

Higher Relapse Rate After stopping Tenofovir Alafenamide Compared With Entecavir; but not Tenofovir Disoproxil Fumarate in HBeAg-Positive Patients

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Research Article

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Abstract

Background/purpose:

This study compares the hepatitis B virus (HBV) relapse rates after discontinuation of entecavir, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) therapy in HBeAg-positive patients.

Methods:

This study was a retrospective analysis of a prospectively collected cohort comprising 427 HBeAg-positive patients without cirrhosis who received entecavir (n=200), TDF (n=133), or TAF (n=94) were enrolled. All patients met the Taiwan National Health Insurance stopping criteria for antiviral therapy.

Results:

At 156 weeks, the cumulative incidences of virological relapse and clinical relapse, and retreatment were higher in the off-TAF group (85.3%, 73.7%, and 76.6%, respectively) than in the off-entecavir group (58.0%, 45.5%, and 38.9%, respectively) (all $p < 0.001$). Compared with the off-TDF group (74.6%, 64.4%, and 58.8%, respectively), the off-TAF group showed comparable rates of virological relapse ($p=0.139$) but significantly higher rates of clinical relapse ($p=0.042$) and retreatment ($p=0.003$). The median time to clinical relapse was earlier in patients discontinuing TAF than in those discontinuing entecavir or TDF (17, 42, and 24 weeks, respectively). Multivariable analysis demonstrated that TAF therapy was an independent risk factor for virological relapse, clinical relapse, and retreatment compared with entecavir, but not with TDF; these findings remained consistent after propensity score matching. Among patients with clinical relapse, HBeAg seroreversion was more frequent in the off-TAF group than in the off-entecavir (73.0% vs. 51.4%, $p < 0.001$) and off-TDF groups (73.0% vs. 56.8%, $p=0.029$).

Conclusions:

Discontinuation of TAF therapy was associated with earlier and higher HBV relapse rates compared with entecavir, but not TDF, in HBeAg-positive patients.

Introduction

Nucleos(t)ide analogues (NAs) suppress replication of the hepatitis B virus (HBV) and improve clinical outcomes but do not eradicate the virus [1]. Entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are potent NAs and are recommended as first-line therapies for chronic hepatitis B (CHB) [2–4]. However, the rate of hepatitis B surface antigen (HBsAg) loss during long-term NA therapy remains low [5, 6], and HBV relapse is common after discontinuation of NA therapy [7–9]. Although indefinite NA therapy has been adopted for many patients, finite treatment with cessation after sustained virological suppression has emerged as an important clinical strategy, particularly in noncirrhotic patients who meet predefined stopping criteria [2–4].

Accumulating evidence suggests that off-therapy outcomes may differ according to the NA used before treatment cessation. Previous studies have shown that stopping TDF therapy is associated with a higher incidence of HBV relapse than stopping entecavir therapy in both HBeAg-negative and HBeAg-positive

patients [10–13]. Our recent study demonstrated that patients who discontinued TAF therapy experienced earlier and higher rates of HBV relapse than those who discontinued entecavir or TDF therapy among HBeAg-negative patients [14]. However, data comparing HBV relapse rates after discontinuation of TAF with those after discontinuation of entecavir or TDF in HBeAg-positive patients remain limited. Therefore, the aim of the present study was to compare the incidence and timing of virological relapse, clinical relapse, and retreatment after cessation of entecavir, TDF, or TAF therapy in HBeAg-positive patients. In addition, we aimed to identify risk factors associated with HBV relapse following NAs discontinuation.

Patients and Methods

Patients

This study was a retrospective analysis of a prospectively collected cohort comprising 200 HBeAg-positive CHB patients without cirrhosis who received entecavir monotherapy between 2008 and 2022, 133 patients who received TDF monotherapy between 2011 and 2022 and 94 patients (8 from China Medical University Hospital) who received TAF monotherapy between 2019 and 2024. All patients were followed-up post-treatment for at least 6 months with median (range: 25-75% IQR) follow-ups after treatment withdrawal for entecavir, TDF and TAF of 167 (54-350) weeks, 89 (48-206) and 46 (28-186) weeks, respectively.

Patients were excluded if they were diagnosed with autoimmune hepatitis, alcoholic liver disease, or co-infected with hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV). Patients who lost HBsAg, or received immunosuppressive therapy during treatment, or had HCC or cirrhosis were also excluded.

Absence of cirrhosis at baseline was established through liver biopsy (n=30) and combined repeated ultrasound findings showing absence of clinical features such as splenomegaly, gastroesophageal varices, or ascites.

All patients fulfilled Taiwan's National Health Plan stopping criteria for antiviral therapy, which are HBeAg loss or seroconversion with undetectable HBV DNA maintained for at least 12 months. The endpoint of follow-up was either the date of retreatment or the last visit date for the non-retreatment group.

The study was conducted in accordance with the Declaration of Helsinki of 1975. Prior to this retrospective study, we obtained Institutional Review Board approval from the Research Ethics Committees of Chang Gung Memorial Hospital (Kaohsiung Taiwan) and China Medical University Hospital (Taichung Taiwan) and informed consent from all enrolled patients.

Methods

After discontinuation of entecavir, TDF or TAF therapy, patients were followed up every 1–3 months during the first 6 months and then every 3 months until their last hospital visit. Biweekly or weekly visits

were made by patients if their alanine aminotransferase (ALT) levels increased beyond the upper limit of normal (ULN) (40 U/L). Serum HBV DNA was assayed every 1–3 months for the first 6 months after therapy withdrawal and every 3–6 months thereafter, and HBV DNA was further assessed when virological or clinical relapse occurred. HBsAg was quantified retrospectively using stored serum, which was collected at treatment initiation and end-of-treatment (EOT).

Definition of HBV relapse and criteria for retreatment

Virological relapse was defined as the reappearance of serum HBV DNA levels >2000 IU/mL and clinical relapse was defined as an episode of ALT elevation >2× ULN (40 U/L) plus HBV DNA >2000 IU/mL after NA withdrawal [15]. The duration of consolidation was calculated from the first demonstration of HBeAg loss and undetectable HBV DNA until EOT.

According to Taiwan's National Health Plan, the criteria for retreatment are an ALT elevation $\geq 2 \times \text{ULN}$ with HBV DNA ≥ 20000 IU/mL in HBeAg-positive patients and ALT elevation $\geq 2 \times \text{ULN}$ and HBV DNA ≥ 2000 IU/mL in HBeAg-negative patients without cirrhosis. The criteria for retreatment of hepatic decompensation are total bilirubin ≥ 2 mg/dL or prothrombin time prolongation ≥ 3 seconds, regardless of HBV DNA levels.

Serology

HBsAg titers were quantified using Elecsys HBsAg II Quant reagent kits (Roche Diagnostics, Indianapolis, IN, USA) according to the manufacturer's instructions with a lower limit of detection of 0.05 IU/mL. Serum HBV DNA was quantified using the COBAS TaqMan HBV test (CAP-CTM; Roche Molecular Systems, Inc., Branchburg, NJ, USA) with a lower limit of detection of 20 IU/mL.

Hepatitis B core related antigen (HBcrAg) was measured using the Chemiluminescent Enzyme Immunoassay (CLEIA) system (Fujirebio Inc., Tokyo, Japan) on a fully automated Lumipulse CLEIA analyzer (Fujirebio Inc.); the automated measurement range varied from 3 to 7 log U/mL. For statistical analysis, an HBcrAg level <3.0 log U/mL was classified as 3.0 log U/mL.

HBV genotyping

HBV genotypes in sera were determined using restriction fragment length polymorphism analysis (RFLP) of the S-gene sequence as previously described [16]. Surface genes were directly sequenced if the results of RFLP were ambiguous or indicated a mixed infection.

Statistical analysis

To compare values between the two or three groups, Chi-square tests, student's t test and ANOVA test were performed to analyze categorical and continuous variables, respectively. A Kaplan-Meier analysis with a log-rank test was used to compare the cumulative incidences of virological and clinical relapse between the off-therapy groups. Univariate and multivariable analyses were performed using Cox

proportional hazards regression models. Variables with a P value of <0.20 in the univariate analysis were included in a multivariable Cox regression analysis following the conventional approach previously proposed [17]. Cox proportional hazards regression models with the forward method were applied to identify independent factors associated with virological and clinical relapse. All statistical tests were two-sided with significance determined at a P -value of 0.05.

The propensity score-matching (PSM) method was used to reduce the significant differences in clinical features between the TAF and entecavir groups and between TAF and TDF groups at a 1:1 to 1:2 ratio, including adjusting for age, gender, ALT levels, HBV genotype, NA-naïve status, HBeAg seroconversion during treatment (positive for anti-HBe), baseline HBV DNA, duration of treatment and consolidation, and HBsAg levels at EOT. Caliper matching was performed on the propensity score (nearest available matching). Pairs (discontinuing and continuing groups) on the propensity score logit were matched to within a range of 0.2 SD [18,19].

Results

Clinical characteristics of the study population

The comparisons of clinical features among the entecavir, TDF and TAF groups are presented in Table 1. The TAF group was older, had lower ALT and total bilirubin levels, a longer duration of treatment, and a lower rate of NA-naïve status compared to both the entecavir and TDF groups.

Comparison of incidence of virological relapse, clinical relapse and retreatment between entecavir, TDF and TAF groups

The cumulative incidences of virological relapse at 13, 26, 52, 104 and 156 weeks were 4.5%, 21%, 40.7%, 54.2% and 58%, respectively in the entecavir group; 37.6%, 57.8%, 68.8%, 72% and 74.6%, respectively in the TDF group; and 43.7%, 67.0%, 75.3%, 81.6% and 85.3%, respectively in the TAF group. The cumulative virological relapse rate in the off-TAF group was significantly higher than in the off-entecavir group ($p < 0.001$), but not the off-TDF group ($p = 0.139$). The off-TDF group relapse rate was also significantly higher than the off-entecavir group ($p < 0.001$) (**Figure 1A**).

The cumulative incidences of clinical relapse at 13, 26, 52, 104 and 156 weeks were 2 %, 6.5%, 30.5%, 42.1% and 45.5%, respectively in the entecavir group, 16.5%, 39.1%, 54.4%, 60% and 64.4%, respectively in the TDF group, and 17.1%, 55.2%, 63.9%, 68.9% and 73.7%, respectively in the TAF group. The cumulative clinical relapse rate in the off-TAF group was significantly higher than in the off-entecavir ($p < 0.001$) or off-TDF group ($p = 0.042$). The relapse rate in the off-TDF group was also significantly higher than in the off-entecavir group ($p < 0.001$) (**Figure 1B**). The median time to clinical relapse was much earlier in off-TAF patients (median: 17 weeks (Q1-Q3:13.5-27) than in off-entecavir (median: 42.5 weeks (Q1-Q3: 32-88.5) ($p < 0.001$), but not off-TDF (median: 24 weeks (Q1-Q3: 15-46)) patients ($p = 0.246$).

In the entecavir and TAF cohorts, multivariable analysis showed that old age, TAF use, HBV genotype C, NA-experienced status, no HBeAg seroconversion and higher HBsAg and HBcrAg levels at EOT were independent risk factors for virological and clinical relapse (Table 2 and supplementary Table 1). In the TDF and TAF cohorts, multivariable analysis disclosed that old age, HBV genotype C, higher HBV DNA levels at treatment initiation, NA-experienced status and higher HBsAg and HBcrAg levels at EOT were independent risk factors for virological and clinical relapse (Table 3 and supplementary Table 2). In the entecavir and TDF groups, age, TDF use, HBV genotype C, NA-experienced status, no HBeAg seroconversion, and higher HBV DNA level at treatment initiation and higher HBsAg and HBcrAg levels at EOT were independent risk factors of virological and clinical relapse.

The cumulative incidences of retreatment at 156 weeks were 38.9%, 58.8% and 76.6% among the entecavir, TDF and TAF groups, respectively. Rates of retreatment in the off-TAF group were significantly higher than in the off-entecavir ($p < 0.001$) or off-TDF group ($p = 0.003$). Furthermore, the retreatment rate in the off-TDF group was significantly higher than in the off-entecavir group ($p < 0.001$). Multivariable analysis revealed that TAF use was an independent risk factor of retreatment in the entecavir and TAF cohorts (adjusted Hazard ratio (HR): 1.704, 95% confidence interval (CI): 1.424-2.039, $p < 0.001$), but not in the TDF and TAF cohorts.

Comparisons of virological relapse and clinical relapse between entecavir and TAF groups and between TDF and TAF groups after propensity score-matching

Propensity score matching yielded 102 and 75 matched patients in the entecavir and TAF groups, respectively, with no significant difference in clinical features between the two groups (Supplementary Table 3). Patients who discontinued TAF therapy exhibited significantly higher rates of virological relapse, clinical relapse (all $p < 0.001$) than did those who discontinued entecavir therapy (**Figure 2**).

In the TDF and TAF groups, propensity score matching gave 90 and 78 matched patients with no significant difference in clinical features (Supplementary Table 4). There was no significant difference between patients discontinuing TDF and TAF therapy in virological ($p = 0.679$) and clinical relapse ($p = 0.386$) than those discontinuing TDF therapy (**Figure 3**).

Propensity score matching yielded 180 and 118 matched patients in the entecavir and TDF groups, respectively, with no significant difference in clinical features between the two groups. Patients who discontinued TDF therapy exhibited significantly higher rates of virological relapse and clinical relapse (all $p < 0.001$) than did those who discontinued entecavir therapy

Predictors of HBV relapse in the TAF group

Multivariable analysis of virological and clinical relapse in the TAF group demonstrated that NA-experienced status ($p = 0.003$), higher HBV DNA at baseline ($p = 0.024$) and higher HBsAg ($p = 0.014$) and HBcrAg ($p = 0.002$) at EOT were independent factors for virological relapse, and that HBV genotype C ($p = 0.044$) and higher HBsAg at EOT ($p = 0.043$) independent factors for clinical relapse.

Severe hepatitis, hepatic decompensation and HBeAg seroreversion rates upon clinical relapse

Of the 252 patients who developed clinical relapses, there was no significant difference in the highest ALT levels found between entecavir and TAF groups and between the TDF and TAF groups (Supplementary Table 5).

Hepatic decompensation was defined as INR >1.5 upon clinical relapse. Among the 252 patients, 3 experienced hepatic decompensation with no significant difference in the rate of hepatic decompensation among the entecavir, TDF and TAF groups (Supplementary Table 5).

Patients who discontinued TAF therapy exhibited significantly higher rates of HBeAg seroreversion rates upon clinical relapse than did those who discontinued entecavir therapy ($p < 0.001$) and TDF therapy ($p = 0.029$) (Supplementary Table 5). In patients who achieved HBeAg loss without anti-HBe seroconversion during treatment, the HBeAg seroreversion rate upon clinical relapse was highest in the TAF group (92.6%), followed by the TDF group (74.3%) and the entecavir group (61.4%) ($p = 0.015$). Similarly, among patients who achieved HBeAg seroconversion (with anti-HBe positivity) during treatment, the HBeAg seroreversion rate upon clinical relapse remained significantly higher in the TAF group (58.3%) compared with the TDF group (29.5%) and the entecavir group (18.7%) ($p < 0.001$) (Supplementary Table 6).

Discussion

Notably, our recent study reported that TAF cessation led to both higher HBV relapse rate and shorter time to relapse compared with entecavir or TDF cessation in HBeAg-negative patients [14]. Our previous study showed that TDF cessation had higher HBV relapse rates compared with entecavir cessation in HBeAg-positive patients [13]. However, HBV relapse rates and patterns following TAF cessation have not been thoroughly investigated in HBeAg-positive CHB patients

This multicenter cohort study demonstrated that cessation of TAF therapy was associated with significantly higher rates of virological relapse, clinical relapse, and retreatment compared with cessation of entecavir therapy (all $p < 0.001$) in both the overall and the propensity score-matched cohorts. However, no significant differences in virological relapse, clinical relapse, or retreatment rates were observed between the off-TAF and off-TDF groups in propensity score-matched cohorts. Importantly, within the first three months after NA discontinuation, a significantly higher proportion of patients experienced virological (43.7%) and clinical (39.1%) relapse after stopping TAF compared with those who discontinued entecavir (4.5% and 2%, respectively), whereas no significant differences were observed compared with those who discontinued TDF (37.6% and 16.5%, respectively). Multivariable analysis further showed that TAF treatment was an independent risk factor for virological and clinical relapse compared with entecavir, but not when compared with TDF. Nevertheless, close monitoring and timely retreatment during the first 3 months after cessation of TAF or TDF therapy may be warranted to mitigate the risk of severe hepatitis or hepatic decompensation.

To our knowledge, this is the first study to investigate HBV relapse rates after TAF cessation in HBeAg-positive patients. Notably, in our previous study of HBeAg-negative patients [14], the off-TAF group had higher HBV relapse rates than the off-TDF group. In contrast, the present study found no significant difference in HBV relapse rates between the off-TAF and off-TDF groups in HBeAg-positive patients. When stratified by HBeAg status, distinct patterns emerged.

Previous studies showed that TDF, old age, only HBeAg loss during treatment, higher HBsAg and HBcrAg at EOT were independently associated with virological and clinical relapse in HBeAg-positive patients after cessation of entecavir or TDF therapy [13]. In our study, old age, NA-naïve status, lower HBV DNA levels at baseline, only HBeAg loss during treatment, HBV genotype C and higher HBsAg and HBcrAg levels at EOT were independently associated with virological and clinical relapse. In the TDF group, 82.9% of patients with only HBeAg loss developed clinical relapse at 12 months, respectively. In contrast, the corresponding cumulative rates were 53.9% and 68.5% in the entecavir group and TAF groups, respectively. Thus, we suggest that HBeAg loss without anti-HBe antibody formation during treatment should not be considered as an endpoint for discontinuation of NAs therapy. Our current study showed that HBV genotype C was an independent factor for HBV relapse. Our previous studies showed that HBV genotype B was an independent factor for HBV relapse after cessation of entecavir or TDF therapy in HBeAg-negative patients. Therefore, the roles of HBV genotypes B and C in post-treatment HBV relapse appear to be opposite in HBeAg-positive and HBeAg-negative patients.

Of the 252 patients who experienced clinical relapse after entecavir, TDF and TAF discontinuation, 24 (9.5%) patients developed severe hepatitis (ALT > 1000 U/L) and 3 (1.2%) developed hepatic decompensation. There was no significant difference in rates of severe hepatitis or hepatic decompensation among the three groups. However, we found that the off-TAF group had a higher rate of HBeAg seroreversion upon clinical relapse than the off-entecavir and off-TDF groups. Furthermore, discontinuation of TAF therapy was associated with a markedly higher risk of HBeAg seroreversion upon clinical relapse, regardless of whether patients achieved HBeAg loss alone or full seroconversion during treatment. The substantially higher rate of HBeAg seroreversion following TAF discontinuation suggests that viral suppression achieved with TAF may be less immunologically durable after treatment withdrawal. Upon cessation, rapid reactivation of residual cccDNA transcription may lead to early viral rebound and re-expression of HBeAg before immune containment is re-established. Because the HBeAg seroreversion rate exceeded 50% among patients who discontinued NAs therapy, HBeAg/anti-HBe status should be reassessed at the time of HBV relapse, particularly in the off-TAF group (> 70%).

HBcrAg is a surrogate marker of transcriptionally active intrahepatic covalently closed circular DNA (cccDNA), the fundamental reservoir of HBV persistence that is not eradicated by NA therapy [20, 21]. Accordingly, higher HBcrAg levels reflect a larger pool of transcriptionally active virus, predisposing patients to rapid viral rebound and subsequent relapse after treatment cessation. In addition, the utility of HBcrAg is less constrained by assay detection limits in HBeAg-positive patients, making it a more reliable biomarker in this population. Our previous study demonstrated that HBcrAg levels at EOT were independent predictors of HBV relapse after discontinuation of entecavir or TDF therapy in HBeAg-

positive patients [13]. Our result was consistent with previous finding. Thus, HBcrAg could be as treatment stopping criteria and post-cessation risk stratification algorithms, particularly in HBeAg-positive patients.

To date, the mechanisms underlying the different HBV relapse patterns observed after discontinuation of entecavir versus TDF or TAF remain incompletely understood. One study has suggested that TDF may exert additional immunomodulatory effects, particularly through modulation of interferon lambda 3 (IFN- λ 3), compared with entecavir [22]. In addition, Yu et al. reported that TDF suppresses the expansion of myeloid-derived suppressor cells (MDSCs), thereby restoring adaptive immune responses via inhibition of the MDSC/IL-10 axis [23]. Based on these observations, we hypothesize that tenofovir-containing agents may exert immunomodulatory effects beyond direct antiviral activity. The withdrawal of these effects after cessation of TDF or TAF could lead to a transient loss of immune control, resulting in more rapid HBV relapse compared with patients discontinuing entecavir therapy. TAF would therefore be expected to demonstrate similar post-treatment outcomes. However, both our previous and current studies showed that TAF discontinuation was associated with a higher relapse rate than TDF in HBeAg-negative patients, but not in HBeAg-positive patients. This finding suggests that host–virus equilibrium, rather than antiviral potency alone, may differentially modulate post-treatment outcomes according to disease phase.

There are several limitations to this study. First, it is a retrospectively analyzed study. There were differences in baseline characteristics among the entecavir, TDF and TAF groups. However, multivariable analysis and a PS matching method to mitigate significant differences in clinical features, and the analysis confirmed our results. Second, the number of patients who discontinued TAF was relatively small. However, to the best of our knowledge, our cohort represents the largest sample size of patients discontinuing TAF with the longest follow-up reported to date. Therefore, our findings should have a certain degree of reliability. Third, our study enrolled only Asian patients, in whom genotypes B and C predominate [16]. Further comparisons of HBV relapse after discontinuation of TAF versus entecavir or TDF in HBeAg-positive patients of different ethnicities and HBV genotypes are required.

In conclusion, among HBeAg-positive patients, discontinuation of TAF was associated with earlier and higher rates of virological and clinical relapse, compared with discontinuation of entecavir, but showed no significant differences compared with TDF. Accordingly, close monitoring and timely retreatment are essential to prevent adverse outcomes after cessation of entecavir, TDF, or TAF therapy, particularly within the first three months after discontinuing TDF or TAF in HBeAg-positive patients.

Abbreviations

ALT, alanine aminotransferase; CHB, chronic hepatitis B; EOT, end-of-treatment; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; PSM, propensity score matching, TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal

Declarations

Conflict of Interest statements:

Cheng-Yuan Peng has served as an advisory committee member for AbbVie, BMS, Gilead, and MSD. Chien-Hung Chen, Kuan-Hung Wan, Yuan-Hung Kuo, Tsung-Hui Hu, Jing-Houng Wang, Chao-Hung Hung, Sheng-Nan Lu declare that they have no conflict of interest.

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions:

Chien-Hung Chen: study concept and design, critical revision of the manuscript for important intellectual content, analysis and interpretation of data and study supervision.

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Tables

Table 1. Clinical characteristics of study population

	Entecavir group n=200	TDF group n=133	TAF group n=94	p value
Age (years)	41.4±11.9	42.2±10.6	49.3±10.8	<0.001
Sex (male: female)	134:66	93:40	59:35	0.528
ALT (U/L)	447.2±459.2	388.6±448.1	250.1±225.3	0.001
Total bilirubin (mg/dL)	1.76±2.39	1.22±0.78	1.08±0.97	0.002
HBV DNA (log IU/mL)	7.00±1.31	7.38±1.23	7.30±1.23	0.015
HBV genotype				
B	110 (55%)	68 (51.1%)	43 (45.7%)	0.373
C	90 (45%)	65 (48.9%)	51 (54.3%)	
HBeAg seroconversion	154 (77%)	98 (73.7%)	58 (61.7%)	0.018
Treatment duration (weeks)	185.5±79.4	190.8±61.7	222.0±99.6	0.004
Consolidation duration (weeks)	96.5±42.4	93.2±36.7	89.0±47.8	0.353
NA-naive	147 (73.5%)	72 (54.1%)	37 (39.4%)	<0.001
HBcrAg at EOT (log U/mL)	4.53±0.64	4.48±0.61	4.24±0..69	0.001
HBsAg at baseline (log IU/mL)	3.74±0.80	3.76±0.83	3.85±0.75	0.428
HBsAg at EOT (log IU/mL)	2.97±0.72	2.70±1.04	2.55±1.06	0.001

ALT, alanine aminotransferase; EOT, end of treatment; NA, nucleos(t)ide analogue; TDF, *tenofovir disoproxil* fumarate TAF, tenofovir alafenamide

Table 2. Factors predictive of clinical relapse for patients after cessation of entecavir or TAF

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Initial treatment				
Age (per year)	1.039 (1.027-1.052)	<0.001	1.033 (1.017-1.048)	<0.001
Sex (Male vs. female)	1.110 (0.806-1.529)	0.523		
TAF vs. Entecavir	1.747 (1.486-2.053)	<0.001	1.690 (1.410-2.025)	<0.001
ALT (per U/L)	1.000 (1.000-1.000)	0.684		
Total bilirubin (per mg/dL)	0.937 (0.860-1.022)	0.140		
HBV DNA (per log IU/mL)	1.240 (1.086-1.416)	0.001		
HBV genotype (C vs. B)	1.762 (1.297-2.393)	<0.001	1.405 (1.010-1.956)	0.044
HBeAg seroconversion	0.471 (0.342-0.647)	<0.001	0.636 (0.452-0.893)	0.009
NA-naïve	0.478 (0.351-0.649)	<0.001	0.556 (0.390-0.793)	0.001
HBsAg at baseline (per log IU/mL)	1.408 (1.148-1.728)	0.001		
End of treatment				
Age (years)	1.040 (1.027-1.053)	<0.001		
ALT (U/L)	0.997 (0.988-1.007)	0.555		
Total bilirubin (mg/dL)	1.304 (1.032-1.649)	0.026		
Treatment duration (per week)	1.001 (1.000-0.1.003)	0.142		
Consolidation duration (per week)	1.000 (0.997-1.004)	0.882		
HBcrAg at EOT (per log U/mL)	1.252 (0.997-1.573)	0.054	1.752 (1.356-2.263)	<0.001
HBsAg at EOT (per log IU/mL)	1.266 (1.035-1.549)	0.022	1.475 (1.181-1.842)	0.001

ALT, alanine aminotransferase; CI, confidence interval; EOT, end of treatment; HR, Hazard ratio; NA, nucleos(t)ide analogue; TDF, *tenofovir disoproxil* fumarate; TAF, tenofovir alafenamide

Table 3. Factors predictive of clinical relapse for patients after cessation of TDF or TAF

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Initial treatment				
Age (per year)	1.040 (1.025-1.054)	<0.001	1.029 (1.012-1.047)	0.001
Sex (Male vs. female)	1.338 (0.950-1.884)	0.096		
TAF: TDF	1.395 (1.007-1.933)	0.045		
ALT (per U/L)	1.000 (0.999-1.000)	0.404		
Total bilirubin (per mg/dL)	0.975 (0.805-1.180)	0.793		
HBV DNA (per log IU/mL)	1.232 (1.063-1.427)	0.006	1.584 (1.107-2.267)	0.016
HBV genotype (C vs. B)	2.007 (1.452-2.775)	<0.001	1.920 (1.314-2.806)	0.012
HBeAg seroconversion	0.567 (0.407-0.790)	0.001	0.700 (0.492-0.995)	0.047
NA-naïve	0.554 (0.401-0.765)	<0.001	0.545 (0.379-0.784)	0.001
HBsAg at baseline (per log IU/mL)	1.179 (0.949-1.465)	0.137		
End of treatment				
Age (years)	1.041 (1.026-1.056)	<0.001		
ALT (U/L)	1.000 (0.992-1.009)	0.976		
Total bilirubin (mg/dL)	1.258 (1.023-1.547)	0.030		
Treatment duration (per week)	1.001 (0.999-1.003)	0.388		
Consolidation duration (per week)	1.000 (0.996-1.005)	0.856		
HBcrAg at EOT (per log U/mL)	1.286 (0.993-1.661)	0.056	1.362 (1.038-1.561)	0.008

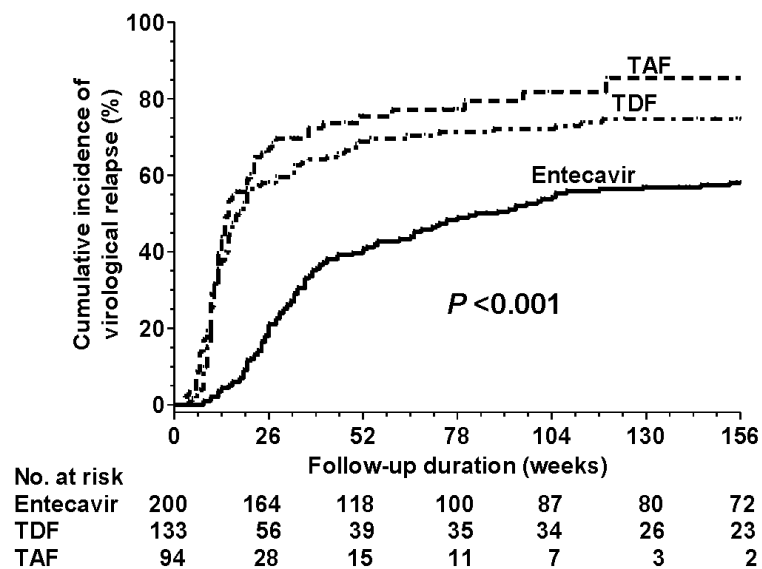
HBsAg at EOT (per log IU/mL)	1.314 (1.115-1.549)	0.001	1.429 (1.099-1.858)	0.005
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ALT, alanine aminotransferase; CI, confidence interval; EOT, end of treatment; HR, Hazard ratio; NA, nucleos(t)ide analogue; TDF, *tenofovir disoproxil* fumarate; TAF, tenofovir alafenamide

Figures

Figure 1

(A)



(B)

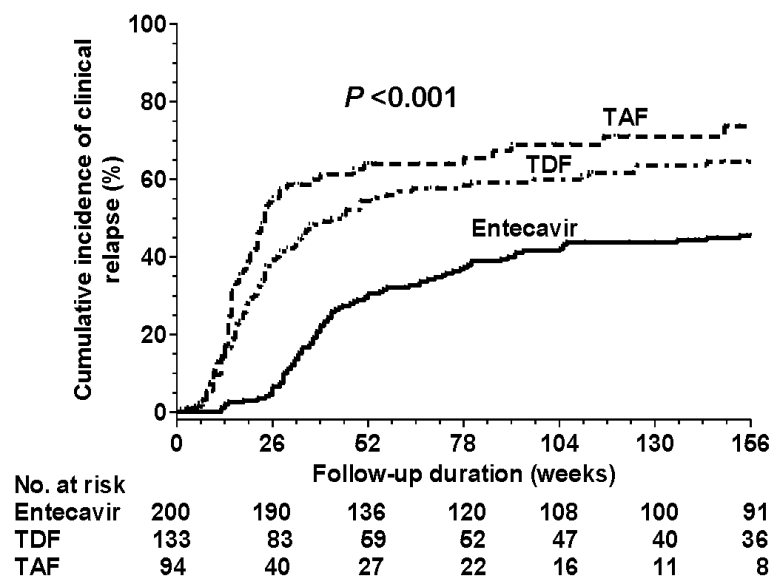
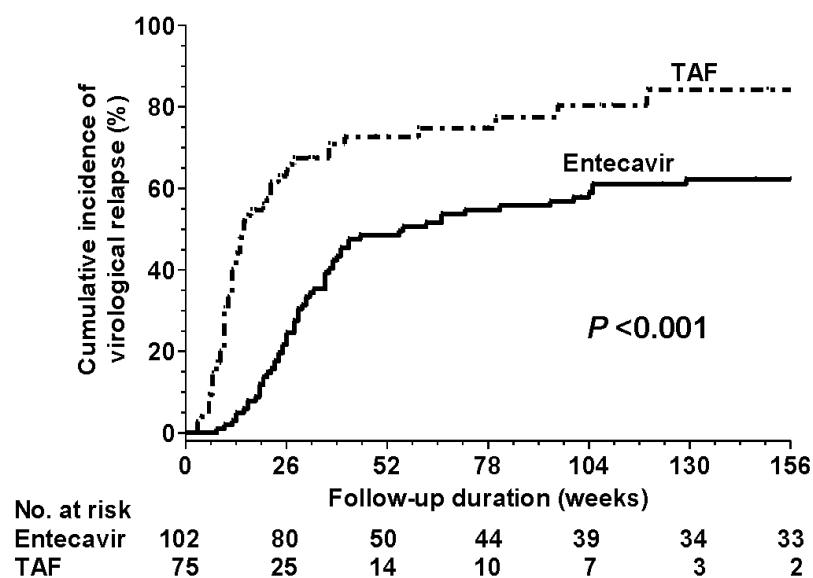


Figure 1

Comparison of cumulative incidences of HBV relapse after cessation of entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) therapy for all patients. (A) virological relapse and (B) clinical relapse.

Figure 2

(A)



(B)

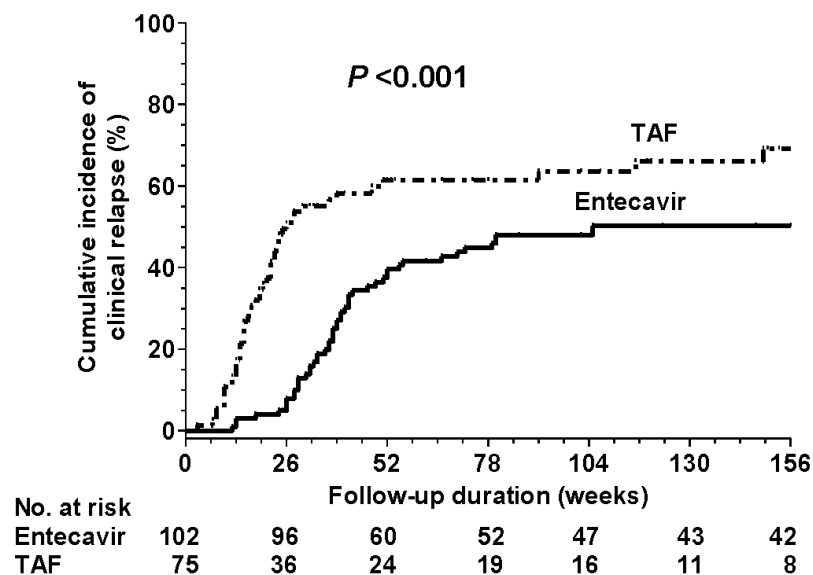
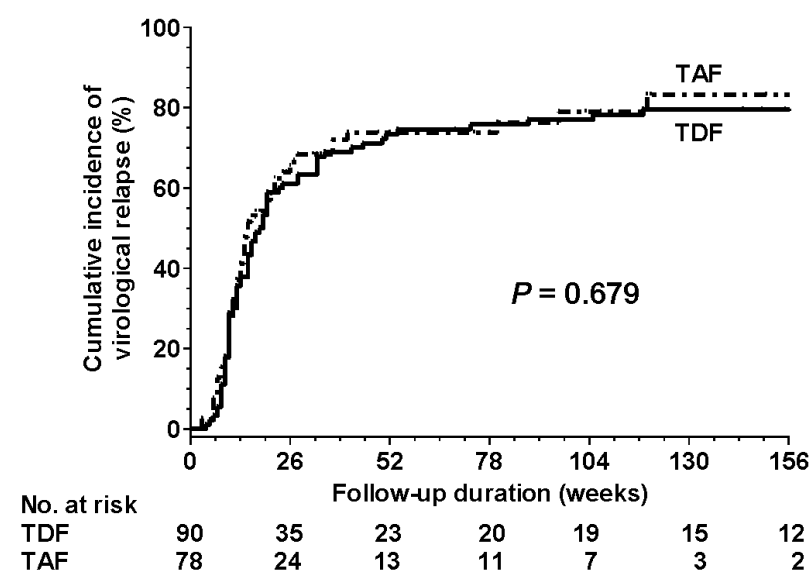


Figure 2

Comparison of cumulative incidences of (A) virological and (B) clinical relapse between entecavir and TAF groups after propensity score-matching.

Figure 3
(A)



(B)

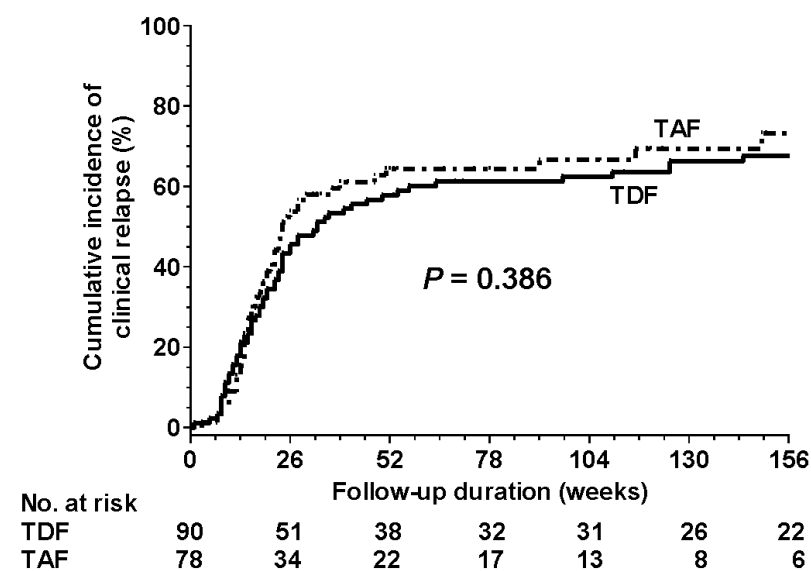


Figure 3

Comparison of cumulative incidences of (A) virological and (B) clinical relapse between TDF and TAF groups after propensity score-matching.

Supplementary Files

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