Outcomes of Sequential Therapy With Tenofovir Alafenamide After Long-term Entecavir

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INTRODUCTION: **Entecavir (ETV) and tenofovir alafenamide (TAF) are both first-line hepatitis B virus (HBV) therapies, but ETV-to-TAF switch outcome data are limited. We aimed to assess outcomes up to 96 weeks after ETV-to-TAF switch.**

METHODS: **ETV-treated (≥12 months) chronic hepatitis B patients switched to TAF in routine practice at 15 centers (United States, Korea, Japan, and Taiwan) were included. Primary outcome was complete viral suppression (CVS) rate (HBV DNA <20 IU/mL).**

RESULTS: **We analyzed 425 eligible patients (mean age 60.7 ± 13.2 years, 60% men, 90.8% Asian, 20.7% with diabetes, 27% with hypertension, 14.8% with cirrhosis, 8.3% with hepatocellular carcinoma, and mean ETV duration before switch 6.16 ± 3.17 years). The mean baseline estimated glomerular filtration rate (eGFR) was 89 ± 19 (chronic kidney disease [CKD] stages: 55.6% stage 1, 35.7% stage 2, and 8.8% stages 3–5). CVS rate increased from 91.90% at switch (from 90.46% 24 weeks before switch) to 95.57% and 97.21% at 48 and 96 weeks after ($P = 0.03$ and 0.02, respectively). Over the 96 weeks after switch, mean HBV DNA ($P < 0.001$) but not alanine aminotransferase or CKD stage decreased. Between switch and 96-week follow-up, 11% (26/235) of CKD stage 1 patients migrated to stage 2 and 8% (12/151) of stage 2 patients to stages 3–5, whereas 18% (27/151) from stage 2 to 1, and 19% (7/37) from stages 3–5 to 2. On multivariable generalized estimated equation analysis adjusted for age, sex, hypertension, diabetes, and cirrhosis, baseline eGFR, age ($P < 0.001$), and CKD stages 2 and 3–5 (vs 1) (both $P < 0.001$) were associated with lower follow-up eGFR.**

DISCUSSION: **After an average of 6 years on ETV, CVS increased from 91.9% at TAF switch to 97.2% at 96 weeks later.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B860

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INTRODUCTION

Tenofovir alafenamide (TAF) is a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor first approved for chronic hepatitis B (CHB) treatment by the US Food and Drug Administration in November of 2016 and followed soon after in many other regions (1). TAF is a new prodrug of tenofovir, whereby TAF is more quickly and thoroughly absorbed into the cells producing higher levels of the active drug—tenofovir, thus

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allowing smaller doses to be given and less circulating tenofovir, leading to less drug exposure to the kidneys, bones, and other organs (2).

Entecavir (ETV), on the other hand, is the oldest first-line and most commonly used CHB medication. ETV was first approved in 2005 compared with tenofovir disoproxil fumarate (TDF), which was first approved in 2008 in the United States but not until 2011 in Asia and, then, not widely reimbursed until 2015 or later (3–7). As a result, most CHB patients remain treated with ETV rather than TDF (8–13). Therefore, current studies are focusing on the efficacy and effectiveness of TAF after switching from ETV. These studies have shown favorable outcomes in that TAF has been found to significantly improve viral clearance whereas not negatively affecting kidney function (14–18). However, study sample size was often limited or largely based on a single center or single country design, and/or the length of time for follow-up postswitch was short (19). In fact, most of the studies' follow-up time has been less than 1 year and include mixed patient populations receiving different nucleoside or nucleotide analogs before TAF switch and/or mixed cohort of treatment-naive and treatment-experienced patients, with some of these previous nucleosides or nucleotides known to be associated with declining renal function, limiting their conclusions (20,21). Thus, we aimed to provide clarifying data to assist clinicians in their decision making on the best course of treatment for their patients by examining virologic, biochemical, and renal outcomes up to 96 weeks postswitch in a large multicenter real-world cohort of treatment-naive CHB patients who were initiated on ETV and then switched to TAF in the United States and Asia Pacific.

METHODS

Study design and study population

We retrospectively registered treatment-naive CHB patients who were initially treated with ETV for at least 12 months and then switched to TAF for any reason as per treating physician and/or patient preference (5 [1.2%] due to viral resistance, 26 [6.1%] due to partial response, 30 [7.1%] due to dose adjustment issue with renal insufficiency, 66 [15.5%] for viral resistance prevention, and 298 [70.1%] due to other/unspecified physician and/or patient preference), without treatment interruption, and monitored every 3–6 months in routine practice at 15 centers in the United States, Korea, Japan, and Taiwan. We excluded patients with HBV treatment before ETV, viral coinfection with hepatitis C, hepatitis D, and/or human immunodeficiency virus, on immunosuppression, received an organ transplant, and severe/uncontrolled comorbidities.

We assessed treatment response after switch to TAF with complete viral suppression (CVS) rate (HBV DNA <20 IU/mL), alanine aminotransferase (ALT) normalization rates based on cutoff of 40 or 35 U/L for men and 25 U/L for women, and complete response rate (CVS plus ALT normalization) (6). We examined similar treatment response parameters for the 48-week period before switch when patients were on ETV. In addition, we assessed changes in ALT, HBV DNA, and quantitative hepatitis B surface antigen (qHBsAg) levels throughout follow-up and at the end of study follow-up up to 96 weeks after TAF switch.

We calculated estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula as $141 \times \min\{\text{creatinine/k}, 1\}^{\alpha} \times \max\{\text{creatinine/k}, 1\}^{-1.209} \times 0.993^{\text{age [years]}} \times 1.018$ [if female subject] where k is 0.7 for female patients and 0.9 for male patients, α is −0.329 for female patients and −0.411 for male patients (22). We defined moderate renal impairment as eGFR <60 mL/min/1.73 m² (chronic kidney disease [CKD] stages 3–5) and mild renal impairment as 60 ≤ eGFR < 90 mL/min/1.73 m² (CKD stage 2), per the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease (23).

Cirrhosis was determined by liver biopsy or elastography, or presence of nodular contour, ascites, hepatic encephalopathy, splenomegaly, esophageal varices, other varices, or thrombocytopenia with platelets <120 K/μL on clinical, radiologic, endoscopic, or laboratory reports. The presence of hypertension and diabetes mellitus were confirmed through medical chart review.

Table 1. Patient baseline (at switch to TAF) characteristics

Characteristics	N = 425
Age (yr)	60.68 ± 13.23
Men	255 (60.00)
Body mass index (kg/m²) (n = 395)	23.09 ± 3.38
Race/ethnicity	
Asian	386 (90.82)
Non-Asian	39 (9.18)
Alcohol use (n = 238)	90 (37.82)
Diuretics	25 (5.88)
ACE inhibitors	27 (6.35)
Diabetes mellitus	88 (20.71)
Hypertension (n = 308)	83 (26.95)
FIB-4 (n = 396)	1.78 (1.19–2.55)
Cirrhosis	63 (14.82)
HCC (n = 424)	35 (8.25)
qHBsAg (IU/mL) (n = 307)	730.03 (106.27–2,000)
Detectable HBV DNA (n = 420)	34 (8.10)
HBV DNA of incomplete responders (IU/mL)	730.5 (79–19,953)
Aspartate aminotransferase (U/L) (n = 424)	23 (19–28.5)
Alanine aminotransferase (U/L) (n = 424)	19 (14–26)
Platelets (10^9/L) (n = 396)	191.47 ± 71.87
Albumin (g/dL) (n = 419)	4.27 ± 0.39
Total bilirubin (mg/dL) (n = 424)	0.84 ± 0.48
Creatinine (mg/dL) (n = 423)	0.84 ± 0.31
Estimated glomerular filtration rate (n = 423)	89.35 ± 19.09
Estimated glomerular filtration rate group (n = 423)	
≥90	235 (55.56)
60–89	151 (35.70)
<60	37 (8.75)
Duration on ETV (yr)	6.16 ± 3.17

Values expressed as mean ± SD, median (interquartile range), or number (%).
ACE, angiotensin-converting enzyme; ETV, entecavir; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; qHBsAg, quantitative hepatitis B surface antigen; TAF, tenofovir alafenamide.

The study protocol was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of Stanford University (Stanford, CA) and at each participating study center.

Statistical analysis

Primary outcome was CVS rate (HBV DNA <20 IU/mL). Rates of virologic, biochemical, and complete response were assessed over the course of ETV and TAF using the χ^2 test. Trends for continuous variables were assessed using the repeated measures ANOVA test. For categorical variables, trends were tested using the Cochran-Armitage test for binary variables and logistic regression for nonbinary variables. We also compared baseline (time of ETV-to-TAF switch) and endpoint laboratories using the Student *t* test for normally distributed continuous variables, Kruskal-Wallis test for nonnormally distributed continuous variables, and χ^2 test for categorical variables. Kaplan-Meier methods were performed to estimate cumulative rates of CVS and biochemical response for patients with incomplete viral or biochemical response at baseline.

We used multivariable generalized estimating equation model to estimate coefficients relating baseline parameters/factors to changes in eGFR. Logistic regression models were used to estimate odds ratios with 95% confidence intervals for factors associated with worsening renal function, defined as a decline in CKD staging by at least 1 stage during follow-up. Generalized linear modeling (GLM) was performed to generate mean eGFR, mean HBV DNA, mean HBsAg, and mean ALT after adjusting for relevant clinical markers. We also performed a sensitivity analysis for all patients who had a clear indication for why they were switched from ETV to TAF.

Statistical significance was defined as a 2-sided *P* value of <0.05. All statistical analyses were performed by Stata 15.1 (StataCorp, College Station, TX).

RESULTS

Study patients

We registered a total of 536 patients who switched from ETV to TAF. After excluding ineligible patients, we included 425 patients for analysis (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B860). The mean duration of for ETV therapy was 6.16 ± 3.17 years before TAF switching. At baseline (defined as time of switch from ETV to TAF), mean age was 60.7 ± 13.2 years, 90.8% were Asian, 60% men, roughly one-quarter had diabetes (20.7%) or hypertension (27.0%), 14.8% had cirrhosis, 8.3% had hepatocellular carcinoma (HCC), and 40.2% had HBeAg+ with a mean eGFR of 89 ± 19 mL/min/1.73 m^2 (55.6% were CKD stage 1, 35.7% CKD stage 2, and 8.8% CKD stages 3–5) (Table 1). The mean follow-up duration after TAF switch was 1.56 ± 0.48 years.

Antiviral response

Virologic, biochemical, and complete response rates. The CVS rates on ETV 24 weeks before TAF switch and at the time of switch were similar: 90.5% (256/283) and 91.9% (386/420) (P = 0.50), respectively. The CVS rate significantly increased to 95.3% (385/404) at 24 weeks postswitch, 97.0% (288/297) at 72 weeks postswitch, and 97.2% (174/179) at 96 weeks postswitch (P = 0.05, 0.01, and 0.02 respectively) (Table 2). Moreover, as noted in Figure 1a, approximately half of the patients who were not virally suppressed at baseline achieved CVS 48 weeks postswitch. By trend analysis, the increase was statistically significant for increasing CVS rates ($P < 0.001$) and decreasing mean HBV DNA ($P < 0.001$) (Table 3).

When comparing HBsAg levels at baseline and last follow-up, the levels significantly decreased (median [interquartile range] = 730.03 [106.26–2000] vs 229.98 [2.06–994.45], $P < 0.001$); but, by trend analysis, the decrease was not statistically significant (P = 0.744). However, on adjusted GLM analysis, the mean HBsAg

Table 2. Changes in virologic, biochemical, and complete response rates before and after switching to TAF

Drug	N (%)	Time (wk)	P[a]
HBV DNA ≤20 IU/mL			
ETV	342/395 (86.58)	−48	0.01
ETV	256/283 (90.46)	−24	0.50
Switch	386/420 (91.90)	0	NA
TAF	385/404 (95.30)	24	0.05
TAF	367/384 (95.57)	48	0.03
TAF	288/297 (96.97)	72	0.01
TAF	174/179 (97.21)	96	0.02
ALT ≤40 U/L			
ETV	375/411 (91.24)	−48	0.82
ETV	267/295 (90.51)	−24	0.89
Switch	385/424 (90.80)	0	NA
TAF	371/406 (91.38)	24	0.77
TAF	349/390 (89.49)	48	0.53
TAF	275/301 (91.36)	72	0.79
TAF	164/180 (91.11)	96	0.90
ALT <35 (men) or ALT <25 U/L (women)			
ETV	336/411 (81.75)	−48	0.97
ETV	243/295 (82.37)	−24	0.86
Switch	347/424 (81.84)	0	NA
TAF	331/406 (81.53)	24	0.91
TAF	315/390 (80.77)	48	0.69
TAF	246/301 (81.73)	72	0.97
TAF	154/180 (85.56)	96	0.27
HBV DNA ≤20 IU/mL and ALT<35 (men) or ALT <25 U/L (women)			
ETV	292/398 (73.37)	−48	0.21
ETV	216/286 (75.52)	−24	0.62
Switch	324/420 (77.14)	0	NA
TAF	306/395 (77.47)	24	0.91
TAF	299/381 (78.84)	48	0.65
TAF	237/296 (80.07)	72	0.35
TAF	139/170 (81.76)	96	0.22

ALT, alanine aminotransferase; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide.
[a]*P* value is in reference to time 0 (switch).

significantly declined over the 96-week follow-up period ($P = 0.016$), whereas the mean DNA levels remained stable over time ($P = 0.989$) (Figure 2b,c).

There was no statistically significant change in the rates of ALT normalization using the 40 U/L and the 35/25 U/L (men/women) ALT cutoffs or in mean ALT levels over 96 weeks postswitch by trend analysis ($P = 0.48$ and 0.97, respectively) or by adjusted GLM analysis ($P = 0.11$) (Tables 2 and 3; Figure 2a). Using the 35/25 U/L cutoff, 81.8% achieved ALT normalization at baseline, 80.8% at 48 weeks, and 85.6% at 96 weeks ($P = 0.27$) (Table 2). Of those who did not achieve ALT normalization at the time of switch, about half achieved ALT normalization 96 weeks postswitch (Figure 1b).

Factors associated with HBV DNA, qHBsAg, and ALT levels. After multivariable analysis for predictors of change at 96 weeks postswitch, we found that baseline HBV DNA (coefficient 0.68, $P < 0.001$) was associated with changes in DNA levels, whereas age (coefficient −21.54, $P = 0.001$) and baseline HBsAg level (coefficient 0.76, $P < 0.001$) were associated with changes in HBsAg levels, and being male (coefficient 4.47, $P < 0.001$), having diabetes mellitus (coefficient 3.83, $P = 0.007$), and higher baseline ALT (coefficient 0.15, $P < 0.001$) were associated with higher ALT levels (Table 4).

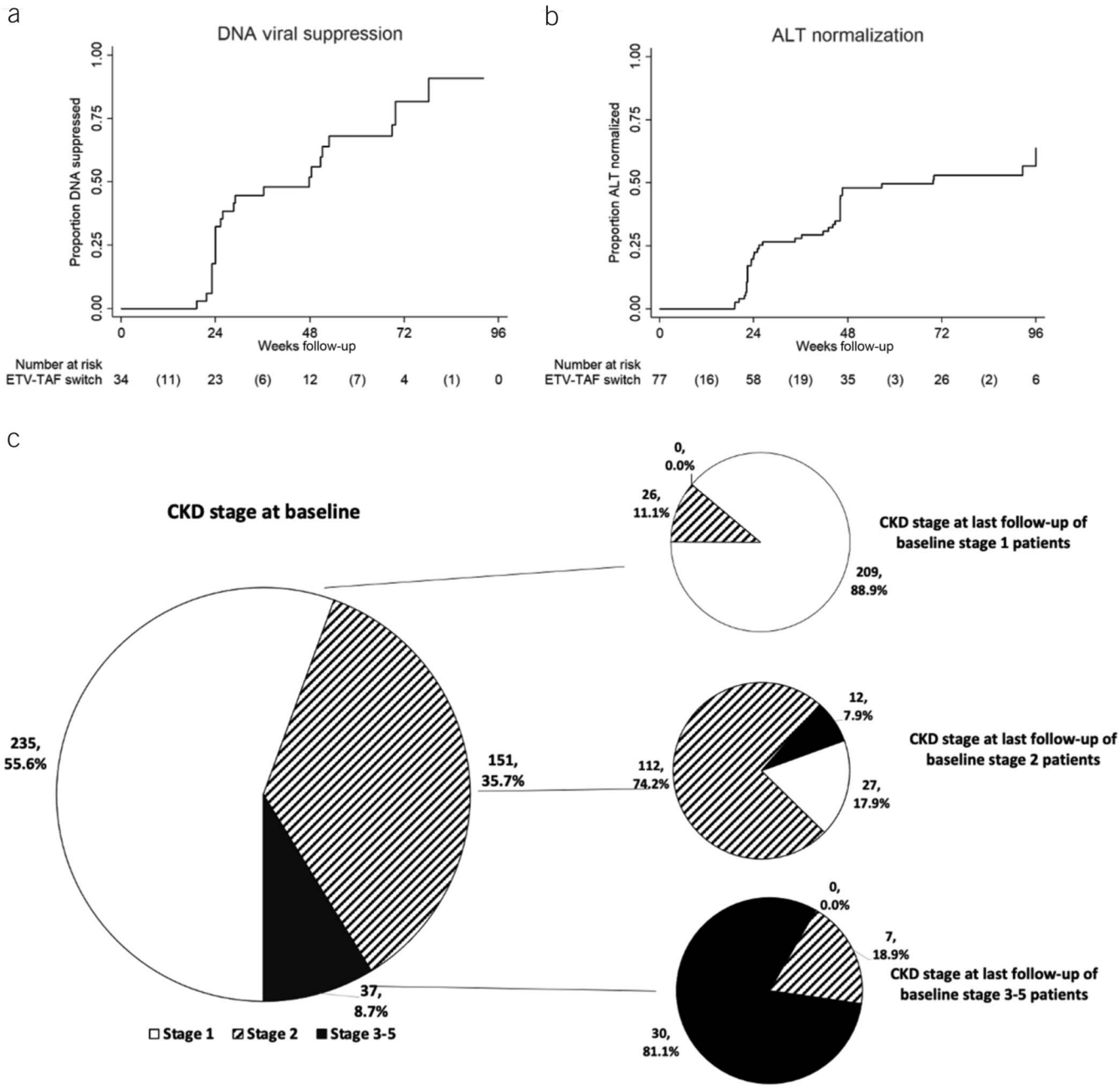


Figure 1. Proportion of patients with (**a**) incomplete viral response who achieved complete viral suppression, (**b**) elevated ALT who achieved ALT normalization, and (**c**) CKD stage migration after switching to TAF. ALT, alanine aminotransferase; CKD, chronic kidney disease; ETV, entecavir; TAF, tenofovir alafenamide.

Table 3. Trends in qHBsAg, HBV DNA, ALT, and eGFR levels after switching to TAF

Characteristics	Time					*P*-trend
	Switch	24 wk after switch	48 wk after switch	72 wk after switch	96 wk after switch	
qHBsAg (IU/mL)	730.03 (106.27–2,000)	579.45 (87.16–1,984.39)	573.19 (82.06–1,841.92)	490.96 (67.64–1,623.7)	229.98 (2.06–994.45)	0.744
HBV DNA (log IU/mL)	3.30 ± 1.74	2.83 ± 1.43	2.80 ± 1.70	2.27 ± 0.41	3.02 ± 1.93	<0.001
HBV DNA <20 IU/mL	386 (91.90)	385 (95.30)	367 (95.57)	288 (96.97)	174 (97.21)	<0.001
ALT (U/L)	23.18 ± 18.56	23.20 ± 14.13	23.66 ± 16.02	23.36 ± 15.44	23.13 ± 17.67	0.971
ALT <35/25 U/L (men/women)	347 (81.84)	331 (81.53)	315 (80.77)	246 (81.73)	154 (85.56)	0.482
eGFR (mL/m^2/min)	89.35 ± 19.09	88.69 ± 19.44	89.32 ± 19.90	89.27 ± 19.56	87.26 ± 21.21	<0.001
≥90	235 (55.56)	223 (55.06)	216 (55.24)	169 (55.78)	103 (56.91)	0.780
60–89	151 (35.70)	138 (34.07)	136 (34.78)	105 (34.65)	54 (29.83)	
<60	37 (8.75)	44 (10.86)	39 (9.97)	29 (9.57)	24 (13.26)	

Values expressed as mean ± SD, median (interquartile range), or number (%).
ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; qHBsAg, quantitative hepatitis B surface antigen; TAF, tenofovir alafenamide.

Renal outcomes

Changes in eGFR and CKD stages. In unadjusted analysis, there was a significant but small decrease in mean eGFR from 89.35 ± 19.09 at baseline to 87.26 ± 21.21 at 96-week follow-up ($P < 0.001$), although there was no statistically significant changes in CKD stages over time by trend analysis ($P = 0.78$) (Table 3). In addition, in GLM analysis adjusted for age, sex, diabetes or hypertension, and cirrhosis, there was no significant change in mean eGFR overall ($P = 0.25$) or when stratified by eGFR ≥ 90 or eGFR <90 ($P = 0.62$ and $P = 0.15$, respectively) (Figure 3a–c).

However, as shown in Figure 1c, at 96 weeks of follow-up, 11% (26/235) CKD stage 1 patients migrated to stage 2 and 8% (12/151) CKD stage 2 migrated to stages 3–5, whereas 18% (27/151) migrated from CKD stage 2 to stage 1 and 19% (7/37) from CKD stages 3–5 to stage 2.

Factors associated with changes in eGFR and worsening CKD stage. The predictors for changes in eGFR at 96 weeks postswitch were age (coefficient −0.35, $P < 0.001$), baseline eGFR 60–89 (coefficient −18.20, $P < 0.001$), and baseline eGFR <60 (coefficient −48.59, $P < 0.001$) (Table 4). In the logistic regression model, only baseline eGFR (adjusted odds ratio: 0.96, 95% confidence interval: 0.94–0.99; $P = 0.002$) was associated with worsening CKD (see Supplemental Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B860).

Sensitivity analysis

In this analysis of 127 patients with a recorded indication as to why their care provider switched their treatment from ETV to TAF, we found similar outcomes to those from our original analysis (see Supplemental Tables 2 and 3, Supplemental Figures 2–4, Supplementary Digital Content 1, http://links.lww.com/AJG/B860).

DISCUSSION

In this study of a large real-world cohort of HBV patients who were switched from ETV to sequential treatment with TAF, we aimed to provide information to assist clinicians with their decision making on treatment of HBV. Because of the longer-term follow-up and the inclusion of patients from both East and West in this study, we are able to provide 3 main findings that clinicians may find of value in their practice.

First, CVS rate significantly improved by 5.3% at 96 weeks. After an average of more than 6 years on ETV, CVS changed from 91.9% at the ETV-to-TAF switch time point to 95.3% at 24 weeks postswitch and then to 97.2% at 96 weeks postswitch. At 24 weeks, HBV DNA levels had also improved after switching to TAF, but the trend was not significant in our adjusted analysis, potentially because of the small sample size of patients who were still viremic on long-term follow-up. In fact, our GLM analysis suggested this as qHBsAg also decreased from about 3000 IU/mL at switch to about 2000 IU/mL at the 96-week follow-up time point. On the other hand, there were no statistically significant trends in ALT normalization rates or ALT levels over time even in adjusted analysis.

Second, we noted in our multivariable analysis that the consistent independent factors associated with decreased HBV DNA, qHBsAg, and ALT were their respective baseline values such that the higher the value at baseline, the less likely one was to have a positive change in their level. The opposite was observed for eGFR with those with higher baseline values being more likely to experience positive changes in eGFR. As such, the decision to switch should be considered in light of cost. Currently, Japan has special coverage for patients with hepatitis B or C where they are required to pay a minimal fee every 3 months, which covers all medical care and medicine because the residual cost is covered by the government so the cost to the patient is not a factor. However, this is not the case for many other countries such that, if the cost of TAF is greater than the cost for ETV, advocating for a change to TAF therapy is not warranted.

Third, although eGFR was noted to have decreased by 96 weeks postswitch, the change was minimal (about 2 mL/m^2/min between switch to 96-week postswitch), and this observation was not adjusted for relevant confounders. In our adjusted overall

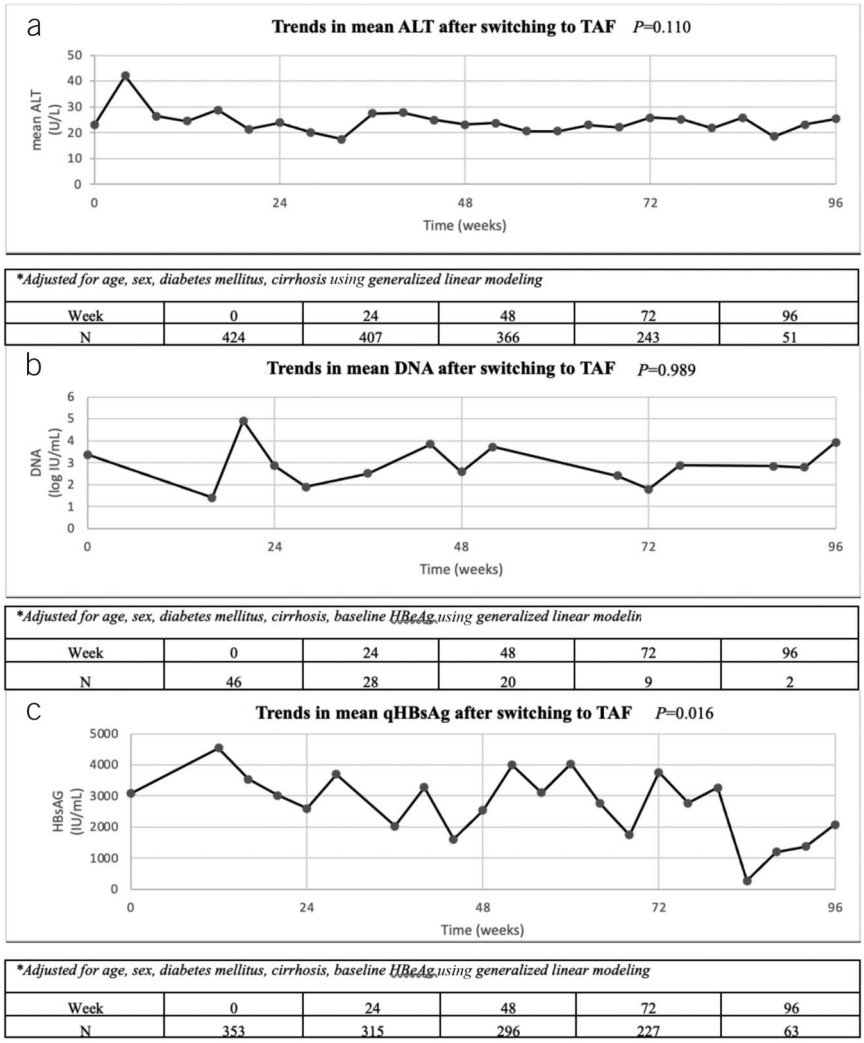


Figure 2. Treatment response after switch to TAF (**a**) ALT, (**b**) HBV DNA, (**c**) qHBsAg. ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; qHBsAg, quantitative HBsAg; TAF, tenofovir alafenamide.

analysis and in subanalysis where we had split the groups by an eGFR ≥90 or <90, there were no discernable differences in the mean eGFR after adjusting for known risk factors. Currently, practice guidelines recommend using TAF treatment as first-line therapy in older patients or those at higher risk of CKD (24). Although these recommendations are very relevant clinically because the CHB population are aging with increasing comorbidities (25–27), our study also found that younger patients were more likely to experience an improvement in eGFR during the postswitch follow-up. We suggest that further study is warranted to investigate renal function changes in patients treated with TAF vs ETV in the younger population (14,28).

On the other hand, it is important to note that the improvement in viral suppression after switching to TAF occurred faster than was occurring while on ETV during the 24 weeks before switch without the worsening of renal function reported in earlier studies on ETV (21,29–31). It is also important to note that these incremental improvements after switch to TAF were significant even though our cohort already received ETV therapy for an average duration of more than 6 years. Finally, we did not find significant positive changes in the ALT levels when on TAF, as others have reported (14,32–34). However, the Kaplan-Meier analysis showed that the proportion of ALT normalization increased approximately 50% over the 96 weeks of follow-up.

This study has several strengths. First, our study consisted of real-life data from a large and geographically diverse international group of patients, which helps to make our data more generalizable. Second, our cohort consists of only treatment-naive ETV patients, thus avoiding confounding effects by previous treatment with agents known to have either poor virological efficacy (e.g., adefovir and lamivudine) and/or deleterious (e.g., adefovir or TDF) or potentially protective (e.g., telbivudine) effect on renal function (12,13,20,21,31). Third, we had long-term follow-up of patients both before switching to TAF and after the switch, which allows a better understanding of the effects of TAF on HBV treatment outcomes. Fourth, we conducted many types of analysis and subanalysis to control for potential confounders and to help explain our findings.

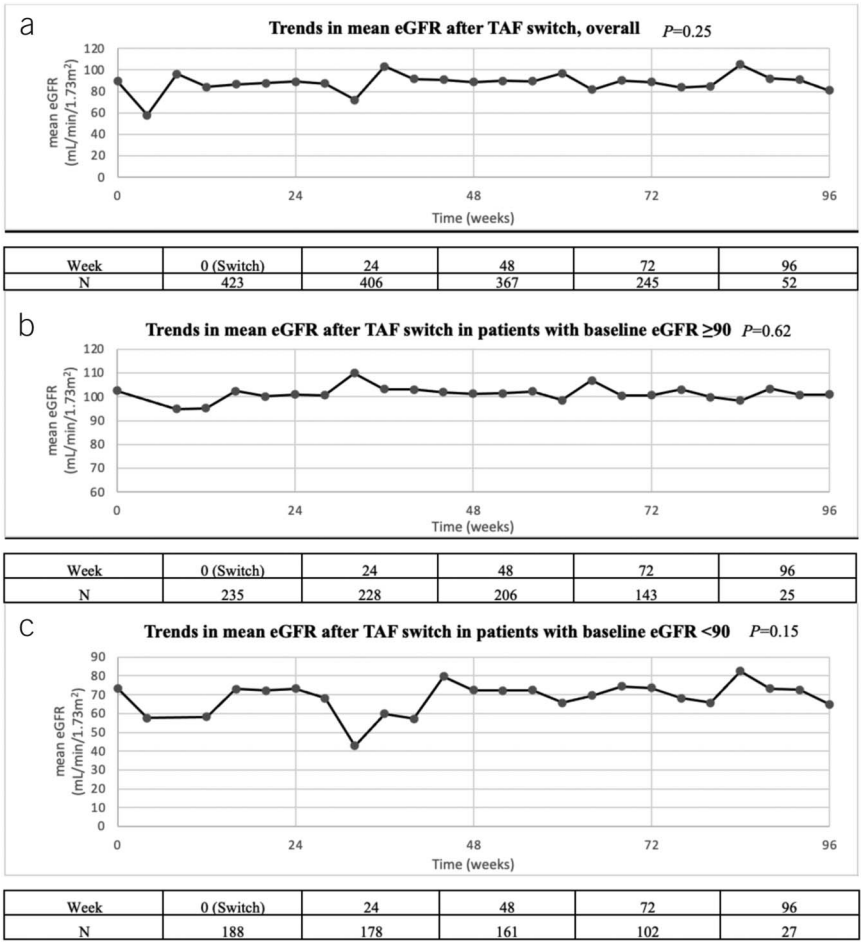
We also acknowledge the following limitations. First, because of the retrospective nature of the study, there were missing data.

Table 4. Generalized estimated equation analysis for estimated predictors of changes in HBV DNA, qHBsAg, ALT, and eGFR levels after switching to TAF

	Coefficient (95% CI)	*P*
HBV DNA		
Age	0.02 (−0.01 to −0.04)	0.106
Sex		
Women	Reference	—
Men	−0.10 (−0.82 to 0.61)	0.787
Diabetes mellitus	0.09 (−0.39 to 0.58)	0.715
Cirrhosis	0.29 (−0.61 to 1.19)	0.533
Baseline HBeAg	0.36 (−0.52 to 1.23)	0.426
Baseline HBV DNA	0.68 (0.53 to 0.83)	<0.001
qHBsAg		
Age	−21.54 (−33.91 to −9.16)	0.001
Sex		
Women	Reference	—
Men	−245.54 (−541.89 to 50.81)	0.104
Diabetes mellitus	−81.00 (−436.90 to 274.90)	0.656
Cirrhosis	−118.70 (−529.97 to 292.57)	0.572
Baseline HBeAg	−176.86 (−476.57 to 122.65)	0.247
Baseline qHBsAg	0.76 (0.74 to 0.78)	<0.001
ALT		
Age	−0.06 (−0.15 to 0.03)	0.211
Sex		
Women	Reference	—
Men	4.47 (2.15 to 6.79)	<0.001
Diabetes mellitus	3.83 (1.04 to 6.61)	0.007
Cirrhosis	−0.47 (−3.71 to 2.77)	0.775
Baseline ALT	0.15 (0.12 to 0.19)	<0.001
eGFR		
Age	−0.35 (−0.42 to −0.27)	<0.001
Sex		
Women	Reference	—
Men	−0.30 (−2.05 to 1.44)	0.734
Hypertension, diabetes mellitus, or cirrhosis	0.16 (−1.62 to 1.95)	0.862
Baseline eGFR		
≥90	Reference	—
60–89	−18.20 (−20.19 to −16.20)	<0.001
<60	−48.59 (−51.85 to −45.33)	<0.001

ALT, alanine aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; qHBsAg, quantitative hepatitis B surface antigen; TAF, tenofovir alafenamide.

However, the number missing was small and could be inferred from the data we had when used in our analyses. Second, knowing how patients experienced this switch of medications would be important because a recent study suggested that patients who were switched to TAF had better adherence (18,35). Third, our study lacks a control arm that remained on ETV; although our study patients were drawn from patients from diverse geographic regions from both East and West, most CHB patients from the



Week	0 (Switch)	24	48	72	96
N	423	406	367	245	52

Week	0 (Switch)	24	48	72	96
N	235	228	206	143	25

Week	0 (Switch)	24	48	72	96
N	188	178	161	102	27

Figure 3. Mean eGFR* after switching to TAF (**a**) overall and by (**b**) eGFR ≥90 or (**c**) <90. *All analyses adjusted for age, sex, diabetes mellitus or hypertension, and cirrhosis using generalized linear modeling. eGFR, estimated glomerular filtration rate; TAF, tenofovir alafenamide.

United States were of Asian descent (10,25). Fourth, our cohort was not a closed cohort, so not everyone reached the endpoint of 96 weeks. However, our study reflects real-world practice where patients are not consistently seen at exact follow-up times. Fifth, we were unable to determine why 70% of clinicians switched from ETV to TAF, but we can surmise that many changed their patients over to TAF after the publications of several pivotal articles which suggested that there may be faster normalization of ALT when using TAF and that the use of TAF added some protection against the development of HCC because the incidence of HCC was noted to decrease in those who were switched to TAF (36–41). However, in our sensitivity analysis of the patients with a clear indication for switching to TAF, there was no difference in our reported outcomes. Finally, we would like to acknowledge that, although our study was funded by Gilead, the funding was requested long after the start period of this study so that all patients who are in this study were switched at the discretion of their healthcare providers and not as part of the study team.

In conclusion, we found that CVS rate and HBV DNA and qHBsAg levels improved after switching from ETV to TAF without any significant changes in renal function. Switching to TAF seems to be a safe and effective treatment option; however, given the size of the incremental changes, healthcare providers must weigh the cost-benefit ratio before automatically switching patients from ETV to TAF. Additional studies are also needed to examine the effects of long-term TAF therapy, including the risk of HCC development.

CONFLICTS OF INTEREST

Guarantor of the article: Mindie H. Nguyen, MD, MAS.
Specific author contributions: M.H.N.: study concept, design, and supervision. All authors: data collection. H.D. and M.H.N.: data analysis. M.H.N., L.H., and H.D.: drafting of the article. All authors: data interpretation and review and/or revision of the manuscript. All authors identified have critically reviewed and approved the final version of this article, including the authorship statement.
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Study Highlights

WHAT IS KNOWN

- ✓ Entecavir (ETV) is the oldest first-line treatment for chronic hepatitis B (HBV).
- ✓ Tenofovir alafenamide (TAF) is thoroughly absorbed into cells, thus allowing usage of smaller doses.
- ✓ Data regarding ETV-to-TAF switch remain limited.

WHAT IS NEW HERE

- ✓ Levels of CVS rate, HBV DNA, and quantitative HBsAg improved after ETV-to-TAF switch.
- ✓ Improvements were significant despite having received ETV therapy for an average duration of 6+ years.
- ✓ After adjustment for relevant clinical markers, renal function remained stable during the 96-week TAF therapy.

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