6 Lost to follow-up at or soon after NA cessation
Patients with complete follow-up data (N = 1,546)


A
HBsAg loss probability (%)
0
6
12
18
24
30
0 6 12 18 24 30 36 42 48
Time since NA cessation (months)
At risk
1546 1232 957 736 579 471 375 311 242
B
Virological relapse probability (%)
0
20
40
60
80
100
0 6 12 18 24 30 36 42 48
Time since NA cessation (months)
At risk
1546 769 435 316 239 186 157 130 103
C
Biochemical relapse probability (%)
0
20
40
60
80
100
0 6 12 18 24 30 36 42 48
Time since NA cessation (months)
At risk
1546 1034 729 556 432 350 296 245 195
D
Clinical relapse probability (%)
0
20
40
60
80
100
0 6 12 18 24 30 36 42 48
Time since NA cessation (months)
At risk
1546 1098 799 609 485 395 332 276 219
E
ALT flare probability (%)
0
20
40
60
80
100
0 6 12 18 24 30 36 42 48
Time since NA cessation (months)
At risk
1541 1166 886 699 565 466 386 317 257
F
Retreatment probability (%)
0
20
40
60
80
100
0 6 12 18 24 30 36 42 48
Time since NA cessation (months)
At risk
1546 1232 957 736 579 471 375 311 242



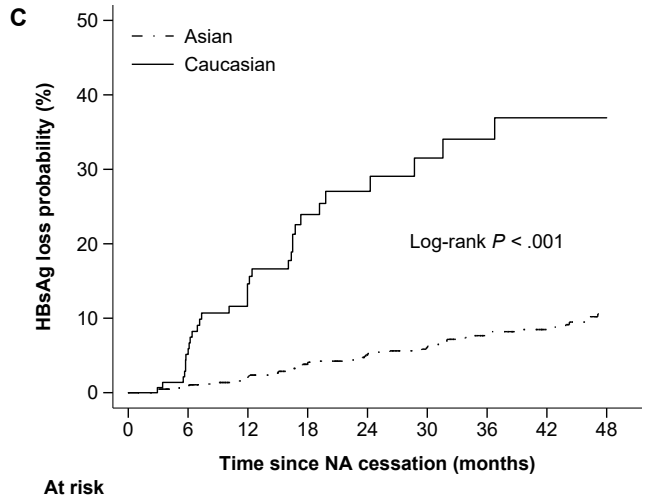
At risk

<50 years	570	479	393	318	262	227	184	153	118
≥50 years	976	753	564	418	317	244	191	158	124



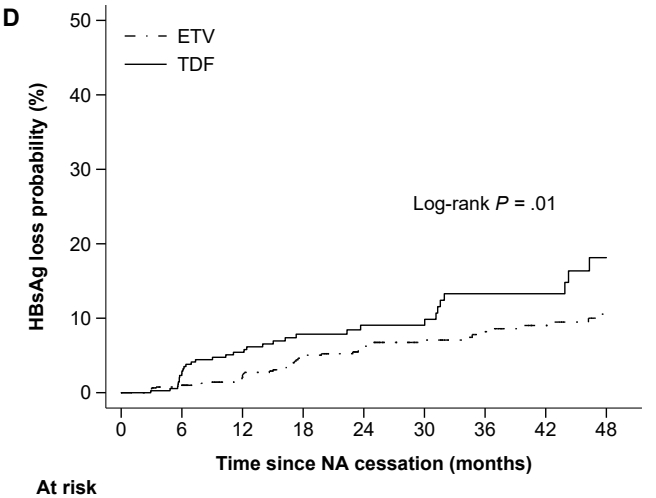
At risk

Female	428	329	264	199	154	128	103	83	69
Male	1118	903	693	537	425	343	272	228	173



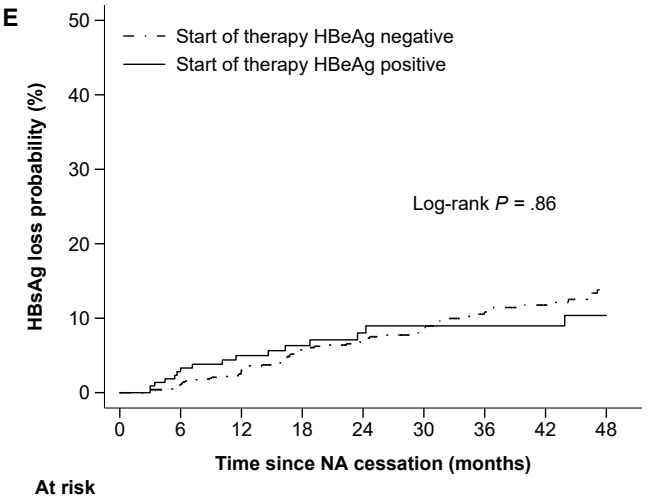
At risk

Asian	1354	1099	865	676	537	440	348	287	227
Caucasian	174	124	85	54	37	27	23	20	11



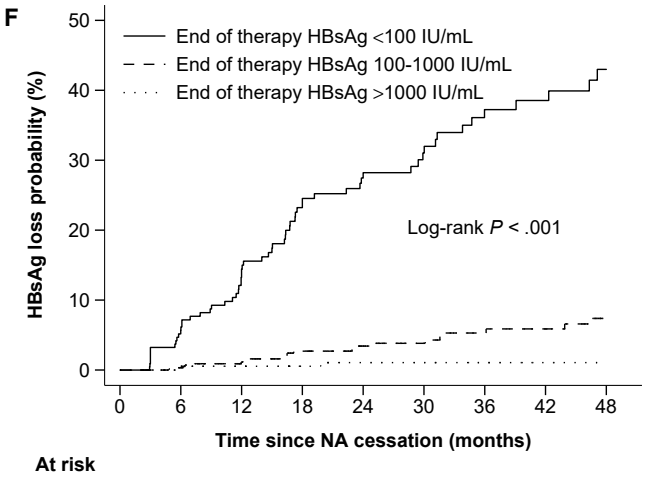
At risk

ETV	979	778	590	471	368	293	234	200	157
TDF	418	328	261	185	142	115	84	63	43



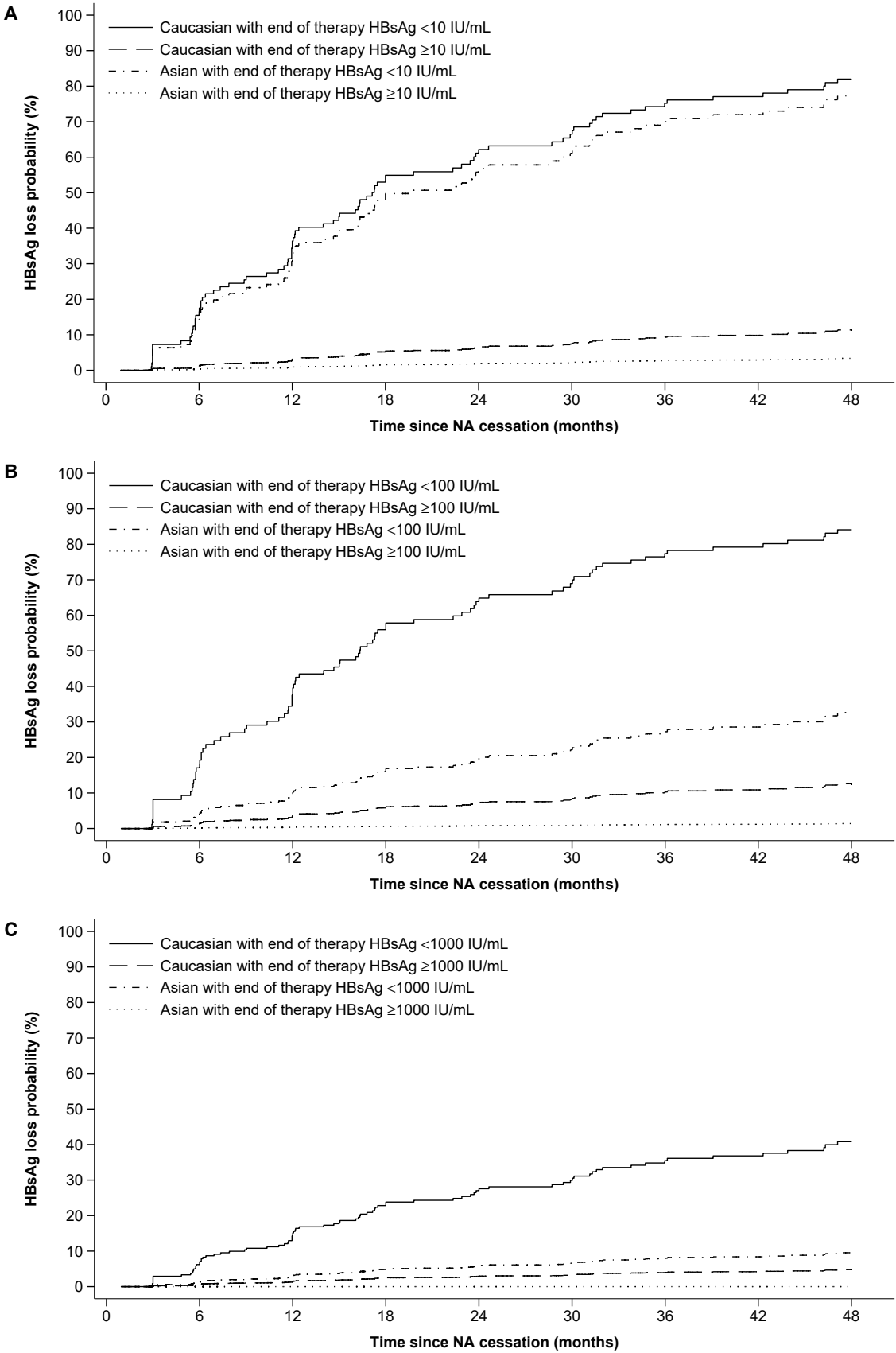
At risk

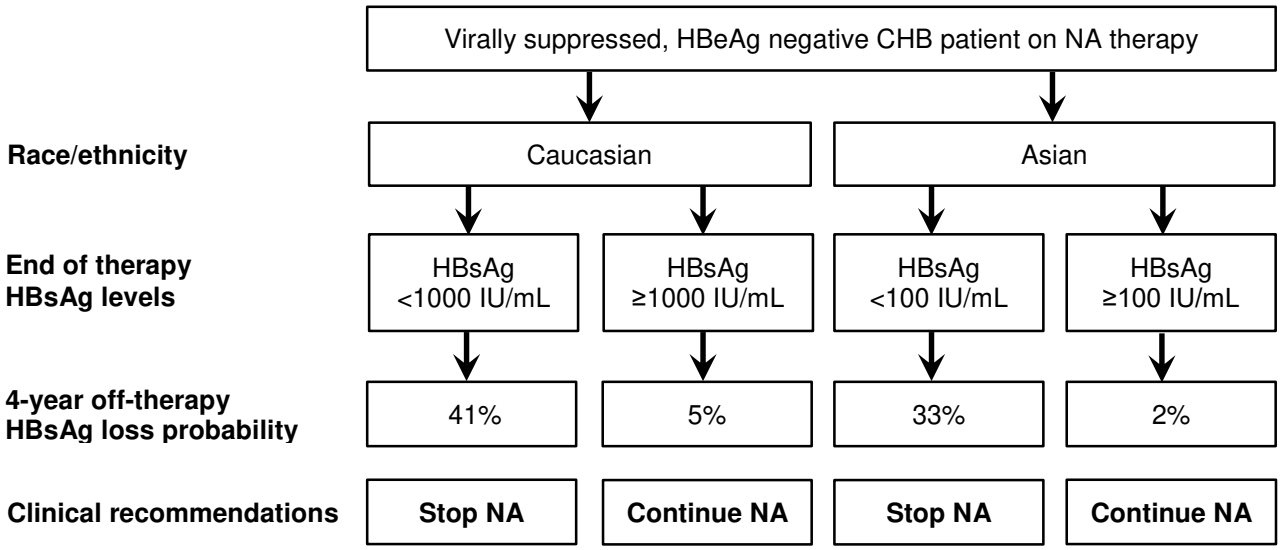
Negative	1304	1027	797	610	479	380	298	243	187
Positive	231	198	156	122	97	89	75	66	53



At risk

<100	223	190	149	117	95	72	55	45	34
100-1000	682	549	423	327	250	204	164	140	105
>1000	463	344	263	201	158	131	101	77	60


A
Caucasian with end of therapy HBsAg <10 IU/mL
Caucasian with end of therapy HBsAg ≥10 IU/mL
Asian with end of therapy HBsAg <10 IU/mL
Asian with end of therapy HBsAg ≥10 IU/mL
HBsAg loss probability (%)
Time since NA cessation (months)
B
Caucasian with end of therapy HBsAg <100 IU/mL
Caucasian with end of therapy HBsAg ≥100 IU/mL
Asian with end of therapy HBsAg <100 IU/mL
Asian with end of therapy HBsAg ≥100 IU/mL
HBsAg loss probability (%)
Time since NA cessation (months)
C
Caucasian with end of therapy HBsAg <1000 IU/mL
Caucasian with end of therapy HBsAg ≥1000 IU/mL
Asian with end of therapy HBsAg <1000 IU/mL
Asian with end of therapy HBsAg ≥1000 IU/mL
HBsAg loss probability (%)
Time since NA cessation (months)


Virally suppressed, HBeAg negative CHB patient on NA therapy
Race/ethnicity
Caucasian
Asian
End of therapy HBsAg levels
HBsAg <1000 IU/mL
HBsAg ≥1000 IU/mL
HBsAg <100 IU/mL
HBsAg ≥100 IU/mL
4-year off-therapy HBsAg loss probability
41%
5%
33%
2%
Clinical recommendations
Stop NA
Continue NA
Stop NA
Continue NA

Supplementary Table 1. **Stopping and retreatment criteria for subjects included in the study**

Supplementary Table 2. **Laboratory methods and tests utilized**

Supplementary Table 3. **Characteristics of included Asian and Caucasian patients**

Supplementary Figure 1. **Cumulative probability of retreatment by patient characteristics: A). Age at NA cessation, B). Sex, C). Race/ethnicity, D). NA type prior to cessation, E). Start of therapy HBeAg status, and F). End of therapy HBsAg levels.** ETV, Entecavir; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.

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 *	Cohort	HBeAg negative for at least 6 months, 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 months of undetectable HBV DNA	At the discretion of the treating physician
Greece	1	Trial	HBeAg negative with at least 36 months of undetectable HBV DNA	Virological relapse, combined relapse, ALT >10x ULN, ALT >3x ULN and HBV DNA >100,000 IU/mL at the same visit, ALT >ULN and HBV DNA >2,000 IU/mL on three 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 months 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 months of undetectable HBV DNA	At the discretion of the treating physician
Hong Kong	3	Cohort, Trial	APASL guidelines	Virological 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 seconds), combined relapse, at the discretion of the treating physician, patient's own initiative
Canada	1	Cohort, Trial	HBeAg negative with at least 12 months 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 >5x ULN on two 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 two consecutive visits at least 4 weeks apart, at the discretion of the treating physician

* Data was centralized at one center however it was collected from 18 centers across Belgium.

APASL, Asia-Pacific Association for the Study of the Liver; ULN, Upper limit of normal.

Supplementary Table 2. Laboratory methods and tests utilized

Site country	Qualitative HBeAg assay	HBsAg assay (quantification limit)	HBV DNA assay (quantification limit)	ALT ULN (U/L)
Belgium	Enzyme-linked immunosorbent assay kit (ELISA), Chemiluminiscent microparticle immunoassay kit	Enzyme-linked immunosorbent assay kit (ELISA), Chemiluminiscent microparticle immunoassay kit	PCR (12 IU/mL)	49
Germany	Enzyme-linked immunosorbent assay kit (ELISA)	Enzyme-linked immunosorbent assay kit (ELISA) (0.22 IU/mL)	PCR (10 IU/mL)	34 (female) and 45 (male)
Greece	N/A	Roche Elecsys HBsAg II Quant reagent kit (0.05 IU/mL)	PCR (50 IU/mL)	40
Netherlands	Chemiluminescent immunoassay kit (CLIA-K)	Chemiluminescent immunoassay kit (CLIA-K) (0.05 IU/mL)	Roche Cobas AmpliPrep/Cobas TaqMan (20 IU/mL)	34 (female) and 45 (male)
Spain	Siemens Advia Centau system	Abbot 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 (N/A)	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), Abbot 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	Abbot Laboratories Architect, Commercial enzyme immunoassay kit	Abbot Laboratories Architect HBsAg QT (0.05 IU/mL), LIAISON XL (0.05 IU/mL)	Roche Cobas TaqMan 48 PCR (20 IU/mL), RT-PCR (N/A)	40, 30 (female) and (male)

ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; PCR, Polymerase chain reaction; RT, Reverse transcription; ULN, Upper limit of normal.

Supplementary Table 3. Characteristics of included Asian and Caucasian patients

	Asian (N = 1359)	**Caucasian** (N = 175)	***P***
Age at end of therapy, years, 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 prior to 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, years: <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, years, 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, months, median (IQR)	2.8 (2.0 – 5.2)	2.4 (1.4 – 3.7)	< .001
Total follow-up duration, months, 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 x 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 x ULN, median (IQR)	0.6 (0.4 – 0.8)	0.6 (0.4 – 0.7)	.79

ALT, Alanine aminotransferase; ETV, Entecavir; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; NA, Nucleos(t)ide analogue; PEG, Pegylated; TDF, Tenofovir disoproxil fumarate; ULN, Upper limit of normal.

Supplementary Figure 1. Cumulative probability of retreatment by patient characteristics: A). Age at NA cessation, B). Sex, C). Race/ethnicity, D). NA type prior to cessation, E). Start of therapy HBeAg status, and F). End of therapy HBsAg levels. ETV, Entecavir; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue; TDF, Tenofovir disoproxil fumarate.