# Incidence of hepatic decompensation after nucleos(t)ide analogue withdrawal : results from a large, international, multi-ethnic cohort of patients with chronic hepatitis B (RETRACT-B study)

# Incidence of hepatic decompensation after nucleos(t)ide analogue withdrawal: Results from a large, international, multi-ethnic cohort of patients with chronic hepatitis B (RETRACT-B study)

**Short title:** Hepatic decompensation after NA withdrawal

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Data acquisition: All authors

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**List of abbreviations**

ALT – Alanine aminotransferase

CHB – Chronic hepatitis B

CI – Confidence interval

DNA – Deoxyribonucleic acid

EOT – End of therapy

HBeAg – Hepatitis B e antigen

HBsAg – Hepatitis B surface antigen

HBV – Hepatitis B virus

HCC – Hepatocellular carcinoma

HIV – Human immunodeficiency virus

HR – Hazard ratio

NA – Nucleos(t)ide analogue

PEG - Pegylated

ULN – Upper limit of normal

**Abstract**

Background: Despite improvements in the management of chronic hepatitis B (CHB), risk of cirrhosis and hepatocellular carcinoma remains. While hepatitis B surface antigen loss is the optimal endpoint, safe discontinuation of nucleos(t)ide analogue (NA) therapy is controversial due to the possibility of severe or fatal reactivation flares.

Methods: Multi-center cohort study of virally suppressed, end-of-therapy HBeAg negative CHB patients who stopped NA therapy (n = 1,557). Survival analysis techniques were used to analyze off-therapy rates of hepatic decompensation, and differences by patient characteristics. We also examined a subgroup of non-cirrhotic patients with consolidation therapy of ≥12 months prior to cessation (n = 1,289). Hepatic decompensation was considered related to therapy cessation if diagnosed off-therapy or within 6 months of starting retreatment.

Results: Among the total cohort (11.8% diagnosed with cirrhosis, 84.2% start of therapy HBeAg negative), 20 developed hepatic decompensation after NA cessation; 10 events among the subgroup. Cumulative incidence of hepatic decompensation at 60 months off-therapy among the total cohort and the subgroup was 1.8% and 1.1%, respectively. Hepatic decompensation rate was higher among patients with cirrhosis (HR 5.08, $P<0.001$), and start of therapy HBeAg positive patients (HR 5.23, $P<0.001$). This association between start of therapy HBeAg status and hepatic decompensation remained significant even among the subgroup (HR 10.5, $P<0.001$).

Conclusion: Patients with cirrhosis and start of therapy HBeAg positive patients should be carefully assessed prior to stopping NAs to prevent hepatic decompensation. Frequent monitoring of viral and host kinetics after cessation is crucial to determine patient outcome.

Keywords: HBV, finite therapy, decompensation, hepatic failure

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## Study Highlights

### WHAT IS KNOWN

- The safe discontinuation of nucleos(t)ide analogue therapy in chronic hepatitis B patients is controversial due to the risk of hepatic decompensation and liver failure.
- Existing literature on off-therapy complications mostly includes case reports and single-site studies.

### WHAT IS NEW HERE

- This is the first large, international, multi-ethnic cohort study to estimate the incidence of hepatic decompensation after nucleos(t)ide analogue withdrawal.
- As expected, but never truly estimated, the rate of hepatic decompensation was higher among patients with cirrhosis. It was also higher among start of therapy HBeAg positive patients.
- The risk of hepatic decompensation remains even among patients without cirrhosis who discontinue therapy as per the guidelines.

## Introduction

Chronic hepatitis B virus (HBV) infection is one of the leading causes of liver cancer and liver-related mortality worldwide.[1] Effective viral suppression with nucleos(t)ide analogues (NAs) has been shown to alleviate the risk of progression to cirrhosis, and development of hepatocellular carcinoma (HCC).[2,3] In recent years, NA withdrawal has become an increasingly popular treatment option because it provides an opportunity for increased hepatitis B surface antigen (HBsAg) loss;[4] HBsAg loss is considered the functional cure because it is associated with favorable outcomes including a reduction in the incidence of liver-related complications.[5] There are three major guidelines that have pre-specified stopping criteria to ensure patient safety after NA withdrawal however, these tend to vary by geographical region and local reimbursement policies.[6–9] As Hepatitis B e antigen (HBeAg) seroconversion comes with increased immune control, the HBeAg status also plays an important role in assessing patient eligibility for treatment cessation.[10]

There have been several case reports and small studies describing severe hepatic flares or acute exacerbation of hepatitis B after NA cessation, which are sometimes fatal.[11–15] Thus far, there has been one large cohort study reporting off-therapy incidence rates of hepatic decompensation and HCC among Asian, pre-therapy HBeAg negative patients who discontinued NAs as per the Asian Pacific Association for the Study of the Liver (APASL) guidelines.[16,17] While most studies have reported a higher incidence of liver-related complications among chronic hepatitis B (CHB) patients with cirrhosis, liver failure associated with HBV reactivation after NA withdrawal among patients without documented cirrhosis has also been reported.[18]

In order to resolve the discrepancies between guidelines, larger cohort studies are needed to understand the characteristics of patients who experience withdrawal-related hepatic decompensation. The main aim of this study was to analyze the incidence of hepatic decompensation after NA withdrawal and describe that cohort of multi-ethnic CHB patients.

## Methods

### *Study setting and patients*

This cohort study included adult, virally suppressed CHB patients who discontinued NA therapy and were HBeAg negative at end of therapy; using the RETRACT-B study cohort with updated information.[4,19] Study inclusion and exclusion criteria, and data collection methods were as previously described.[4] 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 October 2008, and the local national laws governing the conduct of clinical research studies.

### *Study definitions*

The primary outcome analyzed in this study was hepatic decompensation. Hepatic decompensation was defined based on development of a serum total bilirubin level ≥2 mg/dL, INR ≥1.5, onset of ascites, variceal bleeding, or hepatic encephalopathy. Hepatic

decompensation was considered related to treatment withdrawal if diagnosed off-therapy or within 6 months of starting retreatment. Other definitions included virological relapse (HBV DNA ≥2,000 IU/mL), clinical relapse (HBV DNA ≥2,000 IU/mL and ALT ≥2x ULN), and an ALT flare (ALT ≥5x ULN). All outcomes were analyzed off-therapy. The presence of cirrhosis was determined based on histological findings or ultrasonographic evidence.

*Subgroup definition*

Because most guidelines do not recommend NA withdrawal among patients with cirrhosis, and recommend a minimum consolidation period of 12 months,[7,9,20] we also performed subgroup analyses among patients who were non-cirrhotic, virally suppressed and HBeAg negative at EOT with at least 12 months of consolidation therapy were included in the subgroup (Figure 1).

*Statistical analysis*

Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, and categorical variables were presented as frequencies and proportions. Cumulative incidence was estimated using Kaplan–Meier methods; the latest time under which patients were both under observation and at risk was 60 months. Cox regression was used to analyze differences in outcomes by patient characteristics. We also examined the interaction between the presence of cirrhosis and start of therapy HBeAg status for the model for hepatic decompensation. A two-tailed *P* value <.05 was considered statistically significant. Statistical analyses utilized STATA Version 15.1 (StataCorp, College Station, TX).

## Results

*Hepatic decompensation among the total cohort*

We analyzed 1,557 patients in this study of which 20 patients developed hepatic decompensation with a median time to decompensation of 9.9 (IQR: 5.9 – 14.6) months (Figure 1). Among the total cohort, 11.8% had been diagnosed with cirrhosis, and the majority were start of therapy HBeAg negative (84.2%) (Table 1). The median ALT level was normal (0.6 ULN [IQR: 0.4-0.8]) and the mean HBsAg level was 2.6 ± 0.8 $\log_{10}$ IU/mL at end of therapy.

The average incidence rate was 0.41 per 1000 person-years. The cumulative incidence of hepatic decompensation among the total cohort was 1.0% (95% CI 0.6-1.6%), 1.4% (95% CI 0.9-2.2%), 1.6% (95% CI 1.0-2.5%), 1.8% (95% CI 1.1-3.0%), and 1.8% (95% CI 1.1-3.0%) at 12, 24, 36, 48, and 60 months, respectively (Figure 2).

On univariate analyses, there were statistically significant differences in the rate of hepatic decompensation by presence of cirrhosis and HBeAg status at start of therapy (Table 3). At 60 months after NA cessation, the cumulative incidence of hepatic decompensation among patients diagnosed with cirrhosis was 6.4% (95% CI 3.1-12.8%) compared to 1.2% (95% CI 0.6-2.2%) among those without cirrhosis (hazard ratio [HR] 5.08; 95% CI 2.08-12.4) (Table 3, Supplemental Figure 1). The cumulative incidence was 5.4% (95% CI 2.8-10.2%) among start of therapy HBeAg positive patients compared to 1.1% (95% CI 0.6-2.1%) among start of therapy

HBeAg negative patients (HR 5.23; 95% CI 2.18-12.6) (Table 3, Supplemental Figure 1). There was no significant interaction between cirrhosis status and start of therapy HBeAg status; start of therapy HBeAg positive patients had higher rates of decompensation compared to start of therapy HBeAg negative patients, and this association remained significant among patients who had never been diagnosed with cirrhosis.

Most patients who developed hepatic decompensation also experienced at least one additional off-therapy event such as a virological relapse, a clinical relapse, or an ALT flare with the median maximum HBV DNA value of 6.5 (IQR: 5.0-8.2) $\log_{10}$ IU/mL and median maximum ALT x ULN elevation of 13.3 (IQR: 2.5-24.5). Among the 20 decompensated patients, 90.0% experienced a clinical relapse, 65.0% experienced an ALT flare, 60.0% experienced an ALT elevation of ≥10x ULN, 85.0% were retreated, and 35.0% died.[4]

*Hepatic decompensation among the subgroup*

The selection of patients for subgroup analyses has been shown in Figure 1. Among 1,289 patients in the subgroup, 10 patients developed hepatic decompensation with a median time to decompensation of 9.1 (IQR: 6.0–10.8) months (Figure 1). The majority were start of therapy HBeAg negative (87.3%) (Table 2). The median ALT level and mean HBsAg levels at end of therapy were comparable to those of the total cohort.

The average incidence rate was 0.26 per 1000 person-years. The cumulative incidence of hepatic decompensation among the subgroup was 0.7% (95% CI 0.3-1.4%), 0.8% (95% CI 0.4-1.6%),

0.8% (95% CI 0.4-1.6%), 1.1% (95% CI 0.5-2.2%), and 1.1% (95% CI 0.5-2.2%) at 12, 24, 36, 48, and 60 months, respectively (Figure 2). The cumulative incidence remained higher at 5.7% (95% CI 2.4-13.4%) among start of therapy HBeAg positive patients compared to 0.4% (95% CI 0.1-1.0%) among start of therapy HBeAg negative patients (HR 10.5; 95% CI 2.95-37.2) (Table 3, Supplemental Figure 2). Additional off-therapy events among patients who developed hepatic decompensation among the subgroup have been shown in Figure 3.

## Discussion

In this study of CHB patients who discontinued NA therapy, the cumulative incidence of hepatic decompensation was 1.8% and 1.1% at 60 months after NA cessation among the total cohort and the subgroup of patients, respectively. The 5-year cumulative incidence of decompensation reported in this study is higher across all patient groups compared to that reported by Jeng et al.[16] despite having fewer patients with cirrhosis included in the cohort. Among 691 patients, Jeng et al.[16] reported an off-therapy annual incidence rate of 0.3% of hepatic decompensation. This rate is comparable to the subgroup but is higher among the total cohort.

Currently, there are three major guidelines with stopping rule based on HBeAg status: APASL, AASLD, and EASL.[7,9,20] In the absence of HBsAg loss, all three guidelines agree that NAs can be withdrawn in non-cirrhotic HBeAg positive patients after HBeAg seroconversion with a consolidation period of at least 12 months and undetectable HBV DNA. However, in the case of HBeAg negative patients, there is discordance between guidelines. This study showed that start of therapy HBeAg negative patients who were non-cirrhotic and well-suppressed had lower rates

366 of hepatic decompensation compared to start of therapy HBeAg positive patients.[6,21] While not
367 significant, a prior study on the RETRACT-B cohort showed that start of therapy HBeAg
368 positive patients tended to have relatively higher rates of HBsAg loss.[4] Berg et al.[6] and Liem et
369 al.[21] suggested that the differences in off-therapy responses between these groups, particularly
370 the higher rates of retreatment among start of therapy HBeAg positive patients may be
371 attributable to differences in how immune control was established. If confirmed these data may
372 prompt a revision of the guidelines to only withdraw NA in those who are HBeAg negative at
373 start of therapy.
374
375 Most patients who decompensated experienced the event early, within the first 18 months after
376 stopping, and experienced significant viral rebounds and ALT elevations around the
377 decompensating event. Thus, the timing of decompensation indicates that the event was related
378 to treatment withdrawal given that these patients were very well suppressed on long-term therapy
379 prior to cessation. Clinical relapse is often used as a criterion for retreatment in current clinical
380 practice as well as in randomized trials, and it has been shown that the risk of relapse does not
381 differ between start of therapy HBeAg positive and negative patients.[21–23] Given that about 90%
382 of the decompensated patients experienced a clinical relapse after NA cessation, our study
383 suggests that frequent monitoring after stopping therapy remains crucial. While there have been
384 studies showing that an ALT flare is a prerequisite to induce HBsAg loss,[6,16,22,24–26] the results
385 from this study show that a single clinical relapse with ALT elevations ≥2x ULN may also be an
386 indication of impending decompensation. Zhang et al.[27] showed that low-level viremia can result
387 in end-stage liver disease compared to patients with maintained virological response however, a
388 recent study by Papatheodoridi et al.[17] reported conflicting results. However, the probability of

389 decompensation for patients suppressed on-therapy is relatively lower.[2] Thus, in the absence of
390 HBsAg loss, there is sparse evidence to determine whether patients with mildly active disease
391 would benefit from initiating retreatment. Typically, NAs are widely available, lack side effects
392 and long-term resistance, are relatively cheap and effective, and reimbursed in most global
393 regions. Nevertheless, the frequency of follow-up after NA cessation and the biomarkers being
394 measured play a vital role in predicting off-therapy outcomes.
395
396 Although existing studies have shown the ability of HBsAg levels at EOT to reasonably predict
397 HBsAg loss after cessation,[4,28–30] it is unable to estimate the probability that a patient will not
398 experience exacerbation and decompensation of hepatitis B. Other studies have shown that
399 detectable levels of hepatitis B core-related antigen (HBcrAg) and HBV RNA at EOT can
400 predict an unfavourable outcome such as relapses however, the assays lack sensitivity and the
401 undetectability of these markers is not a strong predictor of HBsAg loss.[31–35] Nevertheless, a
402 recent study by Sonneveld et al.,[28] showed that quantification of HBcrAg at EOT may be useful
403 in predicting of-therapy HBsAg loss. The frequency of follow-up at most participating centers in
404 this study was every 3-6 months. ALT and HBV DNA were monitored more closely compared to
405 HBsAg levels during off-therapy follow-up. As suggested by Liaw,[36] frequent i.e., bi-weekly or
406 monthly, quantification of HBsAg levels in addition to HBV DNA and ALT, especially soon
407 after the flare may be more effective in determining patient outcome. A “virus-dominating” flare,
408 marked by increasing viral activity, may lead to decompensation and would be indicative of
409 requiring retreatment. In the case of a “host-dominating flare”, marked by HBsAg decline and
410 potentially HBsAg loss, retreatment can be withheld if we have a high degree of certainty that
411 patients will not decompensate.[36]

This study has limitations. First, due to the differences in local guidelines and policies by geographical location within this cohort, we could not apply and analyze data as per any one particular guideline. However, subgroup analyses ensured reporting of results following recommendations on stopping that are consistent across guidelines. Second, while patients who had been diagnosed with cirrhosis had relatively higher rates, the 60-month cumulative incidence of hepatic decompensation was 1.2% among patients who had never been diagnosed with cirrhosis and this may be attributable to undiagnosed cirrhosis. Thus, even though several patients in the cohort may have had reversal of fibrosis and benefitted from long-term NA use,[2] due to the lack of fibrosis assessments at end of therapy few patients may have had underlying, undiagnosed cirrhosis. Additionally, it is important to note that cirrhosis diagnosis varied by center and location however, each center included in this study are high-volume centers with expertise in treating CHB. Lastly, there may have been additional misclassification bias due to insufficient information on certain factors.

In conclusion, the findings from this study suggest that to evade hepatic decompensation, patients diagnosed with cirrhosis and start of therapy HBeAg positive patients should be very carefully assessed if NA withdrawal is being considered as a treatment option. In contrast, guidelines can consider establishing albeit strict but standardized stopping criteria for patients who begin antiviral therapy in the HBeAg-negative phase.[37] Decompensation was mostly heralded by clinical relapse and flares and these patients may benefit from timely retreatment. Further insight into the dynamics of HBsAg, HBV DNA, ALT and novel biomarkers through

well-designed prospective studies are warranted to determine the balance between successful and detrimental outcome after NA withdrawal.

**Table 1**. Characteristics of the total cohort and those who developed hepatic decompensation.

| | **Overall** (N = 1,557) | **Hepatic decompensation** (N = 20) |
|---|---|---|
| Age at end of therapy, *years*, mean ± SD | 52.9 ± 11.3 | 57.0 ± 13.1 |
| Male sex, n (%) | 1,125 (72.3) | 15 (75.0) |
| Asian race/ethnicity, n (%) | 1,363 (87.5) | 18 (90.0) |
| HBV genotype, n (%) | | |
| A | 9 (0.6) | 0 (0) |
| B | 666 (42.8) | 10 (50.0) |
| C | 170 (10.9) | 3 (15.0) |
| D | 45 (2.9) | 1 (5.0) |
| Unavailable | 667 (42.8) | 6 (30.0) |
| NA withdrawn, n (%) | | |
| Entecavir | 985 (63.3) | 11 (55.0) |
| Tenofovir | 454 (29.2) | 9 (45.0) |
| Other | 118 (7.6) | 0 (0) |
| Duration of continuous NA therapy, *years*, median (IQR) | 3.0 (3.0 – 4.0) | 3.1 (3.0 – 6.9) |
| Duration of consolidation therapy, *years* | | |
| <1 | 90 (5.8) | 3 (15.0) |
| 1 to <2 | 563 (36.2) | 4 (20.0) |
| 2 to <3 | 564 (36.2) | 11 (55.0) |
| ≥3 | 339 (21.8) | 2 (10.0) |
| Prior NA therapy, n (%) | 270 (17.3) | 5 (25.0) |
| Prior interferon therapy, n (%) | 134 (8.6) | 1 (5.0) |
| Cirrhosis, n (%) | 184 (11.8) | 8 (40.0) |
| HBeAg negative at start of therapy, n (%) | 1,311 (84.2) | 10 (50.0) |
| HBsAg at end of therapy, $log_{10}$ *IU/mL*, mean ± SD | 2.6 ± 0.8 | 2.5 ± 0.7 |
| ALT x ULN at end of therapy, median (IQR) | 0.6 (0.4 – 0.8) | 0.5 (0.4 – 0.7) |
| Number of off-therapy visits, median (IQR) | 6 (3 - 9) | 4 (3 – 5.5) |
| Mean time between off-therapy visits, *months*, median (IQR) | 2.8 (2.0 – 5.0) | 2.2 (1.6 – 3.8) |
| Total off-therapy time, *months*, median (IQR) | 19.3 (8.0 – 39.5) | 9.5 (5.7 – 14.6) |

ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; IQR, Interquartile range; NA, Nucleos(t)ide analogue; SD, Standard deviation; ULN, Upper limit of normal.

**Table 2**. Characteristics of the subgroup of patients and those who developed hepatic decompensation.

| | **Overall** (N = 1,289) | **Hepatic decompensation** (N = 10) |
|---|---|---|
| Age at end of therapy, *years*, mean ± SD | 53.0 ± 11.0 | 55.1 ± 13.5 |
| Male sex, n (%) | 929 (72.1) | 6 (60) |
| Asian race/ethnicity, n (%) | 1,125 (87.3) | 10 (100) |
| HBV genotype, n (%) | | |
| A | 6 (0.5) | 0 (0) |
| B | 554 (43.0) | 5 (50.0) |
| C | 131 (10.2) | 3 (30.0) |
| D | 42 (3.3) | 0 (0) |
| Unavailable | 556 (43.1) | 2 (20.0) |
| NA withdrawn, n (%) | | |
| Entecavir | 830 (64.4) | 6 (60.0) |
| Tenofovir | 396 (30.7) | 4 (40.0) |
| Other | 63 (4.9) | 0 (0) |
| Duration of continuous NA therapy, *years*, median (IQR) | 3.0 (3.0 – 3.9) | 3.0 (3.0 – 3.1) |
| Duration of consolidation therapy, *years* | | |
| 1 to <2 | 501 (38.9) | 3 (30.0) |
| 2 to <3 | 495 (38.4) | 7 (70.0) |
| ≥3 | 293 (22.7) | 0 (0) |
| Prior NA therapy, n (%) | 215 (16.7) | 3 (30.0) |
| Prior interferon therapy, n (%) | 111 (8.6) | 0 (0) |
| HBeAg negative at start of therapy, n (%) | 1,125 (87.3) | 4 (40.0) |
| HBsAg at end of therapy, $log_{10}$ *IU/mL*, mean ± SD | 2.6 ± 0.8 | 2.5 ± 0.9 |
| ALT x ULN at end of therapy, median (IQR) | 0.6 (0.4 – 0.8) | 0.4 (0.3 – 0.6) |
| Number of off-therapy visits, median (IQR) | 6 (3 – 9) | 4 (4 – 5) |
| Mean time between off-therapy visits, *months*, median (IQR) | 2.8 (2.0 – 4.7) | 2.2 (1.7 – 3.6) |
| Total off-therapy time, *months*, median (IQR) | 19.6 (7.8 – 38.0) | 9.0 (6.0 – 14.5) |

ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; IQR, Interquartile range; NA, Nucleos(t)ide analogue; SD, Standard deviation; ULN, Upper limit of normal.

485 **Table 3**. Univariate Cox regression models for hepatic decompensation.

| | Total | | Subgroup | |
|---|---|---|---|---|
| | **Hazard Ratio (95% CI)** | ***P*** | **Hazard Ratio (95% CI)** | ***P*** |
| Age at end of therapy, *years* | | | | |
| Sex | 1.04 (1.00 – 1.08) | 0.08 | 1.02 (0.96 – 1.08) | 0.51 |
| Female | 1.00 (reference) | | 1.00 (reference) | |
| Male | 1.14 (0.41 – 3.14) | 0.80 | 0.57 (0.16 – 2.01) | 0.38 |
| Race/ethnicity | | | | |
| Non-Asian | 1.00 (reference) | | | |
| Asian | 1.07 (0.25 – 4.64) | 0.92 | | |
| NA withdrawn | | | | |
| Entecavir | 1.00 (reference) | | 1.00 (reference) | |
| Tenofovir | 1.83 (0.76 – 4.41) | 0.18 | 1.46 (0.41 – 5.17) | 0.56 |
| Duration of continuous NA therapy, *years* | 1.11 (0.97 – 1.26) | 0.14 | 0.99 (0.75 – 1.30) | 0.92 |
| Duration of consolidation therapy, *years* | 0.87 (0.64 – 1.19) | 0.38 | 0.44 (0.18 – 1.05) | 0.06 |
| Prior NA therapy | | | | |
| No | 1.00 (reference) | | 1.00 (reference) | |
| Yes | 1.71 (0.62 – 4.70) | 0.30 | 2.38 (0.61 – 9.20) | 0.21 |
| Prior interferon therapy | | | | |
| No | 1.00 (reference) | | | |
| Yes | 0.56 (0.08 – 4.22) | 0.58 | | |
| Cirrhosis | | | | |
| No | 1.00 (reference) | | | |
| Yes | 5.08 (2.08 – 12.4) | <0.001 | | |
| HBeAg status at start of therapy | | | | |
| Negative | 1.00 (reference) | | 1.00 (reference) | |
| Positive | 5.23 (2.18 – 12.6) | <0.001 | 10.5 (2.95 – 37.2) | <0.001 |
| HBsAg at end of therapy, $log_{10}$ *IU/mL* | 0.88 (0.52 – 1.48) | 0.62 | 0.86 (0.44 – 1.67) | 0.66 |
| ALT x ULN at end of therapy | 0.44 (0.09 – 2.17) | 0.31 | 0.01 (0.00 - 0.65) | 0.03 |

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487 ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue; ULN, Upper limit of normal.
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Author names in bold designate shared co-first authorship.

## Figure Legends

**Figure 1**. Flowchart of patient selection.

**Figure 2**. Cumulative incidence of hepatic decompensation among the total cohort and the subgroup.

**Figure 3**. Additional off-therapy events among patients who developed hepatic decompensation among the subgroup. Clinical relapse was defined as virological relapse (HBV DNA ≥2000 IU/mL) and biochemical relapse (ALT ≥2x ULN). ALT flare was defined as ALT ≥5x ULN. One patient experienced a clinical relapse, 1 patient developed hepatic decompensation, and 1 patient died after 24 months off-therapy and thus, these events are not depicted in Figure A.

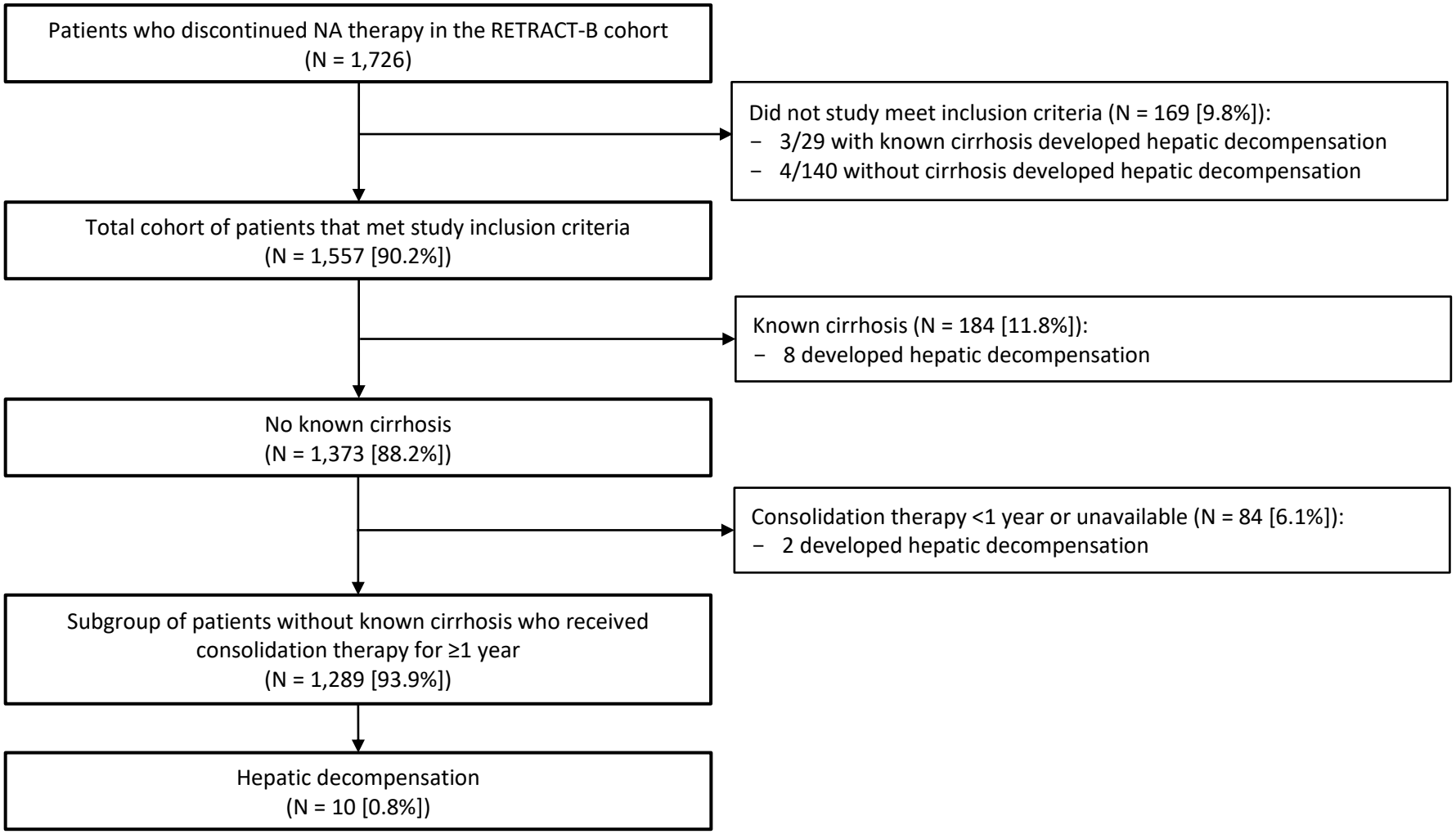



**Figure 1.** Flowchart of patient selection. NA, Nucleos(t)ide analogue.

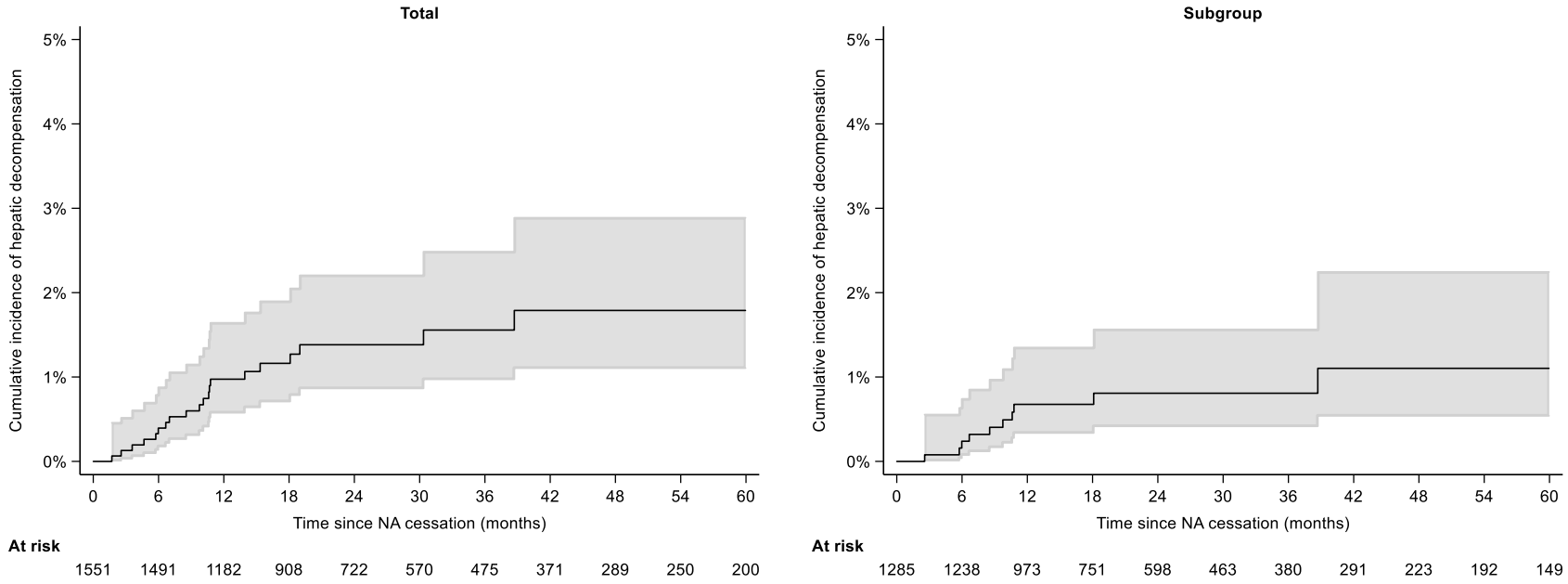



**Figure 2. Cumulative incidence of hepatic decompensation among the total cohort and the subgroup.** NA, Nucleos(t)ide analogue.

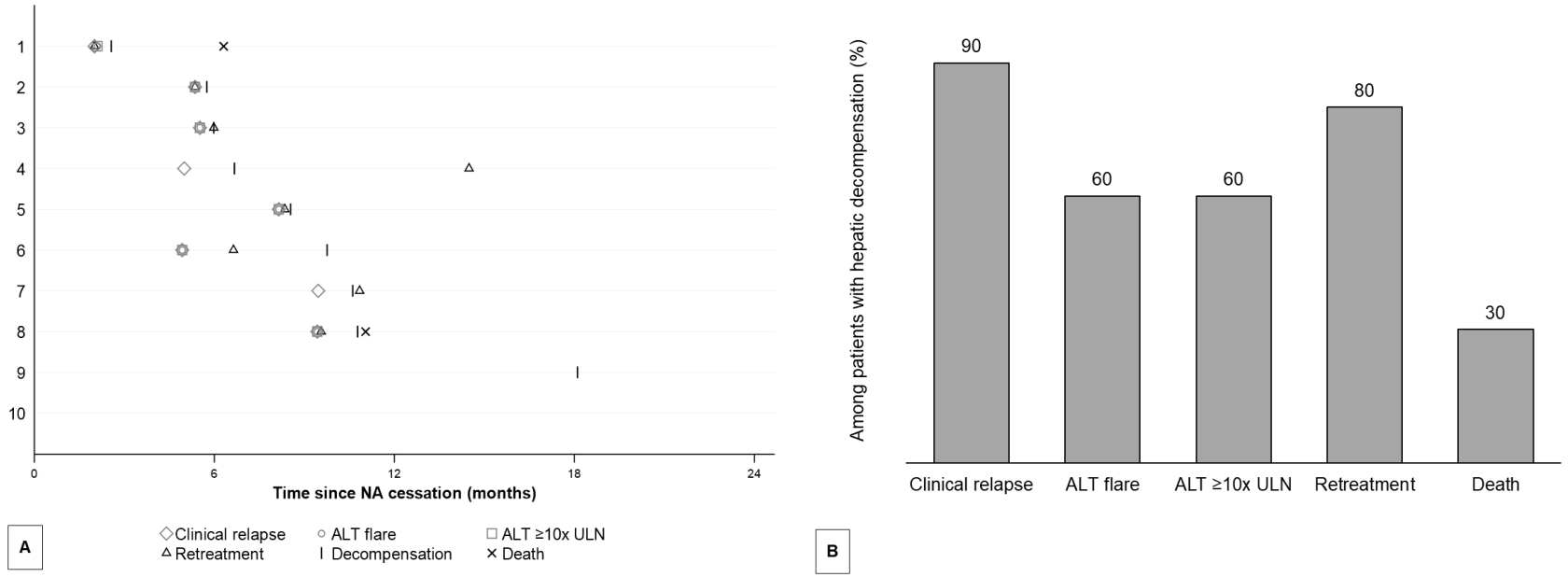



**Figure 3. Additional off-therapy events among patients who developed hepatic decompensation among the subgroup.** Clinical relapse was defined as virological relapse (HBV DNA ≥2000 IU/mL) and biochemical relapse (ALT ≥2x ULN). ALT flare was defined as ALT ≥5x ULN. One patient experienced a clinical relapse, 1 patient developed hepatic decompensation, and 1 patient died after 24 months off-therapy and thus, these events are not depicted in Figure A. ALT, Alanine aminotransferase; ULN, Upper limit of normal.

**Table 1**. Characteristics of the total cohort and those who developed hepatic decompensation.

| | **Overall** (N = 1,557) | **Hepatic decompensation** (N = 20) |
|---|---|---|
| Age at end of therapy, *years*, mean ± SD | 52.9 ± 11.3 | 57.0 ± 13.1 |
| Male sex, n (%) | 1,125 (72.3) | 15 (75.0) |
| Asian race/ethnicity, n (%) | 1,363 (87.5) | 18 (90.0) |
| HBV genotype, n (%) | | |
| A | 9 (0.6) | 0 (0) |
| B | 666 (42.8) | 10 (50.0) |
| C | 170 (10.9) | 3 (15.0) |
| D | 45 (2.9) | 1 (5.0) |
| Unavailable | 667 (42.8) | 6 (30.0) |
| NA withdrawn, n (%) | | |
| Entecavir | 985 (63.3) | 11 (55.0) |
| Tenofovir | 454 (29.2) | 9 (45.0) |
| Other | 118 (7.6) | 0 (0) |
| Duration of continuous NA therapy, *years*, median (IQR) | 3.0 (3.0 – 4.0) | 3.1 (3.0 – 6.9) |
| Duration of consolidation therapy, *years* | | |
| <1 | 90 (5.8) | 3 (15.0) |
| 1 to <2 | 563 (36.2) | 4 (20.0) |
| 2 to <3 | 564 (36.2) | 11 (55.0) |
| ≥3 | 339 (21.8) | 2 (10.0) |
| Prior NA therapy, n (%) | 270 (17.3) | 5 (25.0) |
| Prior interferon therapy, n (%) | 134 (8.6) | 1 (5.0) |
| Cirrhosis, n (%) | 184 (11.8) | 8 (40.0) |
| HBeAg negative at start of therapy, n (%) | 1,311 (84.2) | 10 (50.0) |
| HBsAg at end of therapy, $log_{10}$ *IU/mL*, mean ± SD | 2.6 ± 0.8 | 2.5 ± 0.7 |
| ALT x ULN at end of therapy, median (IQR) | 0.6 (0.4 – 0.8) | 0.5 (0.4 – 0.7) |
| Number of off-therapy visits, median (IQR) | 6 (3 - 9) | 4 (3 – 5.5) |
| Mean time between off-therapy visits, *months*, median (IQR) | 2.8 (2.0 – 5.0) | 2.2 (1.6 – 3.8) |
| Total off-therapy time, *months*, median (IQR) | 19.3 (8.0 – 39.5) | 9.5 (5.7 – 14.6) |

ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; IQR, Interquartile range; NA, Nucleos(t)ide analogue; SD, Standard deviation; ULN, Upper limit of normal.

**Table 2**. Characteristics of the subgroup of patients and those who developed hepatic decompensation.

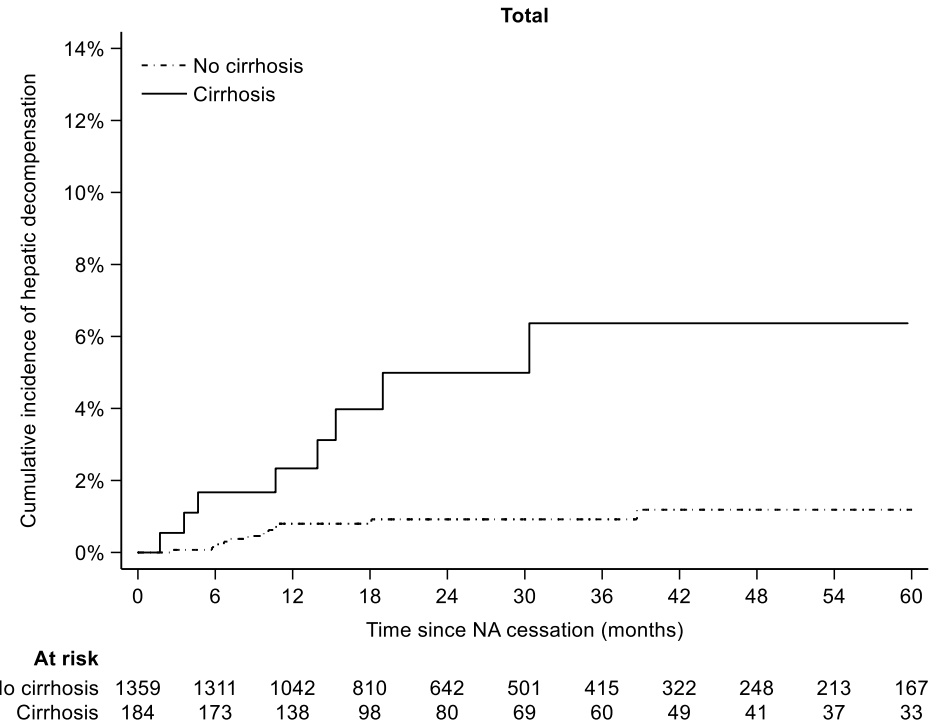
| | **Overall** (N = 1,289) | **Hepatic decompensation** (N = 10) |
|---|---|---|
| Age at end of therapy, *years*, mean ± SD | 53.0 ± 11.0 | 55.1 ± 13.5 |
| Male sex, n (%) | 929 (72.1) | 6 (60) |
| Asian race/ethnicity, n (%) | 1,125 (87.3) | 10 (100) |
| HBV genotype, n (%) | | |
| A | 6 (0.5) | 0 (0) |
| B | 554 (43.0) | 5 (50.0) |
| C | 131 (10.2) | 3 (30.0) |
| D | 42 (3.3) | 0 (0) |
| Unavailable | 556 (43.1) | 2 (20.0) |
| NA withdrawn, n (%) | | |
| Entecavir | 830 (64.4) | 6 (60.0) |
| Tenofovir | 396 (30.7) | 4 (40.0) |
| Other | 63 (4.9) | 0 (0) |
| Duration of continuous NA therapy, *years*, median (IQR) | 3.0 (3.0 – 3.9) | 3.0 (3.0 – 3.1) |
| Duration of consolidation therapy, *years* | | |
| 1 to <2 | 501 (38.9) | 3 (30.0) |
| 2 to <3 | 495 (38.4) | 7 (70.0) |
| ≥3 | 293 (22.7) | 0 (0) |
| Prior NA therapy, n (%) | 215 (16.7) | 3 (30.0) |
| Prior interferon therapy, n (%) | 111 (8.6) | 0 (0) |
| HBeAg negative at start of therapy, n (%) | 1,125 (87.3) | 4 (40.0) |
| HBsAg at end of therapy, $log_{10}$ *IU/mL*, mean ± SD | 2.6 ± 0.8 | 2.5 ± 0.9 |
| ALT x ULN at end of therapy, median (IQR) | 0.6 (0.4 – 0.8) | 0.4 (0.3 – 0.6) |
| Number of off-therapy visits, median (IQR) | 6 (3 – 9) | 4 (4 – 5) |
| Mean time between off-therapy visits, *months*, median (IQR) | 2.8 (2.0 – 4.7) | 2.2 (1.7 – 3.6) |
| Total off-therapy time, *months*, median (IQR) | 19.6 (7.8 – 38.0) | 9.0 (6.0 – 14.5) |

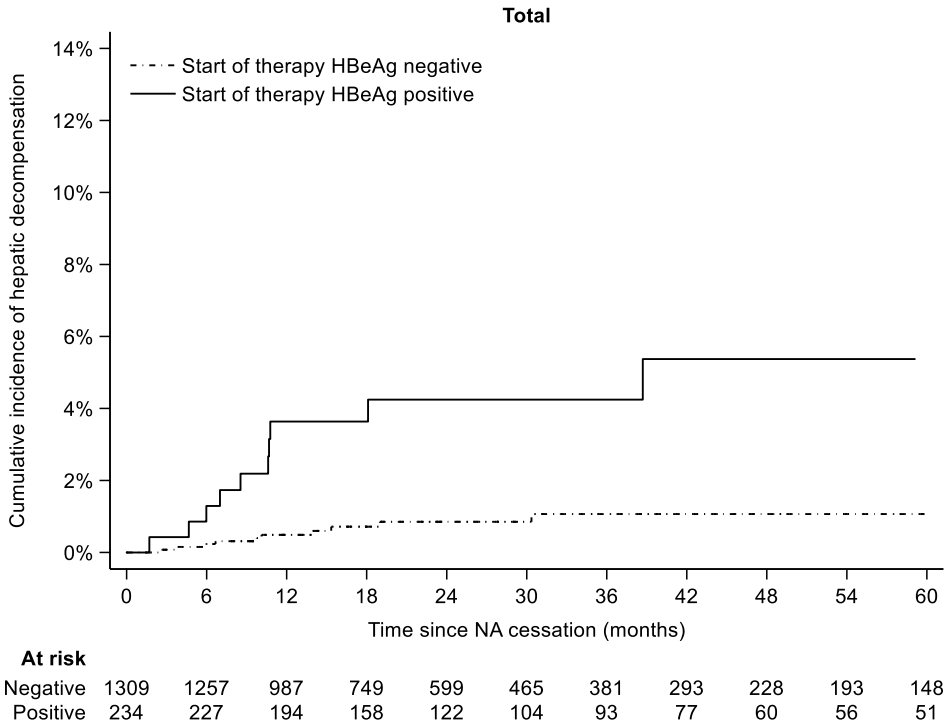
ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; IQR, Interquartile range; NA, Nucleos(t)ide analogue; SD, Standard deviation; ULN, Upper limit of normal.

**Table 3**. Univariate Cox regression models for hepatic decompensation.

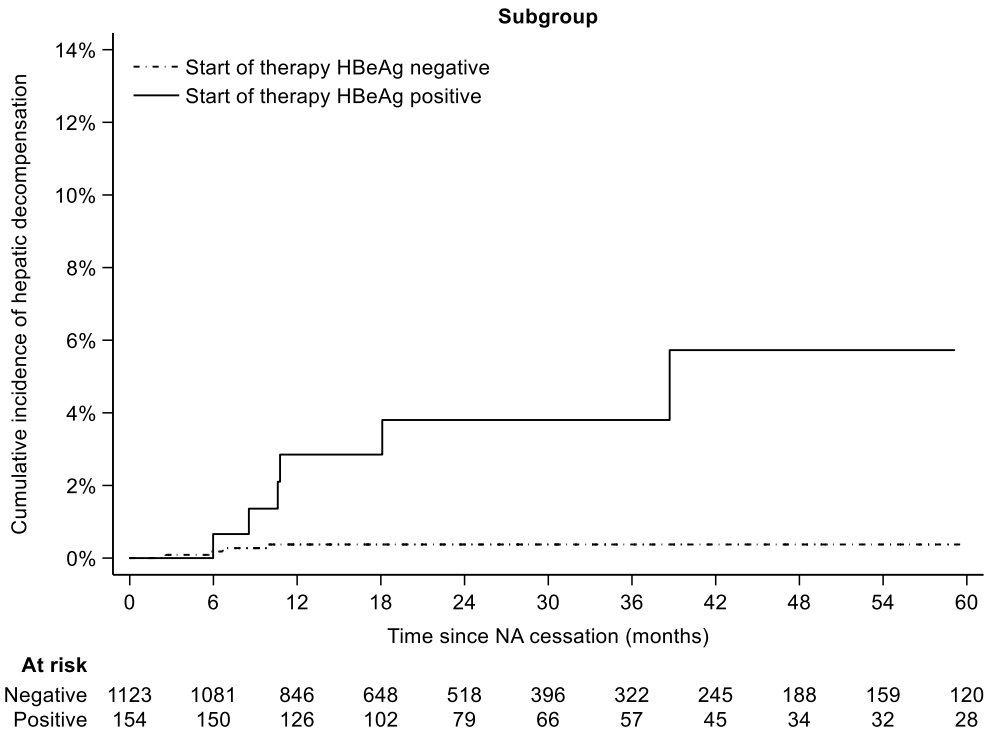
| | **Total** | | **Subgroup** | |
|---|---|---|---|---|
| | **Hazard Ratio (95% CI)** | ***P*** | **Hazard Ratio (95% CI)** | ***P*** |
| Age at end of therapy, *years* | | | | |
| Sex | 1.04 (1.00 – 1.08) | 0.08 | 1.02 (0.96 – 1.08) | 0.51 |
| Female | 1.00 (reference) | | 1.00 (reference) | |
| Male | 1.14 (0.41 – 3.14) | 0.80 | 0.57 (0.16 – 2.01) | 0.38 |
| Race/ethnicity | | | | |
| Non-Asian | 1.00 (reference) | | | |
| Asian | 1.07 (0.25 – 4.64) | 0.92 | | |
| NA withdrawn | | | | |
| Entecavir | 1.00 (reference) | | 1.00 (reference) | |
| Tenofovir | 1.83 (0.76 – 4.41) | 0.18 | 1.46 (0.41 – 5.17) | 0.56 |
| Duration of continuous NA therapy, *years* | 1.11 (0.97 – 1.26) | 0.14 | 0.99 (0.75 – 1.30) | 0.92 |
| Duration of consolidation therapy, *years* | 0.87 (0.64 – 1.19) | 0.38 | 0.44 (0.18 – 1.05) | 0.06 |
| Prior NA therapy | | | | |
| No | 1.00 (reference) | | 1.00 (reference) | |
| Yes | 1.71 (0.62 – 4.70) | 0.30 | 2.38 (0.61 – 9.20) | 0.21 |
| Prior interferon therapy | | | | |
| No | 1.00 (reference) | | | |
| Yes | 0.56 (0.08 – 4.22) | 0.58 | | |
| Cirrhosis | | | | |
| No | 1.00 (reference) | | | |
| Yes | 5.08 (2.08 – 12.4) | <0.001 | | |
| HBeAg status at start of therapy | | | | |
| Negative | 1.00 (reference) | | 1.00 (reference) | |
| Positive | 5.23 (2.18 – 12.6) | <0.001 | 10.5 (2.95 – 37.2) | <0.001 |
| HBsAg at end of therapy, $log_{10}$ *IU/mL* | 0.88 (0.52 – 1.48) | 0.62 | 0.86 (0.44 – 1.67) | 0.66 |
| ALT x ULN at end of therapy | 0.44 (0.09 – 2.17) | 0.31 | 0.01 (0.00 - 0.65) | 0.03 |

ALT, Alanine aminotransferase; HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; NA, Nucleos(t)ide analogue; ULN, Upper limit of normal.




**Supplemental Figure 1.** Cumulative incidence of hepatic decompensation by patient characteristics among the total cohort.




**Supplemental Figure 2.** Cumulative incidence of hepatic decompensation by patient characteristics among the subgroup.