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Switching to tenofovir alafenamide for nucleos(t)ide analogue-experienced patients with chronic hepatitis B: week 144 results from a real-world, multi-centre cohort study

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Summary

Background: Tenofovir alafenamide (TAF) may be preferable to other nucleos(t)ide analogues (NA) regarding outcomes against chronic hepatitis B virus (HBV) infection.

Aims: To evaluate the longer term virological/biochemical effectiveness of TAF and the renal safety of sequential therapy to TAF in real-world settings

Methods: This multi-centre, retrospective cohort study included consecutive adult patients who were switched from other NAs to TAF. We assessed the virological and biochemical responses up to 144 weeks. We performed sensitivity analyses for a subgroup with chronic kidney disease (CKD) at baseline.

Results: We analysed the data of 391 patients with chronic hepatitis B previously treated with entecavir (ETV) ($n = 174$), tenofovir disoproxil fumarate (TDF) ($n = 116$) or an NA combination ($n = 101$) for ≥ 24 months. HBV DNA <10 IU/ml at week 144 was found for 99% of patients, regardless of prior NA regimen or HBV DNA level at baseline. For patients who switched from TDF to TAF, total, low-density lipoprotein, high-density lipoprotein cholesterol and triglycerides were significantly increased after the switch. Patients who switched from a nucleotide analogue to TAF had an improved estimated glomerular filtration rate, although the rate of hypophosphataemia (<2.5 mg/dl) remained 9.7% at week 144. The virological and biochemical responses of patients with CKD were similar to the overall results.

Conclusions: Switching to TAF remained effective and safe for up to 3 years. Given the increasing comorbidities related to ageing, it will be important to carefully follow the change in the lipid levels of patients with a prior TDF-based regimen.

1 | INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains one of the main causes of cirrhosis and hepatocellular carcinoma (HCC) worldwide. The World Health Organization estimated in 2019 that 296 million people had chronic hepatitis B (CHB) and that CHB resulted in approximately 820,000 deaths, primarily due to liver-related complications.[1] Despite the fact that a safe and effective vaccine that offers 98%–100% protection against HBV is available worldwide, 1.5 million people have been newly diagnosed with HBV infection each year.[1] Whilst there is no specific antiviral treatment for acute HBV infection, CHB can now be treated with oral nucleos(t)ide analogues (NAs) to suppress HBV replication, which has resulted in reduced HCC incidence and improvement in survival.[2–4] Although HBsAg loss or seroconversion remains the optimal end point, hepatitis B surface antigen (HBsAg) loss rarely occurs with the current NAs.

According to the current treatment guidelines,[2–4] the preferred NAs are entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). Although these NAs have very low rates of drug resistance and a favourable safety profile, ETV weakens the barrier to resistance of patients previously treated with lamivudine (LAM) because of cross-resistance.[5,6] TDF causes declines in renal function and gradually reduces bone mineral density.[7,8] In addition, HBV itself plays a pivotal role in the acquisition and progression of chronic kidney disease (CKD) because of glomerular dysfunction.[9] The HBV population is ageing worldwide, and the frequency of comorbidities in this population is rising. Published articles from the United States and Hong Kong have shown an increased prevalence of hypertension, diabetes mellitus and CKD with age.[10,11] Therefore, the elimination of HBV is of utmost importance to this ageing population.

TAF is a prodrug of tenofovir, a nucleotide analogue that inhibits reverse transcription of both HBV and human immunodeficiency virus (HIV) and that has greater stability than TDF in plasma. According to phase III trials of the efficacy and safety of TAF versus TDF for CHB patients,[12] TAF was not inferior to TDF in terms of antiviral efficacy up to 96 weeks. However, TAF was associated with greater improvement of renal function and bone mineral density when compared with TDF.[12] Our research group is doing ongoing, real-world studies of the effectiveness and renal safety of TAF for patients who had previously been treated with other NAs. Our results have shown that sequential NA therapy with a switch to TAF is a good option up to 96 weeks in terms of its virological effects[13]; however, longer term follow-up is needed to fully characterise the profile of TAF after switchover. The aim of this study was to evaluate longer term, up to 144 weeks, the virological and biochemical profile of switching from ETV or an NA combination to TAF, especially for patients with CKD.

2 | PATIENTS AND METHODS

2.1 | Patients

The Kyushu University Liver Disease Study (KULDS) Group consists of hepatologists from Kyushu University Hospital and its affiliated hospitals located in the northern Kyushu area of Japan. This multicentre, retrospective, observational cohort study consisted of consecutive patients from March 2017 to December 2018 who switched to a fixed dose of TAF, 25 mg orally once daily (Vemlidy; Gilead Sciences K.K., Tokyo, Japan) with food. TAF dosage remains at 25 mg until the estimated glomerular filtration rate (eGFR) is under 15 ml/min/1.73m^2, based on pharmacokinetics data modelling.[14] We have three patterns for switching to TAF. First, patients with older age (>60 years), deteriorating renal function (eGFR<60 ml/min/1.73m^2 or serum phosphate level <2.5 mg/dl), or osteoporosis/osteopenia who have been treated with adefovir (ADF) or TDF are considered for a switch to TAF.[3] Second, patients with a low-level viraemia who have been treated with ETV monotherapy are considered for a switch to TAF. Third, if patients hope to take an NA with food rather than on an empty stomach, they can switch from ETV to TAF. Even if none of the above apply, each attending physician gives our patients drug information regarding the efficacy, safety and method of administration of all NAs.

Eligible patients (1) were aged 18 years and older with confirmed chronic HBV infection (2) who were switched to TAF monotherapy from an at least 2-year course of ETV, TDF or an NA combination of LAM/ADF, LAM/TDF, ETV/ADF or ETV/TDF. Exclusion criteria included (1) duration of follow-up under 144 weeks; (2) positivity for antibody to HIV or positivity for hepatitis C antibody; (3) past history of HCC; (4) terminal illness and (5) insufficient medical records for primary end points and objectives. The study was conducted in accordance with the ethics principles of the Declaration of Helsinki and the STROBE statement. It was approved by the Ethics Committee of Kyushu University Hospital and is registered as a clinical study on the University Hospital Medical Information Network (ID 000034696).

2.2 | Laboratory assessments

All patients were followed every 12 weeks to at least the 144th week (36th month) of TAF treatment. Laboratory assessments included haematological analysis, serum biochemistry tests, fasting lipid parameters and measures of renal function. The eGFR was calculated with the following formulas[15]; for men, eGFR (mL/min/1.73m^2) = 194 × serum creatinine level (SCr)$^{-1.094}$ × age$^{-0.287}$ and for women eGFR = 194 × SCr$^{-1.094}$ × age$^{-0.287}$ × 0.739. We defined CKD as an eGFR<60 ml/min/1.73m^2. Liver cirrhosis was defined by a METAVIR F4 score on liver biopsy, transient elastography (FibroScan®; Echosens, Paris, France) greater than 12.0 kPa, or imaging examinations with signs of cirrhosis based on nodularity, portal velocity, liver size, caudate hypertrophy, echogenicity, portal vein diameter and spleen size. Baseline status was performed within 3 months before the switch to TAF treatment.

2.3 | Primary and secondary end points

The primary end point was the proportion of patients with HBV DNA <10 IU/ml, as determined by real-time reverse transcriptase PCR assay (COBAS 6800/8800 system HBV) (Roche Molecular Diagnostics, Tokyo, Japan) at week 144 after switching to TAF. We used COBAS TaqMan HBV assay, Version 2.0, to determine the HBV DNA level (the lower limit of quantification: 20 IU/ml) by the end of 2019. This gave us the ability to measure the HBV DNA level of all patients at week 144 with a more sensitive assay than was previously available. Key prespecified secondary end points were the longitudinal change of alanine aminotransferase (ALT), quantitative HBsAg (qHBsAg) level, eGFR, serum phosphate and fasting lipid parameters, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides. A patient was determined to have ALT normalisation if ALT was less than 35 U/L for men or 25 U/L for women, according to the American Association for the Study of Liver Diseases (AASLD) normal range.[2]

2.4 | Statistical analysis

Baseline continuous data are expressed as median (first-third quartile), and categorical variables are reported as frequencies and percentages with 95% confidence interval (CI). Comparisons between three groups were analysed by means of analysis of variance (ANOVA) if the data were normally distributed and a Kruskal–Wallis test if not. Trends for continuous variables were assessed by the repeated measures ANOVA test. The chi-squared test or Fisher's exact test was used to compare the rates of virological and biochemical responses between baseline and various time points after switching to TAF. Continuous variables were analysed using the paired *t*-test, Student's *t*-test or Mann–Whitney *U* test as appropriate. Moreover, we performed sensitivity analyses for the subgroup of patients with CKD at baseline.

A two-sided *p* value less than 0.05 was regarded as statistically significant in all analyses. All statistical analyses were carried out using SPSS Statistics version 27.0 (IBM SPSS Inc).

3 | RESULTS

3.1 | Patient characteristics

A total of 478 patients were switched to TAF during the study period, 87 (18.2%) of whom were excluded in accordance with the criteria, including those who had developed HCC before switching to TAF (*n* = 56) (Figure 1). Of the eligible patients, 174 had received ETV, 116 TDF and 101 an NA combination before switching to TAF at a median

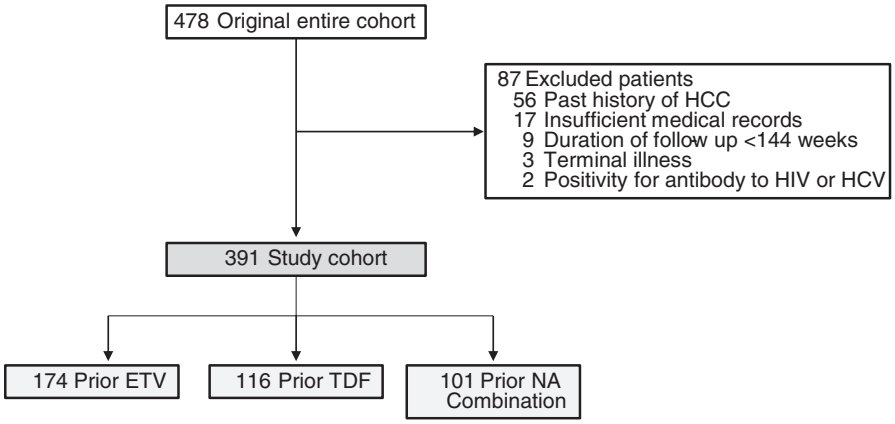


FIGURE 1 Study flow chart. ETV, entecavir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, nucleos(t)ide analogue; TDF, tenofovir disoproxil fumarate.

of 5.3 years. Baseline characteristics of the patients according to the previous NA treatment are shown in Table 1. Because most patients were male (60.4%) and the median age was 59 years, the median eGFR at baseline was relatively low, 73 ml/min/1.73m^2, compared to other TAF switch studies. Approximately 8% were diagnosed with cirrhosis at baseline. Fifty-eight (14.8%) were taking antilipidaemic agents at the time of switching to TAF. Almost all (87.0%) had achieved HBV suppression with their previous NA(s); however, 51 (13.0%) had HBV DNA >20 IU/ml at baseline. Notably, one-fourth of the patients previously treated with ETV were positive for HBV DNA.

3.2 | Antiviral response at week 144 after switching to TAF

The proportions of patients switching to TAF who had HBV DNA <10 IU/ml at week 144 were 98.9% (172/174, 95% CI 95.6–100), 99.1% (115/116, 95% CI 94.8–100) and 99.0% (100/101, 95% CI 94.1–99.9) in the prior ETV, TDF and NA combination groups, respectively (Table 2). None experienced HBV breakthrough during the follow-up period. Of the 39 ETV-treated patients with low-level viraemia (HBV DNA 20–2000 IU/ml), 37 (94.9%) had HBV DNA <10 IU/ml at week 144 (Figure 2A). Switching from TDF or a NA combination to TAF also favoured HBV DNA suppression at week 144, irrespective of a low HBV DNA level at baseline.

Hepatitis B e antigen (HBeAg) loss amongst HBeAg-positive patients who switched to TAF was 23.4% (15/64, 95% CI 14.6–35.2) at week 144. It was 27.8% (5/18), 27.3% (6/22) and 16.7% (4/24) in the prior ETV, TDF and NA combination groups, respectively. The qHBsAg level decreased longitudinally to −0.20 logIU/ml (first-third quartile: −0.32, −0.10) at week 144 (Figure 2B). However, the rate of HBsAg loss at week 144 was only 1.8% (7/391).

3.3 | Biochemical response at week 144 after switching to TAF

Of the patients who switched to TAF, 88.0% (344/391, 95% CI 84.4–90.9) had a normal ALT level by AASLD criteria at week 144, a significantly higher proportion than the 78.3% (306/391) at baseline ($p < 0.001$). The proportion of patients with a normal ALT level who were switched from TDF to TAF increased from 72.4% at baseline to 85.3% at week 144 ($P = 0.016$), a significantly greater change than that of those who switched from ETV to TAF (83.3% to 89.1%, $P = 0.12$) (Table 2). Focusing on the patients who had ALT elevation at baseline ($n = 85$), 53 (62.4%) achieved ALT normalisation at week 144 (Table S1). Notably, 62.5% of those with prior TDF and 70.8% with the prior NA combination achieved ALT normalisation at week 144.

3.4 | Fasting lipid change after switching to TAF

Longitudinal fasting lipid analysis was carried out every 6 months up to week 144, with the patients divided into prior TDF and non-TDF groups (Figure 3). For patients who switched from TDF to TAF, total ($p < 0.001$), LDL ($p < 0.001$) and HDL cholesterol levels ($p < 0.001$) and triglycerides ($p = 0.006$) were significantly increased after switchover compared to those who switched from regimens other than TDF to TAF. These changes were found as early as 24 weeks after switching to TAF and continued throughout the follow-up period. In contrast, the total to HDL cholesterol ratio remained unchanged in both groups ($p = 0.11$ and $p = 0.75$ for the prior TDF and non-TDF groups, respectively). Six patients (three prior TDF, two prior NA combination and one prior ETV) were given antilipidaemic agents during the follow-up period because of the increasing LDL cholesterol levels.

3.5 | Renal safety after switching to TAF

Patients who switched from a nucleotide analogue (TDF or ADF) to TAF had improved eGFR in the first year after switchover (Figure 4A). The eGFR change from baseline was significantly different between the prior TDF or ADF and ETV ($p < 0.05$) groups to 72 weeks. In the analysis of the phosphate level, the rate of hypophosphataemia (<2.5 mg/dl) was slightly decreased, from 13.4% at baseline to 9.7% at week 144 (Figure 4B) in patients switching from a nucleotide analogue (TDF or ADF). In contrast, the rate of hypophosphataemia

TABLE 1 Baseline characteristics: At the time of switch to TAF

Previous NA regimen	Total	ETV	TDF	NA combo	*p* value
Number	391	174	116	101	
Age	59 (47–68)	61 (49–69)	49 (42–64)	59 (52–67)	<0.001
Range	26–90	26–90	29–78	33–84	
Male	236 (60.4)	111 (63.8)	63 (54.3)	62 (61.4)	0.26
Body mass index (kg/m^2)	22.4 (20.4–24.8)	22.4 (20.4–24.2)	22.3 (20.5–25.0)	22.9 (20.7–25.2)	0.60
Cirrhosis	31 (7.9)	13 (7.5)	6 (5.2)	12 (11.9)	0.18
Hypertension	70 (17.9)	48 (27.6)	7 (6.0)	15 (14.9)	<0.001
Diabetes	36 (9.2)	20 (11.5)	6 (5.2)	10 (9.9)	0.20
Hyperlipidaemia	75 (19.2)	41 (23.6)	15 (12.9)	19 (18.8)	0.079
Albumin (g/L)	43 (41–45)	43 (42–45)	43 (42–45)	44 (41–46)	0.95
Total bilirubin (mg/dl)	0.7 (0.6–1.0)	0.8 (0.6–1.1)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.087
AST (U/L)	24 (20–29)	23 (19–28)	25 (22–30)	24 (20–30)	0.035
ALT (U/L)	21 (15–31)	20 (14–27)	24 (18–34)	20 (16–31)	<0.001
γGTP (U/L)	21 (16–38)	24 (16–42)	20 (15–36)	19 (15–34)	0.054
eGFR (mL/min/1.73m^2)	73 (61–83)	73 (62–84)	74 (63–85)	70 (59–81)	0.053
30–60	84 (21.5)	36 (20.7)	23 (19.8)	25 (24.8)	
15–<30	3 (0.8)	1 (0.6)	1 (0.9)	1 (1.0)	
Phosphorus (mg/dl)	3.2 (2.9–3.6)	3.3 (2.9–3.6)	3.3 (2.9–3.8)	3.0 (2.6–3.5)	0.001
AFP (ng/ml)	3.0 (2.0–3.8)	2.8 (2.0–3.3)	3.0 (2.1–4.2)	3.0 (2.1–3.7)	0.25
Platelet count (10^3/μl)	188 (151–228)	182 (150–221)	195 (151–241)	189 (152–223)	0.26
HBeAg positive	64 (16.4)	18 (10.3)	22 (19.0)	24 (23.8)	0.010
HBV DNA (IU/ml)					
<20+ or negative	340 (87.0)	135 (77.6)	111 (95.7)	94 (93.1)	<0.001
20–2000	41 (10.5)	29 (16.7)	5 (4.3)	7 (6.9)	
>2000	10 (2.6)	10 (5.7)	0	0	
Previous NA treatment duration (years)	5.3 (4.0–7.7)	5.0 (4.2–7.4)	3.1 (2.5–3.5)	8.6 (6.0–12.1)[a]	<0.001
Previous NAs combination					
LAM + ADV				34 (33.7)	
LAM + TDF				30 (29.7)	
ETV + ADV				3 (3.4)	
ETV + TDF				34 (33.7)	

Notes: Data are *n* (%) or median (first-third quartile).

Abbreviations: γGTP, gamma-glutamyl transpeptidase; ADV, adefovir; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LAM, lamivudine; NA, nucleos(t)ide analogue; TDF, tenofovir disoproxil fumarate.

[a]Including the duration of time of first NA treatment.

was slightly increased, from 2.3% to 5.7%, in patients switching from ETV.

There was only one case of a 67-year-old woman with HBeAg/HBV DNA negative compensated cirrhosis who had been diagnosed with hypophosphataemic osteomalacia at the time of the switch from ETV/TDF to TAF. The patient had diffuse bone and joint pain, severe tubulopathy, hypophosphataemia (1.8 mg/dl), elevated alkaline phosphatase (ALP) level (more than twice the upper limit of normal), low eGFR (40 ml/min/1.73m^2) and proteinuria. Whilst TAF efficiently suppressed viral replication and improved both ALP and phosphate levels (3.5 mg/dl at week 144), eGFR was improved transiently during the first year of the study period (41.5 ml/min at week 48).

3.6 | Response of patients with CKD

Our study included 87 patients with CKD (eGFR <60 ml/min/1.73m^2) at baseline, mainly CKD stage 3 (n = 84, 96.6%). We did a sensitivity analysis of the virological and biochemical responses and renal safety

TABLE 2 Virological and biochemical response according to the prior NA regimen

TAF	Time	Number of HBV DNA <20 IU/ml (%)	Percentage (%)	*p* value	Number of ALT<35 (male) / 25 (female) U/L	Percentage (%)	*p* value
Overall (*N* = 391)	Baseline	340	86.6	Ref	306	78.3	Ref
	6 months	375	95.9	<0.001	325	83.1	0.085
	12 months	381	97.4	<0.001	333	85.2	0.012
	18 months	381	97.4	<0.001	329	84.1	0.035
	24 months	385	98.5	<0.001	339	86.7	0.002
	30 months	388	99.2	<0.001	342	87.5	<0.001
	36 months[a]	387	99.0	<0.001	344	88.0	<0.001
Prior ETV (*n* = 174)	Baseline	135	77.6	Ref	145	83.3	Ref
	6 months	164	94.3	<0.001	149	85.6	0.55
	12 months	169	97.1	<0.001	150	86.2	0.46
	18 months	170	97.7	<0.001	146	83.9	0.88
	24 months	171	98.3	<0.001	154	88.5	0.17
	30 months	173	99.4	<0.001	154	88.5	0.17
	36 months[a]	172	98.9	<0.001	155	89.1	0.12
Prior TDF (*n* = 116)	Baseline	111	95.7	Ref	84	72.4	Ref
	6 months	113	97.4	0.47	92	79.3	0.22
	12 months	113	97.4	0.47	99	85.3	0.016
	18 months	113	97.4	0.47	96	82.8	0.059
	24 months	114	98.3	0.25	99	85.3	0.016
	30 months	115	99.1	0.10	100	86.2	0.010
	36 months[a]	115	99.1	0.10	99	85.3	0.016
Prior NA combo (*n* = 101)	Baseline	94	93.1	Ref	77	76.2	Ref
	6 months	98	97.0	0.19	84	83.2	0.22
	12 months	99	98.0	0.088	84	83.2	0.22
	18 months	98	97.0	0.19	87	86.1	0.072
	24 months	100	99.0	0.030	86	85.1	0.11
	30 months	100	99.0	0.030	88	87.1	0.045
	36 months[a]	100	99.0	0.030	90	89.1	0.016

Abbreviations: ETV, entecavir; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a]The proportion of patients with HBV DNA <10 IU/ml.

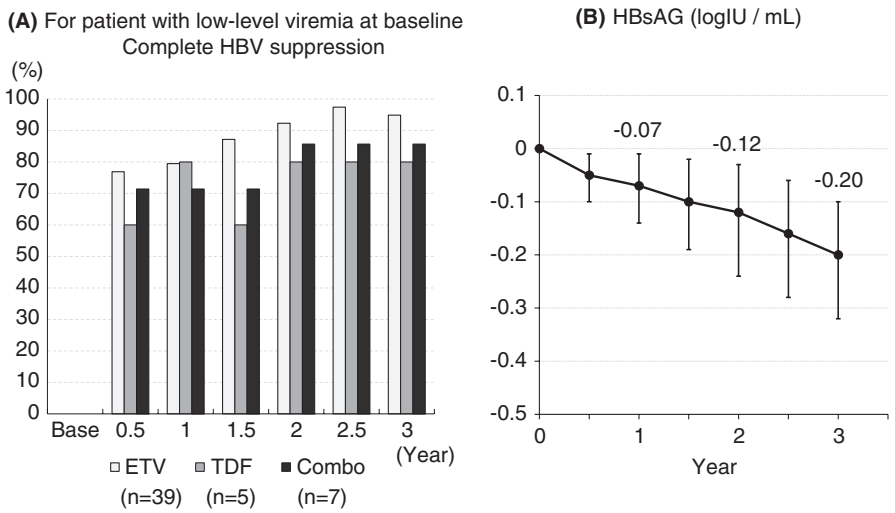


FIGURE 2 Longitudinal change in (A) proportion of HBV suppression up to 144 weeks after switching to TAF for patients with low-level viraemia at baseline and (B) quantitative hepatitis B surface antigen levels. Bars are expressed as median change from baseline (first-third quartile). HBV, hepatitis B virus; TAF, tenofovir alafenamide.

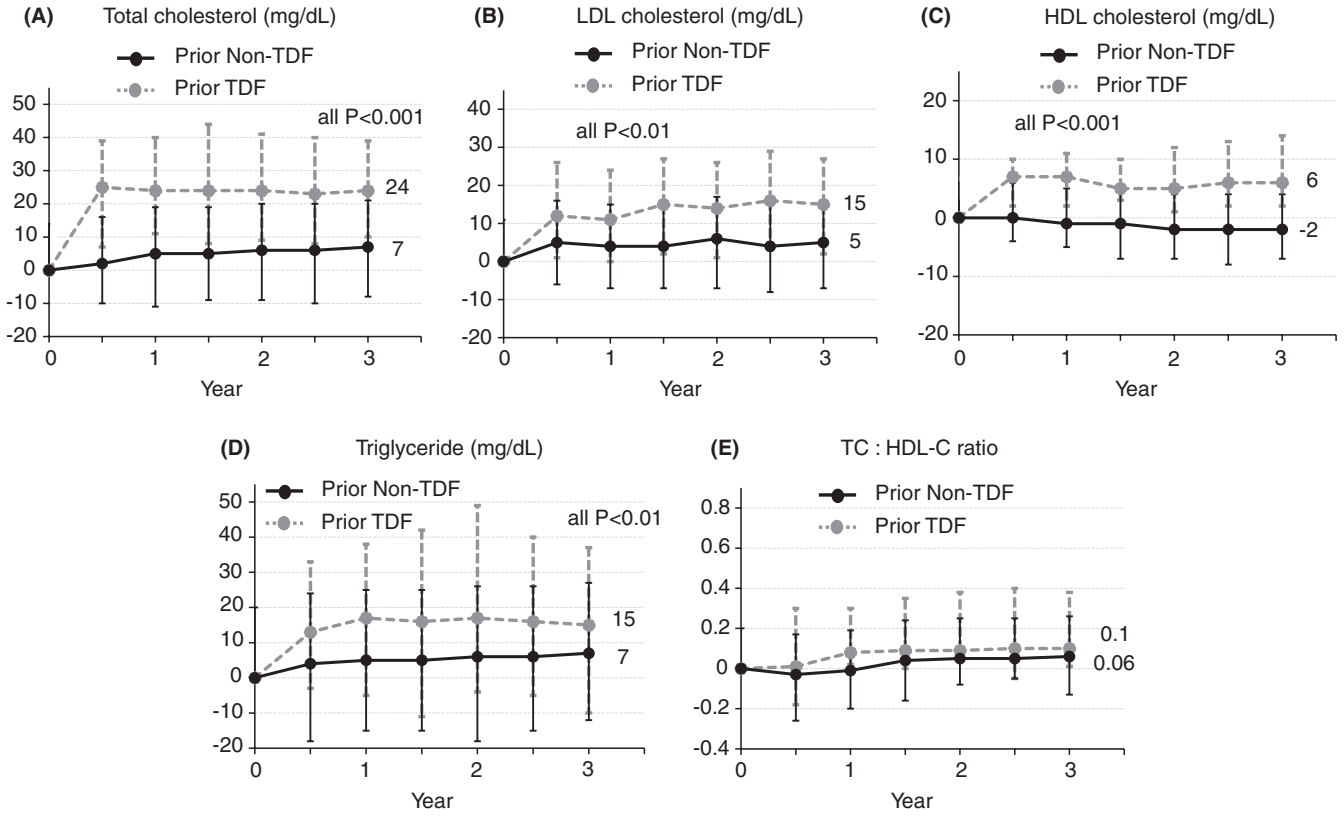
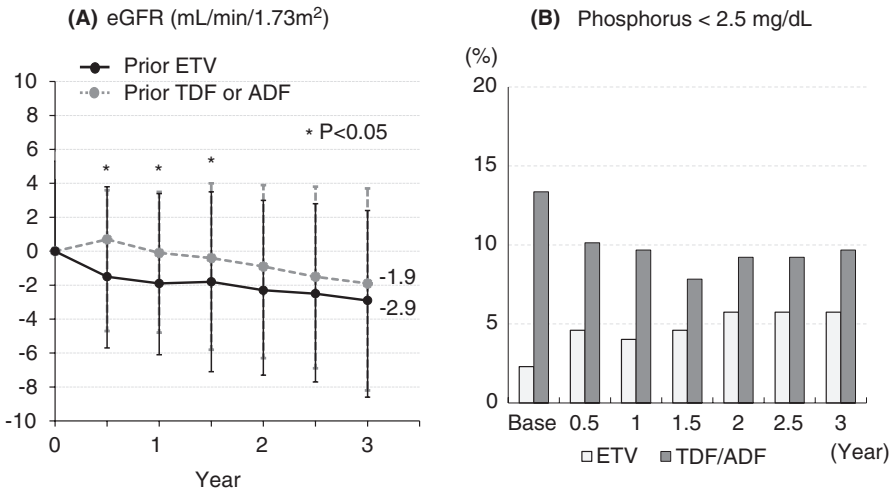


FIGURE 3 Longitudinal change in (A) total cholesterol, (B) LDL cholesterol, (C) HDL-cholesterol, (D) triglyceride and (E) total cholesterol/HDL cholesterol ratio over the 144 weeks after switching to TAF. Bars are expressed as median change from baseline (first-third quartile). HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAF, tenofovir alafenamide.

FIGURE 4 Longitudinal change in (A) eGFR and (B) the proportion of serum phosphorus <2.5 mg/dl over the 144 weeks after switching to TAF. Bars are expressed as median change from baseline (first-third quartile). eGFR, estimated glomerular filtration rate; TAF, tenofovir alafenamide.



for these patients. The proportions of patients who had HBV DNA <10 IU/ml at week 144 were 97.3% (36/37, 95% CI 84.5–100), 100% (24/24, 95% CI 83.7–100) and 100% (26/26, 95% CI 84.8–100) in the prior ETV, TDF and NA combination groups, respectively (Figure S1A). Moreover, the proportions of ALT normalisation at week 144 (by AASLD 2018 criteria) were 89.2% (33/37, 95% CI 74.7–96.3), 91.7% (22/24, 95% CI 73.0–98.8) and 84.6% (22/26, 95% CI 65.9–94.5), respectively, for the above groups (Figure S1B). Although the change in fasting lipid showed a similar trend for the entire cohort (Figure S2), the improvement of eGFR was greater for patients with prior TDF or ADF than for those with prior ETV (Figure S3A). None developed CKD stage 5/5D during the study period. Nevertheless, the rate of hypophosphataemia (<2.5 mg/dl) for patients with prior TDF or ADF remained relatively high, 10.0% at week 144 (Figure S3B).

4 | DISCUSSION

The current HBV treatment guidelines recommended TAF or ETV over TDF for older patients and for those with a risk of renal or bone dysfunction.[2–4] Furthermore, TAF is preferable to ETV for patients with previous NA exposure because of the lower risk of drug resistance. Published reports on switching from TDF to TAF based on clinical studies and real-world settings have recently become available.[16–19] In contrast, data on switching from ETV or other NAs to TAF are more limited compared with those on switching from TDF to TAF. These studies have reported improved or maintained virological and biochemical response from 48 to 96 weeks after switching to TAF. Ongoing cutting-edge research on HBV biology has helped us identify novel target areas in the HBV life cycle where the application of new therapeutics would lead to the achievement of our ultimate goal of developing a safe, effective, well-tolerated, finite duration regimen that will lead to loss of HBsAg.[20] However, combination drugs that include NAs will likely be necessary for some time in the future, thus long-term studies on TAF switching are required to determine if this regimen translates to long-term benefits.

The present 144-week findings in our real-world clinical setting confirm the durability of the favourable antiviral and biochemical effects of TAF switching: outcomes were consistent with those at week 96 in subgroups with prior ETV, TDF and NA combinations. The proportion of patients who had HBV DNA <10 IU/ml was almost 100% in all subgroups. Significant improvements in the proportion of patients who had HBV DNA <10 IU/ml were found for those with low-level viraemia (HBV DNA 20–2000 IU/ml) at baseline. Moreover, no resistance was developed in either prior treatment group through 144 weeks of TAF monotherapy, even by those who were well-controlled virologically by a NA combination. Other real-world studies have reported favourable antiviral and biochemical effects of switching from ETV to TAF[21–23]; however, it was important to prove the efficacy for a longer term, in this case up to 144 weeks. In addition, we have shown longitudinal data on the qHBsAg level, which will be one of the main targets of future HBV treatment. Although we previously reported that a lower qHBsAg level at baseline contributes to the reduction of HBsAg level, the median reduction level reached only 0.20 logIU/ml after 144 weeks of TAF treatment after switchover.

One of the strengths of this study was the relatively high prevalence of CKD at baseline, approximately 22% of the patients studied. Renal dysfunction has been significantly associated with an ageing population with CHB. Because the percentage of patients aged 65 and over with CHB from 2012 to 2016 was estimated to be from 45.6% to 60.7% in Japan,[24] we did a sensitivity analysis focused on a sample of patients with CKD. A high proportion of the patients had HBV DNA <10 IU/ml (86.2% to 98.9%) and ALT normalisation (81.6%–88.5%) elevated to favourable levels compared with baseline. Our previous study up to 96 weeks showed that patients with CKD receive a beneficial improvement of eGFR compared to those without CKD. Notably, this trend continued over the 144 weeks, especially for CKD patients with prior TDF or ADF, with physiological reduction after the peak of improvement at week 24. Also, the proportion of patients with hypophosphataemia (phosphorus <2.5 mg/dl) at 144 weeks after switching remained relatively high for those with previous TDF or ADF. Because prolonged hypophosphataemia may lead to anorexia, muscular weakness and osteomalacia,[25,26] attending physicians must continue over the long term to pay careful attention to the phosphorus level and to hypophosphataemia related to symptoms.

According to clinical trials, patients who switched from TDF to TAF had greater increases in total, LDL and HDL cholesterol compared with those who continued TDF treatment due to high plasma tenofovir levels in TDF-treated patients,[16,17] which has been linked to lipid reductions in patients on TDF. In our current study, fasting lipid analysis was carried out, with the patients divided into groups with and without previous TDF treatment. We found significantly higher increases in total, LDL, and HDL cholesterol and triglycerides for patients with prior TDF treatment. In contrast, there was no significant difference in the total to HDL cholesterol ratio, suggesting few increased risks of cardiovascular disease. However, it should be noted that triglyceride levels were significantly increased when switching from TDF to TAF. In an additional analysis, there were similar trends in fasting lipid levels, even in patients with CKD. Longer term observations will be warranted to determine how or if changes in fasting lipid levels affect atherosclerosis.

There are several limitations to the current study. As we described previously, this is a retrospective design without controls. However, we collected the data of all patients treated with TAF from our wide range of study sites, which allowed us to include a large number of patients aged 65 and over who had comorbidities. Second, our findings at 144 weeks of TAF treatment after switching were similar to those of the week 96 analysis. Nevertheless, longer term data will be required to clarify the effectiveness and safety of switching to TAF, eyeing future trends in HBV treatment. Third, longitudinal data on body weight during the study period were not available. According to recent reports, weight gain could be seen when changing from TDF to TAF in both HIV[27] and HBV-infected populations,[28,29] although the pathophysiological mechanism was unclear. In fact, triglyceride levels were significantly increased in the current study. Therefore, it is important to pay attention to the possible increased risk of cardiovascular events and non-alcoholic steatohepatitis over the long run. Finally, data on renal tubular data, including urinary β2-microglobulin or retinol-binding protein, and bone mineral density are lacking in this cohort; therefore, additional study will be needed to evaluate bone safety after switchover.

In conclusion, TAF remained effective in terms of HBV suppression over the 3 years after switchover, irrespective of the prior NA regimen and renal function at baseline. The virological and renal benefits associated with TAF treatment have the potential to wield favourable influence in the era of an ageing population with CHB. Given the increasing comorbidities associated with ageing, a significant change in the fasting lipid levels of patients with prior TDF-based regimen will be important to consider in the future.

AUTHOR CONTRIBUTIONS

Eiichi Ogawa: Conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (equal); supervision (equal); writing – original draft (lead). **Makoto Nakamuta:** Data curation (equal). **Toshimasa Koyanagi:** Data curation (equal). **Aritsune Ooho:** Data curation (equal). **Norihiro Furusyo:** Data curation (equal). **Eiji Kajiwara:** Data curation (equal). **Kazufumi Dohmen:** Data curation (equal). **Akira Kawano:** Data curation (equal). **Takeaki Satoh:** Data curation (equal). **Kazuhiro Takahashi:** Data curation (equal). **Koichi Azuma:** Data curation (equal). **Nobuyuki Yamashita:** Data curation (equal). **Naoki Yamashita:** Data curation (equal). **Rie Sugimoto:** Data curation (equal). **Hiromasa Amagase:** Data curation (equal). **Masami Kuniyoshi:** Data curation (equal). **Yasunori Ichiki:** Data curation (equal). **Chie Morita:** Data curation (equal). **Masaki Kato:** Data curation (equal). **Shinji Shimoda:** Data curation (equal). **Hideyuki Nomura:** Data curation (equal). **Jun Hayashi:** Conceptualization (equal); project administration (equal); supervision (lead).

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DATA AVAILABILITY STATEMENT

Author elects to not share data.

AUTHORSHIP

Guarantor of the article: Eiichi Ogawa

Author contributions: Eiichi Ogawa was involved with the study concept, writing manuscript, data analysis, and study supervision. All authors contributed to data collections and critical review and/or revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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