Differential Relapse Patterns After Discontinuation of Entecavir vs Tenofovir Disoproxil Fumarate in Chronic Hepatitis B

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BACKGROUND AND AIMS: **Whether entecavir (ETV) and tenofovir disoproxil fumarate (TDF) differentially affect relapse and outcomes following treatment discontinuation across different patient subpopulations remains unclear. We aimed to compare rates of off-therapy hepatitis B surface antigen (HBsAg) loss, virological and clinical relapse, and retreatment between chronic hepatitis B (CHB) patients who discontinued TDF or ETV therapy.**

METHODS: **This study included 1402 virally suppressed CHB patients who stopped either ETV (n = 981) or TDF (n = 421) therapy between 2001 and 2020 from 13 participating centers across North America, Europe, and Asia. All patients were hepatitis B e antigen–negative at treatment discontinuation. Inverse probability of treatment weighting was used to balance the treatment groups. Outcomes were analyzed using survival methods.**

RESULTS: **During a median off-treatment follow-up of 18 months, HBsAg loss occurred in 96 (6.8%) patients overall. Compared with ETV, TDF was associated with a higher rate of HBsAg loss ($P = .03$); however, the association was no longer significant after statistical adjustment ($P = .61$). Virological relapse occurred earlier among TDF-treated patients ($P < .01$); nonetheless, rates became comparable after the first year off therapy ($P = .49$). TDF was significantly associated with a higher clinical relapse rate than ETV throughout follow-up ($P < .01$). The development of a virological or clinical relapse did not affect the rate of HBsAg loss. Retreatment rates were not significantly different between the treatment groups.**

Abbreviations used in this paper: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; EOT, end of therapy; ETV, entecavir; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; IFN, interferon; IPTW, inverse probability of treatment weighting; IQR, interquartile range; NA, nucleos(t)ide analogue; PEG, pegylated; SOT, start of therapy; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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CONCLUSIONS: **TDF and ETV have differential relapse patterns but are associated with similar rates of HBsAg loss and retreatment following discontinuation. Finite therapy can be considered for CHB patients on either TDF or ETV therapy.**

Keywords: Tenofovir; Entecavir; Nucleos(T)Ide Analogue Withdrawal; Off-Therapy Outcomes; Chronic Hepatitis B.

Chronic hepatitis B virus (HBV) infection affects an estimated 296 million individuals worldwide, leading to 820,000 deaths per year, mostly from cirrhosis and hepatocellular carcinoma (HCC).[1] Despite the development of effective vaccines, chronic hepatitis B (CHB) remains a global burden, as a sterilizing cure remains unattainable with current therapeutic options. The treatment goal for CHB is to prevent or significantly delay liver-related morbidity and mortality. Nucleos(t)ide analogues (NAs), namely entecavir (ETV) and tenofovir disoproxil fumarate (TDF), are used as first-line therapy, as they have an excellent safety profile and effectively induce viral suppression. However, sustained hepatitis B surface antigen (HBsAg) loss (ie, functional cure), which defines the optimal treatment endpoint, rarely occurs with NA treatment. Thus, lifelong therapy is often necessary to maintain viral control.

The concept of finite therapy has emerged due to concerns regarding cost, adherence, and safety, and some studies have demonstrated potential for sustained disease remission following treatment discontinuation.[2–5] Nonetheless, NA withdrawal requires caution, as virological relapse and severe alanine aminotransferase (ALT) flares are frequently observed posttreatment, which could lead to hepatic decompensation.[6–10] Interestingly, ETV and TDF have exhibited different rates of relapse following withdrawal. TDF has been associated with higher rates of virological and clinical relapse compared with ETV, mostly occurring in the earlier months off-therapy in Asian cohorts.[11–14] Whether this association holds across different patient populations and how these relapse patterns further relate to outcomes remain to be answered in a global cohort.

Therefore, the current study aim was to study the association between the NA type and HBsAg loss, relapse, or retreatment after ETV or TDF cessation.

Materials and Methods

Subjects

Data used in the current study were derived from a global, multicenter, multiethnic study of CHB patients who discontinued NA therapy between 2001 and 2020 from 13 participating centers across Asia, Europe, and North America.[15] Included were adult ($\geq$18 years of age) patients with CHB (HBsAg-positive for $>$6 months) treated with ETV or TDF prior to discontinuation. All patients were hepatitis B e antigen (HBeAg)–negative and virally suppressed at the end of therapy (EOT). Patients with a prior diagnosis of HCC, viral coinfection (hepatitis C or D virus, and/or human immunodeficiency virus), or history of conventional or pegylated (PEG) interferon α (IFNα) treatment within 12 months before discontinuation were excluded from this study. The study was approved by the respective institutional review boards at all participating centers and conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice.

Data Acquisition

A standardized case record form was used to collect anonymized data from sites. All data cleaning, quality evaluations, and analyses were performed at the central site, the Toronto Centre for Liver Disease. Quantitative data on HBsAg (quantification limit: 0.05–0.22 IU/mL), HBV DNA (quantification limit: 10–50 IU/mL), and ALT (using the center-specific upper limit of normal [ULN]) were obtained at each center, using in-house or commercially available assays. Prior NA was defined as treatment with an NA different from the most recent NA given before discontinuation. Prior (PEG-)IFN was defined as any (PEG-)IFN treatment received more than 12 months before NA discontinuation. Because few patients underwent a liver biopsy at the time of NA withdrawal, the presence of cirrhosis at EOT was defined as diagnosis of cirrhosis based on histological findings or ultrasonographic evidence any time prior to treatment cessation.

Follow-Up and Outcomes

Total off-therapy follow-up duration was calculated from the time of NA cessation to retreatment or last follow-up date. The primary outcomes of the study were virological relapse, clinical relapse, and off-treatment HBsAg loss with or without seroconversion, and retreatment following ETV or TDF cessation. A virological relapse was defined as a single elevation of HBV DNA $\geq$2000 IU/mL, and clinical relapse was defined as elevations of HBV DNA $\geq$2000 IU/mL and ALT $\geq 2\times$ ULN on the same visit. Patients were retreated according to the regional guidelines and at the discretion of the treating physician.

Statistical Analyses

Characteristics of the study cohort were presented as mean $\pm$ SD or median (interquartile range [IQR]), when

appropriate, for continuous variables and proportions for categorical variables. The chi-square test was used to compare categorical variables, with Student's *t* test or the Mann-Whitney *U* test for continuous variables. Cumulative rates of outcomes were calculated using the Kaplan-Meier method, using the log-rank test for comparisons. To account for differences between the treatment groups, analyses were conducted in both unweighted and weighted study populations. In unweighted analyses, rates of outcomes were analyzed using Cox proportional hazards regression and the Kaplan-Meier method without weights (ie, raw comparisons). In weighted analyses, inverse probability of treatment weighting (IPTW) estimated with propensity scores was used to balance the treatment groups. The groups were balanced on age, sex, race, NA therapy duration, treatment (other NAs or [PEG-]IFNα) history, HBeAg status at the start of therapy (SOT), presence of cirrhosis, and ALT and HBsAg levels at EOT. Standardized differences were evaluated to ensure balance between the groups. Weighted results will mainly be presented; unweighted results will be provided in the Supplementary Materials.

Confirmatory analyses were conducted using stratified Cox regression in place of IPTW; models were built using stepwise regression to identify factors associated with the off-treatment outcomes. Multivariable models were stratified by race and included the following predictors: age, sex, NA given prior to cessation (ETV or TDF), HBeAg status at SOT, total duration of continuous NA therapy, treatment history, cirrhosis, and HBsAg and ALT levels at EOT. Only the final models are presented. For the HBsAg loss endpoint, the effects of virological and clinical relapse were assessed using time-dependent covariates. For the virological relapse endpoint, analysis was performed separately for the first 12 months and after 12 months off-therapy to satisfy the proportional hazards assumption. Patients were censored at the last recorded visit date, date lost-to-follow-up, or retreatment date, whichever came first.

Sensitivity analyses were conducted to examine the influence of data from each center and check for interactions between covariates that may have significantly impacted the effect of the main variable of interest–the NA type (ETV or TDF). A 2-sided *P* value $<.05$ was considered statistically significant.

IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY), SAS software version 9.4 (SAS Institute, Cary, NC), and STATA version 15.1 (StataCorp, College Station, TX, USA) were used to perform all statistical analyses.

Results

Study Cohort

A total of 1402 patients with CHB, who were HBeAg-negative with undetectable levels of serum HBV DNA at treatment discontinuation, were included in the current study. Characteristics of the overall study cohort are described in the supporting document (Supplementary Table 1). Of the total, 1244 patients were included in the weighted analysis, which excluded 158 patients with missing information on the balanced variables. After weighting, patient characteristics were balanced between the TDF and ETV groups, except for median ALT levels at EOT (Table 1 and Supplementary Figure 1). Although median ALT levels remained imbalanced (TDF vs ETV: 0.61× ULN vs 0.53× ULN; $P < .01$), mean ALT levels were balanced (0.70 × ULN vs 0.66× ULN; $P = .15$). Either way, ALT levels at EOT were well below the ULN in both groups.

What You Need to Know

Background

Tenofovir disoproxil fumarate has been associated with higher rates of virological and clinical relapse compared with entecavir (ETV) following withdrawal in chronic hepatitis B (CHB) patients. Whether this is a true phenomenon and, if so, how it relates to clinical outcomes remain to be addressed in a large multiethnic cohort.

Findings

In this global study of 1402 chronic hepatitis B CHB relapse rates than ETV. Nonetheless, clinical outcomes did not differ between the 2 groups.

Implications for Patient Care

Finite therapy can be an option for CHB patients on either tenofovir disoproxil fumarate or ETV therapy. For patients with a history of or current advanced fibrosis, ETV treatment may be recommended when considering finite therapy.

HBsAg Loss

During a median off-treatment follow-up of 18 (IQR, 7–37) months, HBsAg loss was observed in 96 (6.8%) patients, 61 of whom were ETV treated and 35 of whom were TDF treated. The cumulative incidence of HBsAg loss at 6, 12, and 24 months was 1.2%, 3.0%, and 6.4% in the TDF group and 0.7%, 1.9%, and 6.7% in the ETV group, respectively. In the unweighted population, TDF treatment was associated with a higher rate of HBsAg loss compared with ETV ($P = .03$) (Supplementary Figure 2*A*); however, the difference became insignificant in the weighted analysis ($P = .61$) (Figure 1*A*) after balancing all measured variables. This was confirmed in the multivariable Cox regression analysis, stratified by race (TDF vs ETV: adjusted hazard ratio [aHR], 1.4; 95% confidence interval [CI], 0.8–2.2; $P = .24$) (Table 2). Longer NA therapy duration (aHR, 1.2; 95% CI, 1.1–1.3; $P < .01$) and lower HBsAg levels at EOT (aHR, 0.3; $P < .01$) were also significantly associated with HBsAg loss. The

Table 1. Characteristics of the Combined Study Cohort

Variable	ETV (n = 872)[a]	TDF (n = 358)[a]	*P* Value
Male	644 (73.9)	267 (74.6)	.830
Race/ethnicity			.698
Caucasian	53 (6.1)	24 (6.7)	
Asian	819 (93.9)	334 (93.3)	
HBeAg-negative at start of therapy[b]	768 (88.1)	317 (88.5)	.846
Number of off-treatment follow-up visits	6 (3–8)	6 (4–8)	.192
Time between off-treatment visits, mo	2.8 (1.6–3.7)	2.8 (1.6–3.6)	.853
Total off-treatment follow-up duration, mo	19.4 (7.8–39.4)	19.0 (10.6–36.3)	.941
At treatment discontinuation[c]			
Age, y	53.7 ± 11.2	53.6 ± 11.1	.915
Cirrhosis	101 (11.6)	40 (11.2)	.922
ALT × ULN			
Median (interquartile range)	0.53 (0.40–0.75)	0.61 (0.46–0.80)	<.001
Mean ± Standard deviation	0.66 ± 0.44	0.70 ± 0.45	.154
HBsAg, $\log_{10}$ IU/mL	2.6 ± 0.8	2.6 ± 0.8	.667
Prior use of other NAs[d]	121 (13.9)	52 (14.5)	.787
Prior (PEG-)interferon	58 (6.7)	29 (8.1)	.392
NA therapy duration, y	3.0 (3.0–3.6)	3.0 (3.0–3.3)	.668

Values are n (%), median (interquartile range), or mean ± Standard deviation.
ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; PEG, pegylated; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.
[a]Weighted analysis: inverse probability of treatment weighting excluded patients with missing information on age, sex, race, HBeAg status at start of therapy, treatment history, NA therapy duration, cirrhosis status, ALT, or HBsAg levels at end of therapy.
[b]HBeAg status at start of therapy was unavailable for 11 (0.8%).
[c]At end of therapy, ALT and HBsAg levels were unavailable for 42 (3%) and 129 (9%) patients, respectively. Information on cirrhosis was unavailable for 6 (0.4%) patients.
[d]Patients who received (PEG-)interferon treatment within 12 months prior to NA cessation were excluded from this study. Prior (PEG-)interferon was defined as any (PEG-)interferon treatment received more than 12 months before NA discontinuation.

development of a virological or clinical relapse following treatment discontinuation did not impact the rate of HBsAg loss ($P = .51$ and $P = .74$, respectively), and no significant interaction was identified.

Virological and Clinical Relapse

Overall, 1097 (78%) patients experienced a virological relapse during the off-treatment study period. The cumulative incidence of VR at 6, 12, and 24 months was 65%, 76%, and 83% in the TDF group and 42%, 69%, and 79% in the ETV group, respectively (Figure 1*B*). The rate of virological relapse was higher among patients treated with TDF vs ETV in the first year off therapy ($P <$ .01). Interestingly, virological relapse rates in the 2 groups converged after the first year. In a confirmatory analysis using multivariable Cox regression stratified by race, TDF was an independent predictor of virological relapse only in the first year (aHR, 1.9; 95% CI, 1.6–2.2; $P <$ .01) (Supplementary Table 2); the association was lost thereafter (aHR, 0.9; 95% CI, 0.5–1.4; $P = .49$) (Table 3). Other independent predictors of virological relapse in the first year included older age (aHR, 1.01; 95% CI, 1.00–1.03; $P <$ .01), HBeAg negativity at SOT (HBeAg-positive vs HBeAg-negative: aHR, 0.6; 95% CI, 0.4–0.7; $P <$ .01), and higher HBsAg levels at EOT (aHR, 1.6; 95% CI, 1.4–1.7; $P <$ .01).

Overall, clinical relapse occurred in 598 (43%) patients. The cumulative incidence of clinical relapse at 6, 12, and 24 months was 31%, 42%, and 58% in the TDF group and 11%, 29%, and 44% in the ETV group, respectively (Figure 1*C*). Clinical relapse occurred more frequently among patients treated with TDF vs ETV ($P <$ .01). Unlike virological relapse, the difference in clinical relapse rates between the groups remained constant throughout off-treatment follow-up. TDF was associated with a significantly higher rate of ALT flares ≥5 (HR, 2.1; 95% CI, 1.6–2.7; $P <$ .01) or 10× ULN (HR, 2.4; 95% CI, 1.7–3.5; $P <$ .01). The 2 treatment groups did not differ with respect to the rate of hepatic decompensation ($P =$ .31). In the confirmatory analysis using multivariable Cox regression stratified by race, TDF was consistently associated with a higher rate of clinical relapse (aHR, 1.7; 95% CI, 1.5–2.1; $P <$ .01) (Table 4). Other independent predictors of clinical relapse included older age (aHR, 1.02; 95% CI, 1.02–1.03; $P <$ .01), male sex (aHR, 1.6; 95% CI, 1.3–2.0; $P <$ .01), prior use of other NAs (aHR, 1.4; 95% CI, 1.1–1.7; $P <$ .01), higher HBsAg levels at EOT (aHR, 1.7; 95% CI, 1.5–2.0; $P <$ .01), presence of

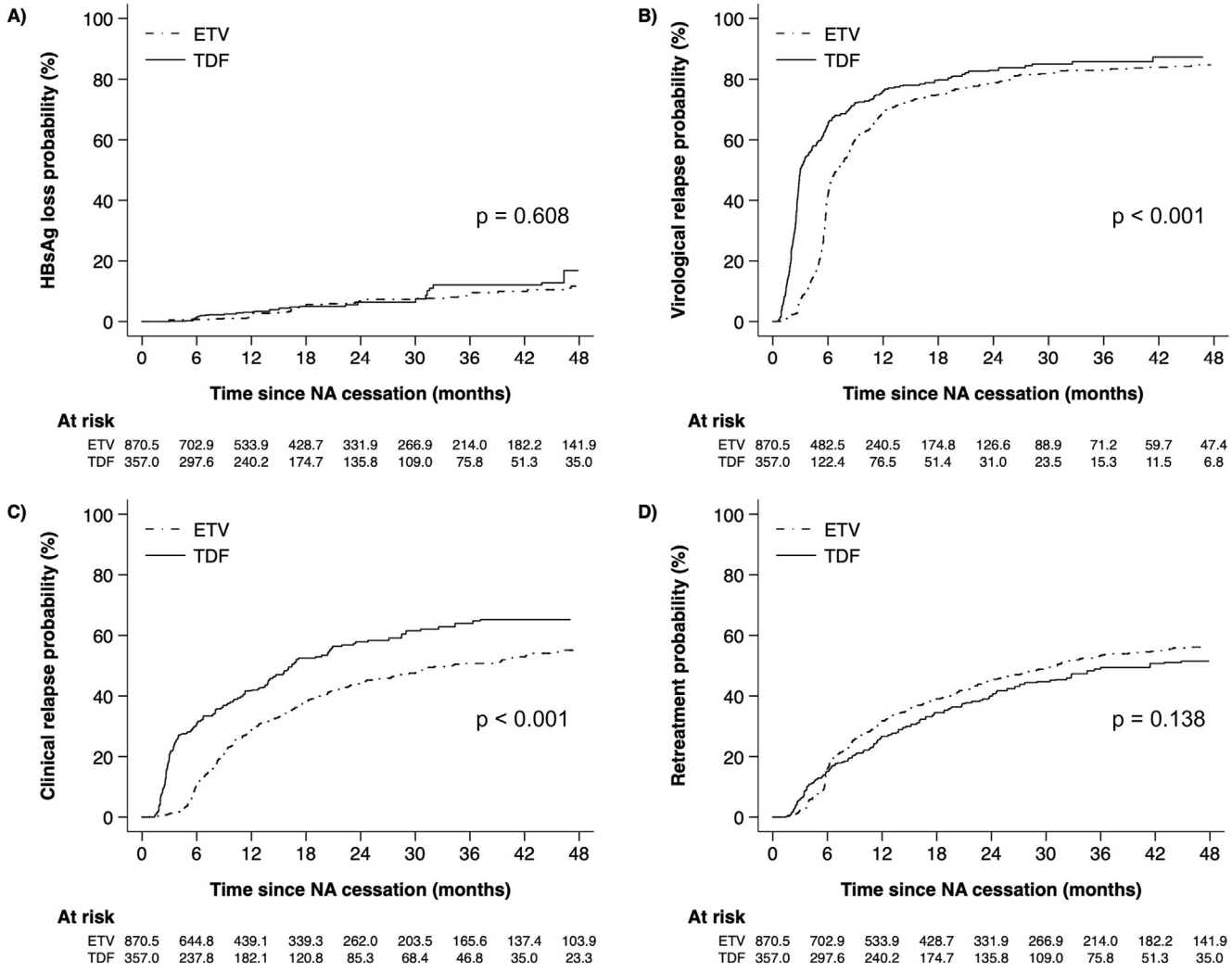

Figure 1. Comparison of cumulative incidence of (*A*) HBsAg loss, (*B*) virological relapse, (*C*) clinical relapse, (*D*) retreatment between ETV- and TDF-treated patients.

cirrhosis by EOT (aHR, 1.4; 95% CI, 1.1–1.8; $P < .01$), and higher ALT levels at EOT (aHR, 1.3; 95% CI, 1.2–1.5; $P < .01$). The association between TDF treatment and higher relapse rates remained consistent in the subgroup analysis by HBeAg status at SOT.

Among patients who experienced a clinical relapse, the peak ALT level was higher in those treated with TDF vs ETV (median 7.4× [IQR, 4.1×–13.8×] ULN vs 4.9× [IQR, 3.3×–8.8×] ULN; $P < .01$). Levels became comparable between the groups at 6 (1.3× [IQR, 0.7×–3.0×] ULN vs 1.1 [IQR, 0.7×–2.8×] ULN; $P = .63$) and 12 months (1.4× [IQR, 0.6×–2.8×] ULN vs 1.1× [IQR, 0.8×–2.4×] ULN; $P = .97$) after the start of relapse.

Retreatment

Of the total cohort, 667 (48%) patients were retreated. Retreatment rates did not differ significantly between the treatment groups ($P = .14$) (Figure 1*D*). This was confirmed in the multivariable Cox regression analysis stratified by race (TDF vs ETV: aHR, 0.9; 95% CI, 0.8–1.1; $P = .52$) (Table 5). Older age (aHR, 1.02; 95% CI, 1.01–1.03; $P < .01$), HBeAg negativity at SOT (HBeAg-positive vs HBeAg-negative: aHR, 0.7; 95% CI, 0.5–0.9; $P = .01$), presence of cirrhosis by EOT (aHR, 1.3; 95% CI, 1.0–1.6; $P = .06$), and higher HBsAg levels at EOT (aHR, 1.8; 95% CI, 1.6–2.1; $P < .01$) independently predicted retreatment. A significant interaction was identified between the type of NA and HBeAg status at SOT ($P < .01$). Among SOT HBeAg-positive individuals, TDF was associated with a higher rate of retreatment (TDF vs ETV: aHR, 1.8; 95% CI, 1.0–3.2; $P = .06$). Such association was not observed among those who were HBeAg-negative at SOT (TDF vs ETV: aHR, 0.9; 95% CI, 0.7–1.0).

Discussion

In this cohort study of 1402 CHB patients who stopped NA therapy, ETV and TDF exhibited differential relapse patterns following treatment cessation. Despite higher rates of virological and clinical relapse seen early after TDF discontinuation, virological relapse rates in the

Table 2. Cox Regression HRs for Off-Treatment HBsAg Loss

	Univariable		Multivariable[a]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at EOT	1.01 (0.99–1.03)	.272	0.98 (0.97–1.00)	.082
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.53 (0.92–2.56)	.104	1.02 (0.59–1.79)	.933
Race				
Asian	1.00 (reference)			
Caucasian	5.21 (3.27–8.30)	<.001		
Prior (PEG-)interferon	1.63 (0.89–2.99)	.114		
Prior NA	1.38 (0.84–2.29)	.206		
NA duration	1.17 (1.11–1.24)	<.001	1.17 (1.05–1.31)	.004
HBeAg at SOT				
Negative	1.00 (reference)			
Positive	0.81 (0.46–1.42)	.455		
HBsAg at EOT	0.28 (0.24–0.33)	<.001	0.26 (0.21–0.31)	<.001
HBsAg at EOT				
≥1000 IU/mL	1.00 (reference)			
100–1000 IU/mL	2.55 (1.04–6.21)	.040		
<100 IU/mL	16.99 (7.33–39.35)	<.001		
Any cirrhosis by EOT	0.81 (0.39–1.68)	.576		
ALT at EOT	0.99 (0.65–1.51)	.954		
Treatment type				
ETV	1.00 (reference)		1.00 (reference)	
TDF	1.58 (1.04–2.40)	.032	1.35 (0.82–2.20)	.235

ALT, alanine aminotransferase; CI, confidence interval; EOT, end of therapy; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HR, hazard ratio; NA, nucleos(t)ide analogue; PEG, pegylated; SOT, start of therapy; TDF, tenofovir disoproxil fumarate.
[a]Final multivariable model stratified by race (stratified Cox).

2 groups converged after the first year off therapy, and HBsAg loss and retreatment rates were comparable between the 2 groups throughout follow-up. The current study used individual patient data to comprehensively compare and confirm patterns of relapse and off-treatment clinical outcomes in a large global multiethnic cohort of patients who discontinued TDF or ETV treatment, controlling for important factors such as race and HBeAg status at SOT. Furthermore, using IPTW (ie, weighted analysis), the treatment groups were balanced on all measured variables with minimized loss of information.

Both TDF and ETV are recommended by the international guidelines as first-line NAs, owing to their high potency and high genetic barrier to resistance. The 2 drugs can induce comparable rates of viral suppression, and both have an excellent safety profile. Over the past decade, there has been strong interest in understanding whether one drug is superior to the other in terms of preventing or delaying HCC development or viral relapse following treatment discontinuation. To date, several studies have reported significantly higher rates of relapse following TDF discontinuation compared with that of ETV, mostly in Asian cohorts. Unadjusted virological and clinical relapse rates at 1-year off therapy range from 59% to 67% and from 31% to 52% among TDF-treated patients and from 32% to 53% and from 23% to 34% among ETV-treated patients, respectively.[11,12,16] Our results are largely in line with these findings, though a higher rate of virological relapse was seen in our ETV group. Although virological relapse occurred earlier among those who had been treated with TDF vs ETV, rates became comparable after the first year off therapy. Overall virological relapse rates reached 80% in both groups by year 2, suggesting that virological relapse is inevitable for the majority of patients who stop antiviral treatment, whether it be TDF or ETV. Nonetheless, clinical relapse rates remained higher in the TDF group than the ETV group throughout the observed follow-up period, with ALT elevations of a higher magnitude. However, ALT levels became comparable by 6 months from the start of a clinical relapse, and the adjusted rates of hepatic decompensation did not differ between the groups. Thus, there is insufficient evidence to support the use of one drug vs another for finite NA therapy.

Table 3. Cox Regression HRs for Virological Relapse After 12 Months Off-Therapy

	Univariable		Multivariable[a]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at EOT	1.01 (0.99–1.02)	.490	1.02 (1.00–1.04)	.039
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	0.76 (0.55–1.06)	.110	0.93 (0.63–1.37)	.698
Race				
Asian	1.00 (reference)			
Caucasian	1.02 (0.52–2.00)	.957		
Prior (PEG-)interferon	0.76 (0.41–1.40)	.382		
Prior NA	1.21 (0.79–1.85)	.385		
NA duration	1.02 (0.95–1.09)	.580		
HBeAg at SOT				
Negative	1.00 (reference)		1.00 (reference)	
Positive	0.83 (0.56–1.22)	.337	0.58 (0.36–0.95)	.032
HBsAg at EOT			2.06 (1.58–2.69)	<.001
HBsAg at EOT				
≥1000 IU/mL	1.00 (reference)			
100–1000 IU/mL	0.81 (0.56–1.16)	.246		
<100 IU/mL	0.32 (0.18–0.58)	<.001		
Any cirrhosis by EOT	1.43 (0.88–2.31)	.146		
ALT at EOT	0.45 (0.21–0.95)	.036		
Treatment type				
ETV	1.00 (reference)		1.00 (reference)	
TDF	0.83 (0.57–1.22)	.346	0.85 (0.53–1.35)	.485

ALT, alanine aminotransferase; CI, confidence interval; EOT, end of therapy; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HR, hazard ratio; NA, nucleos(t)ide analogue; PEG, pegylated; SOT, start of therapy; TDF, tenofovir disoproxil fumarate.
[a]Final multivariable model stratified by race (stratified Cox).

Furthermore, the difference in clinical relapse rates was not reflected in the retreatment rates, suggesting that clinical relapse occurring at a higher rate in the TDF group may be transient and not have a significant clinical impact, necessitating retreatment. However, because retreatment criteria were not fully standardized, more information on the kinetics of biomarkers following relapse is needed. Of note, a significant interaction was present between the NA type and HBeAg status at SOT. It is possible that those who were HBeAg-positive at SOT were at an earlier stage in chronic HBV infection and thus had higher levels of viral expression (eg, HBsAg, covalently closed circular DNA).[17] Discontinuation of TDF may thus have triggered a more vigorous response, leading to higher rates of relapse among these patients. More mechanistic studies would be required to test this hypothesis.

Prior studies have suggested that finite antiviral therapy offers an advantage in achieving higher rates of HBsAg loss over a shorter period vs continuing therapy in certain subpopulations.[2,8,18] It is of great interest whether one drug can increase the chance of attaining the desired endpoint vs the other. In our combined cohort, TDF was associated with a higher rate of HBsAg loss compared with ETV; however, this association was no longer significant after statistical adjustment. Lower HBsAg levels at EOT were the most prominent independent predictor for HBsAg loss. Jeng et al[8] reported different findings with rates of HBsAg loss that were higher among ETV-treated patients in a Taiwanese cohort of HBeAg-negative patients. Nonetheless, this difference was similarly lost in the multivariable analysis. Differences in patient characteristics such as HBeAg status at SOT, ethnicity, and HBV genotype may have caused the discrepancy.

Our data indicate that the occurrence of virological or clinical relapse itself does not significantly impact the overall rate of HBsAg loss; relapse does not appear to be a prerequisite for HBsAg loss. In fact, HBsAg loss was seen more frequently among those who did not experience a relapse following treatment cessation; 61 and 85 out of 96 cases of HBsAg loss occurred in patients without a virological relapse and clinical relapse, respectively. These results align with the findings previously reported.[8] However, it is possible that, though not be potent enough to induce HBsAg loss, viral relapse

Table 4. Cox Regression HRs for Clinical Relapse

	Univariable		Multivariable[a]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at EOT	1.01 (1.01–1.02)	.001	1.02 (1.02–1.03)	<.001
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.43 (1.18–1.74)	<.001	1.61 (1.31–1.99)	<.001
Race				
Asian	1.00 (reference)			
Caucasian	0.93 (0.67–1.28)	.646		
Prior (PEG-)interferon	1.12 (0.84–1.51)	.442		
Prior NA	1.51 (1.23–1.84)	<.001	1.38 (1.11–1.71)	.004
NA duration				
HBeAg at SOT				
Negative	1.00 (reference)			
Positive	0.86 (0.68–1.07)	.178		
HBsAg at EOT	1.38 (1.23–1.56)	<.001	1.74 (1.52–2.01)	<.001
HBsAg at EOT				
≥1000 IU/mL	1.00 (reference)			
100–1000 IU/mL	0.96 (0.80–1.15)	.661		
<100 IU/mL	0.44 (0.32–0.60)	<.001		
Any cirrhosis by EOT	1.53 (1.21–1.93)	<.001	1.41 (1.10–1.80)	<.001
ALT at EOT	1.31 (1.16–1.48)	<.001	1.32 (1.17–1.51)	<.001
Treatment type				
ETV	1.00 (reference)		1.00 (reference)	
TDF	1.62 (1.37–1.91)	<.001	1.74 (1.45–2.08)	<.001

ALT, alanine aminotransferase; CI, confidence interval; EOT, end of therapy; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HR, hazard ratio; NA, nucleos(t)ide analogue; PEG, pegylated; SOT, start of therapy; TDF, tenofovir disoproxil fumarate.
[a]Final multivariable model stratified by race (stratified Cox).

triggers a robust immune response, resulting in HBsAg decline and perhaps even covalently closed circular DNA degradation and sustained remission.[19] Further in-depth analyses of HBV biomarkers following relapse are warranted to test whether TDF and the relapse following its discontinuation are associated with antiviral response and higher rates of sustained disease remission.

At this time, no clear explanation can be given for the differential patterns of relapse associated with TDF and ETV. The 2 drugs have shown similar efficacy in achieving HBV DNA suppression with current assay sensitivities and neither with a significant effect on the covalently closed circular DNA. It has recently been postulated that TDF, a nucleotide analogue, may have different or additional immunomodulatory effects involving IFNλ3 compared with ETV, a nucleoside analogue.[16,20] Thus, a sudden withdrawal of TDF and subsequent absence of the observed immunomodulatory effect could result in earlier and more vigorous relapse following treatment cessation. Nevertheless, the difference in their immunomodulatory effects is likely modest, as viral suppression rates are similar and HBsAg loss rates remain low regardless of the type of drug. We cannot be certain of the underlying mechanisms leading to such differences in relapse patterns without further in-depth, head-to-head comparisons of the 2 agents with respect to immunology, virology, and pharmacokinetics.

The limitations of our study primarily stem from the inherent limitations of the retrospective design. HBV genotypes were unknown for a large percentage of patients due to long-term viral suppression on antiviral therapy. Furthermore, owing to the suboptimal length and frequency of longitudinal data on HBsAg and other biomarkers following relapse, we could not adequately compare the kinetics of viral markers between the treatment groups.

In conclusion, findings from our combined multiethnic cohort demonstrate that TDF and ETV have differential relapse patterns. Despite the high rates of relapse occurring earlier after TDF withdrawal, HBsAg loss and retreatment rates in the 2 groups were comparable, suggesting that clinical outcomes following treatment discontinuation are similar between the 2 groups. Therefore, finite therapy could be an option for CHB patients on either TDF or ETV therapy. However, virological relapse accompanied by ALT elevations occur

Table 5. Cox Regression HR for Retreatment

	Univariable		Multivariable[a]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at EOT	1.01 (1.01–1.02)	<.001	1.02 (1.01–1.03)	<.001
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.03 (0.87–1.23)	.738	1.15 (0.95–1.39)	.140
Race				
Asian	1.00 (reference)			
Caucasian	0.89 (0.65–1.23)	.486		
Prior (PEG-)interferon	0.85 (0.63–1.16)	.309		
Prior NA	1.18 (0.96–1.44)	.110		
NA duration	1.00 (0.96–1.04)	.986		
HBeAg at SOT				
Negative	1.00 (reference)		1.00 (reference)	
Positive	0.80 (0.64–1.00)	.055	0.70 (0.53–0.92)	.010
HBsAg at EOT	1.48 (1.32–1.67)	<.001	1.79 (1.56–2.05)	<.001
HBsAg at EOT				
≥1000 IU/mL	1.00 (reference)			
100–1000 IU/mL	0.83 (0.70–0.97)	.023		
<100 IU/mL	0.31 (0.23–0.43)	<.001		
Any cirrhosis by EOT	1.36 (1.08–1.70)	.008	1.25 (0.99–1.58)	.061
ALT at EOT	0.88 (0.74–1.05)	.152		
Treatment type				
ETV	1.00 (reference)		1.00 (reference)	
TDF	0.89 (0.75–1.05)	.169	0.94 (0.78–1.13)	.517

ALT, alanine aminotransferase; CI, confidence interval; EOT, end of therapy; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HR, hazard ratio; NA, nucleos(t)ide analogue; PEG, pegylated; SOT, start of therapy; TDF, tenofovir disoproxil fumarate.
[a]Final multivariable model stratified by race (stratified Cox).

earlier, and higher peak ALT levels are seen during clinical relapse in patients who stop TDF treatment. In this regard, closer off-therapy monitoring may be required early after TDF discontinuation to ensure continued safety, with an option to use ETV prior to stopping therapy in patients with a history of or current advanced fibrosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.07.005.

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Drafting of the manuscript: Hannah S.J. Choi.
Critical revision of the manuscript for important intellectual content: all authors.
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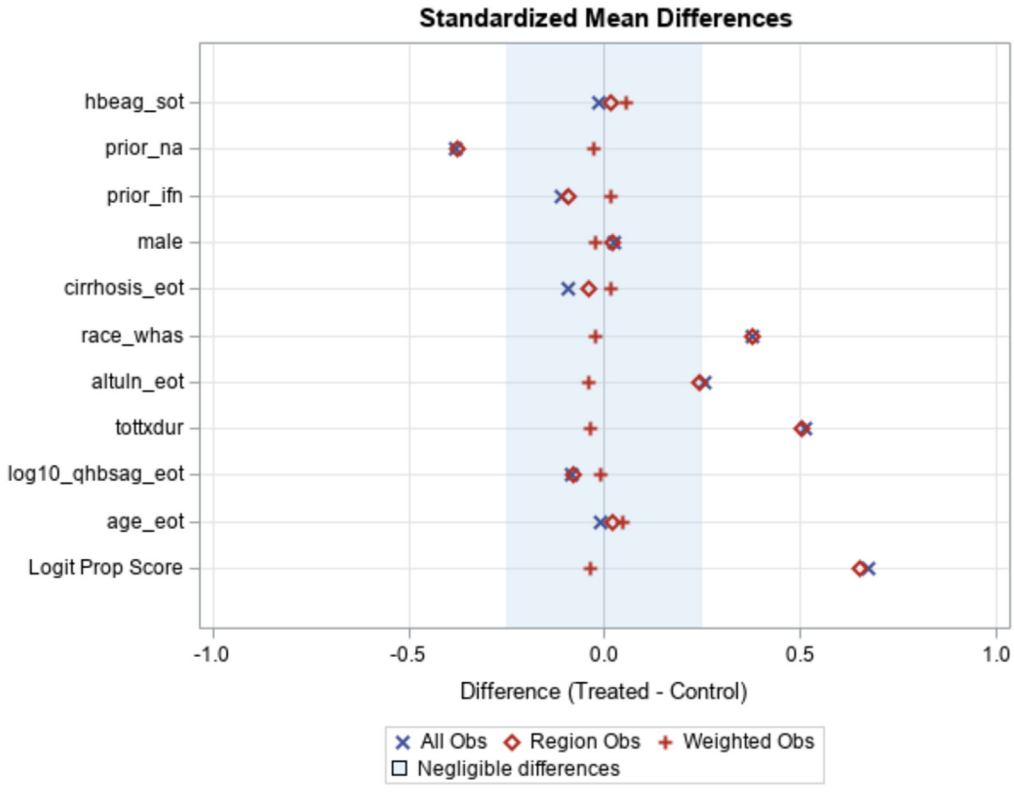
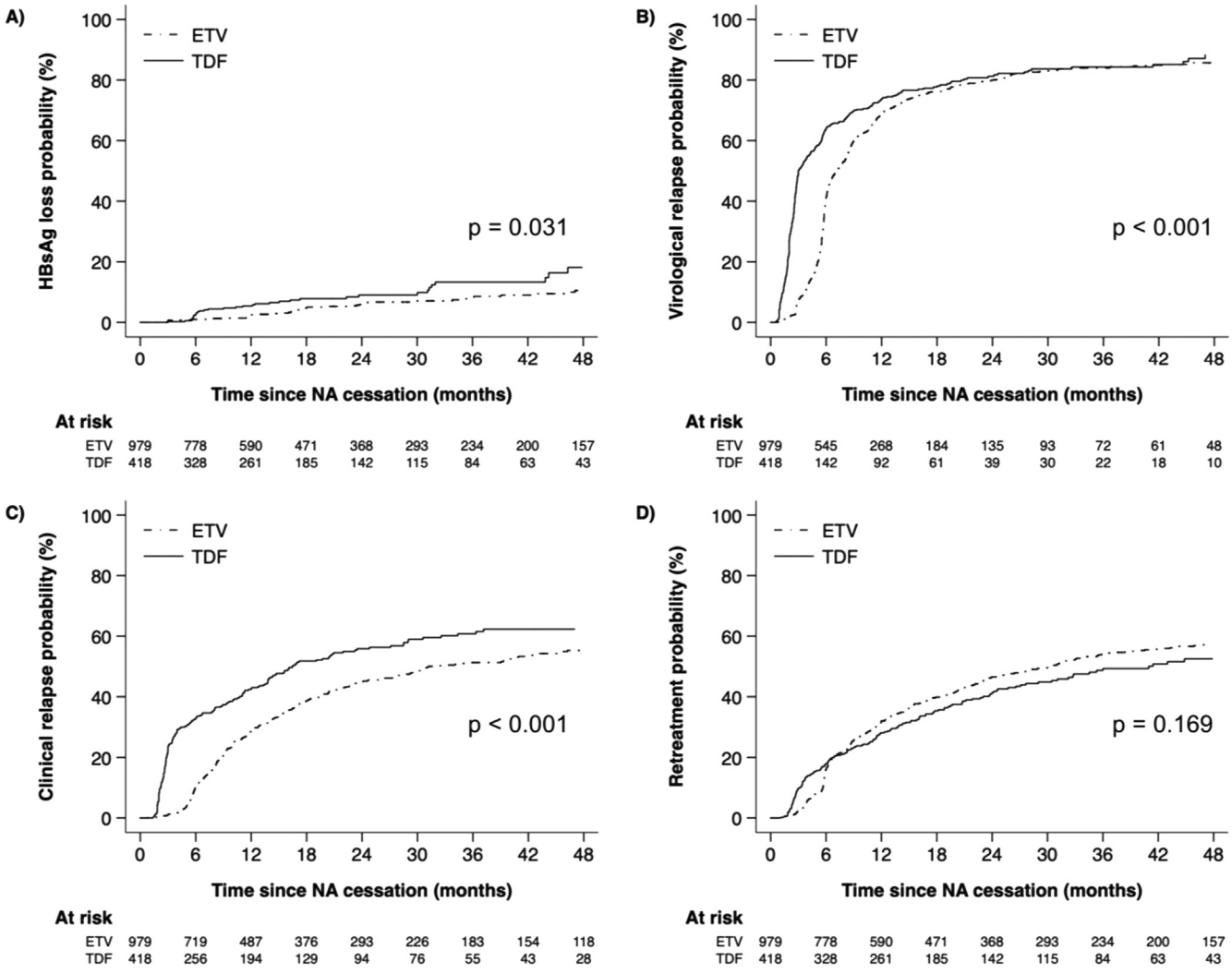
Conflicts of Interest
These authors disclose the following: Tung-Hung Su has received research grants from Gilead Sciences; and served on the speakers bureau for AbbVie, Bayer, Bristol Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, and Takeda. Wai-Kay Seto has received speaker's fees from AstraZeneca, Mylan, AbbVie, and Gilead Sciences; served on the advisory board for CSL Behring, AbbVie, and Gilead Sciences; and received research support from Gilead Sciences. Sabela Lens has received speaker and advisor fees from AbbVie and Gilead Sciences; and grant support from Gilead Sciences. Grace Wong has received research support from AbbVie and Gilead Sciences, served on the advisory board or as a consultant for Gilead Sciences and Janssen; and served as a speaker for Abbott, AbbVie, Bristol Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche. Jordan Feld has received research grants from AbbVie, Gilead, Janssen, Enanta, and Eiger; and served as a consultant for AbbVie, Gilead, Finch, Arbutus, and GlaxoSmithKline. Milan Sonneveld has received speaker fees and research support from Roche, Bristol Myers Squibb, Gilead Sciences, and Fujirebio. Henry L.Y. Chan has served as a consultant for AbbVie, Aligos, Arbutus, Hepion, Janssen, GlaxoSmithKline, Gilead Sciences, Merck, Roche, Vaccitech, VenatoRx, and Vir Biotechnology; and received honoraria for lectures for Gilead Sciences, Mylan, and Roche. Xavier Forns has served an advisor for AbbVie and Gilead Sciences. George V. Papatheodoridis has served as an advisor/lecturer for AbbVie, Dicerna, Gilead Sciences, GlaxoSmithKline, Ipsen, Janssen, Merck Sharp and Dohme, Roche, Spring Bank, and Takeda; and received research grants from AbbVie and Gilead Sciences. Thomas Vanwolleghem has received grants from Gilead Sciences, Roche, and Bristol Myers Squibb; served as a consultant for Janssen Pharmaceuticals, Gilead Sciences, AbbVie, Bristol Myers Squibb; and served as a sponsored lecturer for W.L. Gore, Gilead Sciences, and Bristol Myers Squibb. Man-Fung Yuen has served as an 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, Spring Bank Pharmaceuticals, and Roche; and received grant or research support from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myers Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Spring Bank Pharmaceuticals, Sysmex Corporation, and Roche. Yao-Chun Hsu has received research support from Gilead Sciences; served on the advisory committee for Gilead Sciences; and served as a speaker for AbbVie, Bristol Myers Squibb, Roche, Novartis, and Gilead Sciences. Jia-Horng Kao has served as a consultant or on the advisory board for AbbVie, Roche, Gilead Sciences; and as a speaker for AbbVie, Fujirebio, and Gilead Sciences. Markus Cornberg has received 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 the 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 Gilead; and served as 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 served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Merck, Roche, Arbutus, and Vir Biotechnology. The remaining authors disclose no conflicts.

Supplementary Materials

A total of 1402 patients with chronic hepatitis B, who were hepatitis B e antigen–negative with undetectable levels of serum hepatitis B virus DNA at treatment discontinuation, were included in the current study. The combined study cohort included mostly Asians (90%), with a median age of 54 (interquartile range, 46–60) years. Unweighted patient characteristics, stratified by the type of nucleos(t)ide analogue (NA) (entecavir [ETV] or tenofovir disoproxil fumarate [TDF]) given prior to cessation, are shown in Supplementary Table 1. Compared with patients treated with ETV (n = 981), a higher proportion of those treated with TDF (n = 421) were Caucasian (16.6% vs 5.3%; $P < .01$) and had been treated with other NAs (27.3% vs 11.0%; $P < .01$) or (pegylated) interferon α (9.7% vs 6.4%; $P < .04$) prior to ETV or TDF treatment. They also had a higher median alanine aminotransferase level at end of therapy (0.65× upper limit of normal vs 0.53× upper limit of normal; $P < .01$), slightly longer duration of total continuous NA therapy (median 3.1 years vs 3.0 years; $P < .01$), and shorter time between off-treatment visits (median 2.6 months vs 2.8 months; $P < .01$) compared with those treated with ETV. The two treatment groups were otherwise comparable.



Supplementary Figure 1. Plot illustrating standardized mean differences of each covariate between the entecavir and tenofovir disoproxil fumarate treatment groups.



Supplementary Figure 2. Comparison of unweighted cumulative incidence of (*A*) hepatitis B surface antigen (HBsAg) loss, (*B*) virological relapse, (*C*) clinical relapse, (*D*) retreatment between entecavir (ETV)- and tenofovir disoproxil fumarate (TDF)–treated patients. NA, nucleos(t)ide analogue.

Supplementary Table 1. Unweighted Characteristics of the Combined Study Cohort

Variable	ETV (n = 981)	ETV (n = 421)	*P* Value
Male	717 (73.1)	307 (72.9)	.948
Race/ethnicity			<.001
Caucasian	52 (5.3)	70 (16.6)	
Asian	921 (93.9)	342 (81.2)	
Other	8 (0.8)	9 (2.1)	
HBeAg-negative at start of therapy[a]	836 (85.8)	358 (85.9)	1.000
Number of off-treatment follow-up visits	6 (3–8)	6 (4–9)	.221
Time between off-treatment visits, mo	2.8 (1.6–3.5)	2.6 (1.4–3.3)	.001
Total off-treatment follow-up duration, mo	18.6 (7.3–38.3)	17.1 (8.3–34.8)	.224
At treatment discontinuation[b]			
Age, y	53.1 ± 11.1	53.0 ± 11.1	.806
Cirrhosis	112 (11.4)	40 (9.6)	.349
ALT × ULN			
Median (interquartile range)	0.53 (0.39–0.72)	0.65 (0.50–0.85)	<.001
Mean ± SD	0.64 ± 0.44	0.78 ± 0.60	<.001
HBsAg, $\log_{10}$ IU/mL	2.6 ± 0.8	2.6 ± 0.8	.388
Prior use of other NAs	108 (11.0)	115 (27.3)	<.001
Prior (PEG-)interferon[c]	63 (6.4)	41 (9.7)	.035
NA therapy duration, y	3.0 (3.0–3.5)	3.1 (3.0–6.1)	<.001

Values are n (%), median (interquartile range), or mean ± SD.

ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; PEG, pegylated; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

[a]HBeAg status at start of therapy was unavailable for 11 (0.8%).

[b]At end of therapy, ALT and HBsAg levels were unavailable for 42 (3%) and 129 (9%) patients, respectively. Information on cirrhosis was unavailable for 6 (0.4%) patients.

[c]Patients who received (PEG-)interferon treatment within 12 months prior to NA cessation were excluded from this study. Prior (PEG-)interferon was defined as any (PEG-)interferon treatment received more than 12 months before NA discontinuation.

Supplementary Table 2. Cox Regression HRs for Virological Relapse for the First 12 Months Off Therapy

	Univariable		Multivariable[a]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at EOT	1.01 (1.00–1.01)	.004	1.01 (1.00–1.03)	.005
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	0.99 (0.86–1.15)	.901	1.13 (0.96–1.32)	.133
Race				
Asian	1.00 (reference)			
Caucasian	1.46 (1.16–1.84)	.001		
Prior (PEG-)interferon	0.97 (0.75–1.26)	.836		
Prior NA	1.35 (1.13–1.59)	.001	1.18 (0.98–1.43)	.077
NA duration	1.05 (1.02–1.08)	.002		
HBeAg at SOT				
Negative	1.00 (reference)		1.00 (reference)	
Positive	0.64 (0.52–0.79)	<.001	0.56 (0.44–0.72)	<.001
HBsAg at EOT	1.39 (1.27–1.52)	<.001	1.57 (1.42–1.74)	<.001
HBsAg at EOT				
≥1000 IU/mL	1.00 (reference)			
100–1000 IU/mL	0.90 (0.78–1.04)	.145		
<100 IU/mL	0.48 (0.38–0.61)	<.001		
Any cirrhosis by EOT	1.08 (0.88–1.32)	.481		
ALT at EOT	0.90 (0.78–1.04)	.141	0.88 (0.75–1.02)	.096
Treatment type				
ETV	1.00 (reference)		1.00 (reference)	
TDF	1.71 (1.49–1.97)	<.001	1.89 (1.62–2.20)	<.001

ALT, alanine aminotransferase; CI, confidence interval; EOT, end of therapy; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HR, hazard ratio; NA, nucleos(t)ide analogue; PEG, pegylated; SOT, start of therapy; TDF, tenofovir disoproxil fumarate.
[a]Final multivariable model stratified by race.