Sequential HBV treatment with tenofovir alafenamide for patients with chronic hepatitis B: week 96 results from a real-world, multicenter cohort study

Eiichi Ogawa1 · Makoto Nakamuta2 · Toshimasa Koyanagi3 · Aritsune Ooho4 · Norihiro Furusyo5 · Eiji Kajiwara6 · Kazufumi Dohmen7 · Akira Kawano8 · Takeaki Satoh9 · Kazuhiro Takahashi10 · Koichi Azuma11 · Nobuyuki Yamashita12 · Naoki Yamashita2 · Rie Sugimoto13 · Hiromasa Amagase14 · Masami Kuniyoshi15 · Yasunori Ichiki16 · Chie Morita17 · Masaki Kato18,19 · Shinji Shimoda20 · Hideyuki Nomura21 · Jun Hayashi22 · The Kyushu University Liver Disease Study (KULDS) Group

Received: 26 February 2021 / Accepted: 24 December 2021 / Published online: 25 January 2022 © Asian Pacific Association for the Study of the Liver 2022

Abstract
Background and aims Outcome data of sequential hepatitis B virus treatment with tenofovir alafenamide (TAF) are limited. We aimed to assess the effectiveness and renal safety of TAF in chronic hepatitis B (CHB) patients who were previously treated with entecavir (ETV), tenofovir disoproxil fumarate (TDF), or a nucleos(t)ide analogue (NA) combination.

Methods This multicenter, retrospective, cohort study included 458 consecutive CHB patients who switched to TAF monotherapy after at least 2 years of treatment with another NA. The longitudinal virological/laboratory responses were evaluated up to 96 weeks after switchover. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m².

Results The proportions of complete viral suppression (CVS) (HBV DNA < 20 IU/mL) at week 96 were 99.0%, 98.5%, and 98.4% in the prior ETV (n = 198), TDF (n = 137), and NA combination (n = 123) groups, respectively. Almost all patients with HBV DNA of 20–2000 IU/mL at baseline achieved CVS at week 96. On multivariable generalized estimated equation analysis, a low quantitative hepatitis surface antigen (qHBsAg) level at baseline was associated with a lower follow-up qHBsAg level (coefficient 0.81, p < 0.001). The eGFR showed greater improvement in patients with CKD compared to those without (coefficient 21.7, p < 0.001). However, the increase of eGFR reached a peak between weeks 24 and 48.

Conclusions Based on this longitudinal data analysis up to 96 weeks, sequential NA therapy with a switch to TAF is a good option to achieve high viral suppression and renal safety.

Keywords Hepatitis B virus · Tenofovir alafenamide · Entecavir · Tenofovir disoproxil fumarate · Sequential therapy

Abbreviations
AASLD American Association for the Study of Liver Diseases
ADF Adefovir
ALT Alanine aminotransferase
BMI Body mass index
CHB Chronic hepatitis B
CI Confidence interval
CKD Chronic kidney disease
CVS Complete viral suppression

*Eiichi Ogawa
e.ogawa.a65@m.kyushu-u.ac.jp

Extended author information available on the last page of the article
**Introduction**

Chronic hepatitis B (CHB) remains one of the leading causes of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality worldwide [1, 2]. The decision to initiate treatment is primarily based upon the presence or absence of cirrhosis, the alanine aminotransferase (ALT) level, and the hepatitis B virus (HBV) DNA level [3–5]. Approved first-line antiviral HBV treatment by international guidelines involves either a finite course of pegylated interferon-alpha-2a, which stimulates the natural immune response against HBV, or an oral antiviral nucleos(t)ide analogue (NA), which suppresses replication of HBV, such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) [3–5]. These three NAs have very low rates of drug resistance in NA-naïve patients unlike lamivudine, adefovir, and telbivudine; moreover, tenofovir has very low rates of drug resistance in NA-experienced patients. In contrast, the use of pegylated interferon as primary therapy in patients with CHB has been limited by its poor efficacy and tolerability. Improvement of the quality of life and the survival can be achieved through the elimination of HBV replication by antiviral treatment. Currently, hepatitis B surface antigen (HBsAg) seroclearance is regarded as the functional cure and is uncommon among treated patients [6, 7], thus for almost all patients lifelong NA treatment is necessary. In addition, HBV-related comorbidities, such as cirrhosis, diabetes mellitus, hypertension, and chronic kidney disease (CKD) should be monitored, especially for older patients [3–5].

TAF, the newest NA drug, was approved for use in HBV treatment in Japan at the end of 2016. It is a prodrug of tenofovir, a nucleotide analogue that inhibits reverse transcription of both HBV and human immunodeficiency virus (HIV) [8]. ETV and TDF were approved in 2005 and 2008, respectively, and good virological efficacy has been provided [9–11], although impaired kidney function and decreased bone mineral density have been reported in long-term TDF treatment [12, 13]. According to ongoing phase III trials of the efficacy and safety of TAF vs. TDF for CHB patients [14–16], TAF has been shown to be virologically effective and well tolerated, with improved renal and bone safety for patients switching from TDF. Unfortunately, data on the effectiveness and safety of TAF following switching from ETV or NA combination is limited.

We recently published real-world data on the effectiveness and renal safety of TAF for patients who had previously been treated with ETV or NA combination [17]. Our results showed that the rate of complete viral suppression (CVS) increased and that a continued reduction of the quantitative HBsAg (qHBsAg) level was noted at week 48. Although advantages from the switchover were elucidated, the length of time for follow-up be postswitch was somewhat short. Thus, the purpose of this study was to examine virological, biochemical, and renal outcomes up to 96 weeks in a multicenter, real-world cohort of CHB patients who switched to TAF from ETV, TDF, or NA combination.

**Patients and methods**

**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 multicenter, retrospective, observational cohort study consisted of consecutive patients from March 2017 until December 2018 who switched to a fixed-dose of TAF, 25 mg orally once daily (Vemlidy; Gilead Sciences K.K., Tokyo, Japan).

Eligible patients (1) were aged 18 years and older with confirmed chronic HBV infection, and (2) had NA treatment switching to TAF monotherapy from an at least 2-year course of ETV, TDF, or an NA combination of lamivudine (LAM)/adefovir (ADF), LAM/TDF, ETV/ADF, or ETV/TDF. Exclusion criteria included (1) duration of follow-up under 2 years; (2) positivity for antibody to HIV or positivity for hepatitis C antibody; (3) terminal illness; and (4) insufficient medical records for primary endpoints and objectives.

**Laboratory, and virological assessments**

All patients were followed every 8–12 weeks during TAF treatment. Laboratory assessments included hematological analysis, serum biochemistry tests, and urinalysis, including measures of renal function. The estimated glomerular filtration rate (eGFR) was calculated with the following formulas [18]:

\[ \text{eGFR}_{\text{mL/min/1.73m}^2} = 194 \times \text{serum creatinine level}^{-1.094} \times \text{age}^{-0.287} \]

and for women eGFR

\[ \text{eGFR}_{\text{mL/min/1.73m}^2} = 194 \times \text{Scr}^{-1.094} \times \text{age}^{-0.287} \times 0.739. \]

As a renal safety endpoint, we defined CKD and the lower limit of the serum phosphorus level as an eGFR < 60 mL/min/1.73 m². To evaluate renal safety more accurately, we added 0.5 years to age at week 24, 1.0 year at week 24, 1.5 years at week 72, and 2.0 years at week 96 for the calculation of eGFR. Liver cirrhosis was defined by liver biopsy demonstrating a METAVIR F4 score, transient elastography
(FibroScan®, Echosens, Paris, France) greater than 12.0 kPa [19], or imaging examinations with signs of cirrhosis based on nodularity, portal velocity, liver size, caudate hypertrophy, echogenicity, portal vein diameter, and spleen size. These assessments were performed within 3 months before the initiation of TAF treatment.

**Primary and secondary endpoints**

The primary endpoint was the proportion of patients with CVS (less than 20 IU/mL, the lower limit of quantitation) as determined by real-time reverse transcriptase PCR assay (COBAS TaqMan HBV assay, Version 2.0) (Roche Molecular Diagnostics, Tokyo, Japan) at week 96 after switching to TAF. Key prespecified secondary endpoints were the longitudinal change of ALT, qHBsAg level, and eGFR. A patient was determined to have ALT normalization 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 [3]. Moreover, we calculated complete response rates with both CVS and ALT normalization.

**Statistical analysis**

Statistical analyses were conducted using SPSS Statistics version 25.0 (IBM SPSS Inc, Chicago, IL, USA). Baseline continuous data are expressed as median (first-third quartile) or mean (± standard deviation) and categorical variables are reported as frequencies and percentages. Trends for continuous variables were assessed using the repeated measures ANOVA test. Univariate analyses were done using the Chi-square, Student’s t, Mann–Whitney U test, or Kruskal–Wallis test, as appropriate. We used the multivariable generalized estimating equation (GEE) model adjusted for age, sex, body mass index (BMI), cirrhosis, hypertension, diabetes mellitus, and previous NA regimen to estimate coefficients associated with baseline parameters or factors to changes in ALT, qHBsAg level, and eGFR. The results are expressed as coefficients and their 95% confidence interval (CI). A two-sided p value less than 0.05 was regarded as statistically significant in all analyses.

**Results**

**Patient characteristics**

A total of 478 patients who switched to TAF were identified during the study period. Twenty were excluded in accordance with the criteria, leaving the data of 458 available for analysis. Of the eligible patients, 198 (43.2%) received ETV, 137 (29.9%) TDF, and 123 (26.9%) NA combination before switching to TAF. Demographic and baseline characteristics according to the previous NA treatment are shown in Table 1. Median treatment durations of the previous drug for the ETV, TDF, and NA combination groups were 5.0, 3.2, and 8.8 years, respectively. There were significant differences among these three groups in age (p < 0.001), aspartate aminotransferase (p = 0.038), ALT (p < 0.001), eGFR (p = 0.039), phosphorus (p < 0.001), previous NA treatment duration (p < 0.001), the frequency of hypertension (p = 0.002), HBeAg positive (p = 0.005), and undetectable HBV DNA (p < 0.001). Of the patients with prior ETV monotherapy, 12 (6.1%) had HBV DNA > 2000 IU/mL at baseline. Five of them had started with LAM, developed resistance, and ADF was, therefore, added to LAM. This contributed to an eventual CVS; however, the withdrawal of ADF was required due to ADF-induced Fanconi syndrome caused by the long-term administration. They have since been treated with ETV monotherapy.

**Virological and biochemical responses 96 weeks after switching to TAF**

The proportions of CVS at week 96 after switchover were 99.0% (196/198), 98.5% (135/137), and 98.4% (121/123) in the prior ETV, TDF, and NA combination groups, respectively. Of the 46 patients who had prior ETV with HBV DNA of ≥ 20 IU/mL at baseline, most achieved CVS from the early stage of TAF treatment, and at week 96 the proportion was 95.7% (44/46) (Table 2). For 57 patients who had a history of HCC, all achieved CVS at week 96. Regardless of the prior treatment regimen, none experienced HBV breakthrough during the follow-up period. In contrast, the achievement rates of HBeAg loss for patients HBeAg-positive at baseline remained low; under 30% in all prior treatment groups (Table 2). Even though patients had a low-titer of HBeAg (< 10 S/CO) at baseline, only 35–40% achieved HBeAg loss at week 96.

The longitudinal ALT levels after switching to TAF are shown in Figs. 1, 2 and 3 according to the prior NA regimen. Approximately 80% with prior ETV or NA combination had normal ALT at baseline. This showed no significant trend in the longitudinal levels, although the rates of ALT normalization slightly improved, from 82.3 to 90.4% and 78.0 to 83.7% in the prior ETV and NA combination groups, respectively. In contrast, the prior TDF group, in which the proportion of ALT normalization at baseline was relatively low (71.5%), achieved a significant increase in the rate of ALT normalization (86.1%) (p < 0.05). The proportions of complete response (both ALT normalization and CVS) at week 96 were 89.4%, 85.4%, and 82.9% in the prior ETV, TDF, and NA combination groups, respectively (Supplementary Table 1). There were significant decreases in the qHBsAg level across all timepoints, irrespective of prior NA...
regimen (all \( p < 0.001 \)). Only seven patients (1.5%) achieved HBsAg loss by week 96.

Analysis of the longitudinal eGFR and serum phosphorus level, Figs. 1, 2 and 3, found no significant trend in patients who switched from ETV to TAF. In contrast, the eGFR of patients with CKD who switched from TDF or NA combination improved from the early stage. The increase of eGFR reached a peak between weeks 24 and 48, then decreased slightly over time.

Factors associated with the changes of ALT, qHBsAg level, and eGFR

Results of our analysis of the factors associated with the changes in ALT, qHBsAg level, and eGFR at 96 weeks after switching to TAF are shown in Table 3. After adjusting for age, sex, BMI, cirrhosis, diabetes mellitus, and prior NA regimen, baseline BMI (coefficient 1.69, 95% CI 0.89–2.49, \( p < 0.001 \)) and cirrhosis (coefficient 4.03, 95% CI 0.32–7.74, \( p = 0.033 \)) were associated with a longitudinal change in the ALT level. After adjusting for age, sex, cirrhosis, baseline

| Table 1 | Baseline characteristics according to the previous nucleos(t)ide analogue (NA) treatment |
|-----------------|---------------------------------|-----------------|-----------------|-----------------|
| Previous NA regimen | Entecavir | Tenofovir disoproxil fumarate | NA combination | \( p \) value |
| Number | 198 | 137 | 123 | <0.001 |
| Age (years) | 61 (50–69) | 51 (43–66) | 61 (53–68) | <0.001 |
| Male | 124 (62.6) | 78 (56.9) | 81 (65.9) | 0.32 |
| Body mass index (kg/m\(^2\)) | 22.4 (20.3–24.3) | 22.3 (20.5–24.9) | 22.9 (20.9–25.2) | 0.55 |
| Cirrhosis | 27 (13.6) | 20 (14.6) | 23 (18.7) | 0.46 |
| History of HCC | 19 (9.6) | 16 (11.7) | 22 (17.9) | 0.088 |
| Hypertension | 58 (29.3) | 14 (10.2) | 25 (20.3) | 0.002 |
| Diabetes | 26 (13.1) | 14 (10.2) | 16 (13.0) | 0.70 |
| Albumin (g/L) | 43 (41–45) | 43 (41–45) | 44 (41–46) | 0.93 |
| Total bilirubin (mg/dL) | 0.8 (0.5–1.1) | 0.7 (0.5–1.0) | 0.7 (0.4–1.0) | 0.061 |
| AST (U/L) | 24 (19–29) | 25 (22–32) | 24 (20–30) | 0.038 |
| ALT (U/L) | 20 (14–27) | 24 (18–34) | 20 (16–31) | <0.001 |
| \( \gamma \)GTP (U/L) | 24 (17–44) | 21 (15–40) | 21 (15–42) | 0.26 |
| eGFR (mL/min/1.73 m\(^2\)) | 71 (61–82) | 74 (62–85) | 69 (55–81) | 0.039 |
| Albumin (g/L) | 43 (41–45) | 43 (41–45) | 44 (41–46) | 0.93 |
| Total bilirubin (mg/dL) | 0.8 (0.5–1.1) | 0.7 (0.5–1.0) | 0.7 (0.4–1.0) | 0.061 |
| AST (U/L) | 24 (19–29) | 25 (22–32) | 24 (20–30) | 0.038 |
| ALT (U/L) | 20 (14–27) | 24 (18–34) | 20 (16–31) | <0.001 |
| \( \gamma \)GTP (U/L) | 24 (17–44) | 21 (15–40) | 21 (15–42) | 0.26 |
| eGFR (mL/min/1.73 m\(^2\)) | 71 (61–82) | 74 (62–85) | 69 (55–81) | 0.039 |
| 30–60 | 3 (1.0) | 2 (1.5) | 3 (2.4) | <0.001 |
| 15–<30 | 2 (1.0) | 2 (1.5) | 3 (2.4) | <0.001 |
| Phosphorus (mg/dL) | 3.3 (3.0–3.6) | 3.3 (2.8–3.7) | 3.0 (2.6–3.5) | <0.001 |
| AFP (ng/mL) | 2.9 (2.0–3.4) | 3.0 (2.2–4.4) | 3.0 (2.1–3.7) | 0.094 |
| Platelet count (10\(^3\)/μL) | 178 (146–218) | 184 (144–235) | 183 (139–221) | 0.65 |
| HBV DNA (IU/mL) | 28 (14.1) | 31 (22.6) | 27 (22.0) | 0.005 |
| 20–2000 | 34 (17.2) | 7 (5.1) | 10 (8.1) | 0.005 |
| >2000 | 12 (6.1) | 0 | 0 | 0.005 |
| Previous NA treatment duration (years) | 5.0 (4.3–7.4) | 3.2 (2.6–3.5) | 8.8 (6.2–12.5) | <0.001 |
| Previous NA treatment combination | | | | |
| LAM + ADV | 44 (35.8) | | | |
| LAM + TDF | 39 (31.7) | | | |
| ETV + ADV | 3 (2.4) | | | |
| ETV + TDF | 37 (30.1) | | | |

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

HCC hepatocellular carcinoma, AST aspartate aminotransferase, ALT alanine aminotransferase, \( \gamma \)GTP gamma-glutamyl transpeptidase, eGFR estimated glomerular filtration rate, AFP alpha-fetoprotein, HBeAg hepatitis B e antigen, HBV hepatitis B virus, LAM lamivudine, ADV adefovir, ETV entecavir, TDF tenofovir disoproxil fumarate

\(^a\)Including the duration of time of first NA treatment

\(^b\)Including the duration of time of first NA treatment

\(^c\)Including the duration of time of first NA treatment

\(^d\)Including the duration of time of first NA treatment

\(^e\)Including the duration of time of first NA treatment

\(^f\)Including the duration of time of first NA treatment
HBeAg, baseline qHBsAg level, and prior NA regimen, age (coefficient -7.75, 95% CI − 14.3 to −1.24, \(p=0.020\)) and baseline qHBsAg level (coefficient 0.81, 95% CI 0.74–0.88, \(p<0.001\)) were associated with a longitudinal change in the qHBsAg level. Finally, after adjusting for age, sex, BMI, cirrhosis, diabetes mellitus, hypertension, baseline eGFR, and prior NA regimen, age (coefficient − 0.48, 95% CI −0.60 to −0.36, \(p=0.020\)) and baseline eGFR < 60 (coefficient 21.7, 95% CI 19.2–24.1, \(p<0.001\)) were associated with a longitudinal change in eGFR.

**Discussion**

In our previous cohort study, we showed the virological effectiveness and renal safety 48 weeks after switching to TAF [17]. Other recent studies regarding switching to TAF in CHB treatment have been published for previous ETV [20–22] and TDF [23–25] treatment. We felt that the durability of the results would need confirmation in a longer follow-up. The present study, done post-96 weeks, confirmed the previous findings and clarified the long-term effects of switching to TAF. We divided patients into three groups according to the prior NA regimen (ETV, TDF, or NA combination). Almost all achieved CVS by week be 96 post switchover, even those treated with NA combination. We believe that our study provides important insights into the effectiveness of a switch to TAF for patients with CHB who had been treated with older NAs.

Virological efficacy, including CVS and a decrease of the qHBsAg level, has contributed to a decline of the HCC incidence rate, especially for patients with cirrhosis [26–28]. Thus, the underlying histology would be helpful for making therapeutic decisions. A liver biopsy is usually recommended to determine the stage of fibrosis; however, the diagnostic accuracy of liver biopsy is imperfect.
because of the possible sampling error or intra- and inter-observer variability in histological interpretation [29]. Therefore, the role of imaging for evaluating fibrosis has been increasing recently. Radiographic techniques, including transient elastography, magnetic resonance (MR) elastography, acoustic radiation force impulse imaging, and diffusion-weighted MR imaging have been introduced, and they are being increasingly used to assess the severity of liver disease in clinical practice [3–5, 19, 30–33]. One of the major roles of these non-invasive imaging tools is to provide a surveillance tool that predicts clinical outcome and long-term prognosis, which would lead to better determination of treatment strategies.

In our prior ETV group, the CVS rate at the time of switch was 76.8%. The CVS rate significantly increased to 98.0% at 48 week postschist and to 99.0% at 96 week
postswitch. According to a similar real-world cohort study, the CVS rate significantly improved from 91.9% at the time of switch to 95.6% and 97.2% at 48 and 96 weeks, respectively [22]. In fact, the CVS rate of the group that switched to TAF was significantly higher than their continuous ETV group [21]. Improvement of the CVS rate was also seen in the prior TDF and NA combination groups in this study. The finding of virological improvement after switchover was consistent with other recent reports, irrespective of prior NA and follow-up duration [21, 22, 25]. These incremental improvements following switching to TAF were significant, even though our patients had already received NA treatment for an average duration of more than 7 years. It is noteworthy that none of the patients under a controlled virological condition by a prior NA regimen experienced viral breakthrough during 96 weeks after switchover. In contrast, virological

---

**Fig. 2** Longitudinal change in a ALT, b qHBsAg level, c eGFR, and d serum phosphorus level from baseline to 96 weeks after switching from TDF to TAF. Bars are expressed as mean ± standard deviation.

**Switch from TDF to TAF**

**a** ALT (U/L)

- Non-cirrhosis
- Cirrhosis

**b** HBsAg (logIU/mL)

- HBsAg ≥ 3.0
- HBsAg < 3.0

**c** eGFR (mL/min/1.73m²)

- eGFR ≥ 60
- eGFR < 60

**d** Phosphorus (mg/dL)

- eGFR ≥ 60
- eGFR < 60

**ALT** alanine aminotransferase, **qHBsAg** quantitative hepatitis B surface antigen, **eGFR** estimated glomerular filtration rate, **TDF** tenofovir disoproxil fumarate, **TAF** tenofovir alafenamide
response with HBeAg loss was not adequately achieved at week 96. For those with a low-titer of HBeAg (< 10 S/CO) at baseline, fewer than half experienced HBeAg loss. The rate of HBsAg loss remained very low, and the decline in the qHBsAg levels were small (approximately 0.1 logIU/mL annually). When comparing other studies regarding longitudinal HBsAg levels, the reductions of the HBsAg levels were almost the same and HBsAg significantly declined over the 96 week follow-up period [20, 22]. Moreover, a lower qHBsAg level at baseline was significantly associated with a decreased qHBsAg level.

We did not observe significant positive changes in the rates of ALT normalization at 96 weeks after switching to TAF. More patients in the prior TDF group who had an elevated ALT level at baseline achieved ALT normalization, similar to a recent report [25]; however, those who had

Fig. 3 Longitudinal change in a ALT, b qHBsAg level, c eGFR, and d serum phosphorus level from baseline to 96 weeks after switching from NA combination to TAF. Bars are expressed as mean ± standard deviation. ALT alanine aminotransferase, qHBsAg quantitative hepatitis B surface antigen, eGFR estimated glomerular filtration rate, NA nucleos(t)ide analogue, TAF tenofovir alafenamide
higher baseline BMI and cirrhosis were less likely to have an improvement in the ALT level at 96 weeks after adjustment for confounding factors. It is important to note that replacing TDF with TAF has been associated with weight increase and worsening serum lipid levels in patients with HIV [34], although the mechanism has not been well clarified. We suggest that further study of metabolic change and steatohepatitis will be warranted in the monitoring of HBV patients with elevated ALT levels who switch to TAF.

The high prevalence of renal dysfunction highlights the long-term need for careful monitoring or switching to TAF from ADF or TDF treatment, as is recommended in the guidelines [3, 4]. Phase III clinical trials in which virologically suppressed CHB patients were switched from TDF to TAF have shown significant improvements in kidney parameters at week 96 after switching [35]. On the other hand, a recent real-world cohort study has shown that there was no significant improvement in the mean eGFR after switching from TDF to TAF, irrespective of CKD stage at the time of switch [25]. In our study, it is important to note that the incremental improvements following switching to TAF peaked between 24 and 48 weeks then decreased physiologically, but without a statistically significant trend. In our multivariable GEE analysis that controlled cofounding factors with kidney function, patients of older age and without CKD were less likely to experience positive changes in eGFR.

One of the strengths of this study was the inclusion of patients with prior ETV or NA combination therapy, all of whom were treated with TAF for at least 96 weeks. In general, patients with CKD also had a significantly higher risk of eGFR decline than those non-CKD under the same condition of receiving NA. ADF and TDF are both associated with a dose-dependent, but usually reversible, proximal renal tubular toxicity [36], and pre-existing renal sufficiency in ETV treatment is also a risk factor for declining eGFR [37]. There was no statistically significant trend in eGFR over time for patients with or without CKD: the decrement was approximately 0.75 mL/min/1.73 m² per year for elderly persons [38], which is considered to be physiological reduction. Taken together, it seems reasonable that there were a variety of trends of eGFR change between CKD and non-CKD after switchover, especially in light of the enrollment of many patients 65 and over.

Data on the 96 weeks after TAF switchover is currently lacking, so longer term follow-up will be needed to fully characterize the virological and safety profiles. In addition to the fact that our patients had been previously treated with ETV or NA combination, the strengths of this study are that it included many patients 65 and over (n = 167) and CKD patients (n = 114), which empower our interpretation. Moreover, we used GEE modeling, which controls for collinearity across variables, allows a bigger sample size to be examined, and makes it possible to better evaluate the related factors for improvements of ALT, qHBsAg level, and eGFR.

This study has several limitations. First, control with continuing NA groups and data on bone mineral density are lacking. Such data will be necessary in future study to better determine differences in clinical outcomes. However, we have provided the data of 458 patients who have been treated with TAF for 96 weeks and, to our knowledge, this is one of the largest real-world studies of sequential treatment with TAF. Second, there is possible selection bias in the
switching of the patients to TAF monotherapy, because we were unable to determine in detail each clinician’s rationale for switching. Learning the background of and/or reasons for the switch for each patient would be more useful to more deeply understand the outcomes. We can surmise that most of the clinicians expected improved adherence to treatment, based on a recent study that suggested that patients who were switched to TAF had better adherence [39]. Last, we have not shown detailed data on the NA drug resistance profile for patients with HBV DNA > 2000 IU/mL at baseline. Further information regarding the resistance profile would be helpful for the monitoring of intractable cases.

In summary, switching the drug used in HBV treatment to TAF was effective for HBV suppression and continued qHBsAg reduction at 96 weeks. Patients with CKD who were previously treated with TDF or NA combination had a favorable outcome, with an improvement of eGFR within 1 year of switchover that was maintained over the 96 weeks of study.

**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1007/s12072-021-10295-3](https://doi.org/10.1007/s12072-021-10295-3).

**Author contributions** All authors were involved in the design of the study, acquisition of samples and/or analysis. EO drafted the manuscript. All authors contributed to the critical discussion of the results and approved the final version of the article.

**Funding** This study was funded by Gilead Sciences.

**Declarations**

**Conflict of interest** Eiichi Ogawa has received speaker fees from Gilead Sciences and AbbVie. Makoto Nakamuta, Toshimasa Koyanagi, Arisune Ooho, Norhiro Furusyo, Eiji Kajiwara, Kazufumi Dohmen, Akira Kawano, Takeaki Sato, Kazuhiko Takahashi, Koichi Azuma, Nobuyuki Yamashita, Naoki Yamashita, Rie Sugimoto, Hiromasa Amagase, Masami Kuniyoshi, Yasunori Ichiki, Chie Morita, Masaki Kato, Shinji Shimoda, Hideyuki Nomura, and Jun Hayashi declare that they have no conflicts of interest.

**Ethical approval** The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the STROBE statement. It was approved by the Ethics Committees of Kyushu University Hospital and each study site and is registered as a clinical study on the University Hospital Medical Information Network (ID 000034696).

**References**

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–2128
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546–1555
3. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560–1599
4. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–398
5. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B. a 2015 update. Hepatol Int. 2016;10:1–98
6. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol. 2016;67:847–861
7. Cornberg M, Lok AS, Terrault NA, Zoulim F. EASL-AASLD HBV treatment endpoints conference faculty. Guidance for design and endpoints of clinical trials in chronic hepatitis B—report from the 2019 EASL-AASLD HBV treatment endpoints conference. J Hepatol. 2019;2020(72):539–557
8. Ogawa E, Furusyo N, Nguyen MH. Tenofovir alafenamide in the treatment of chronic hepatitis B: design, development, and place in therapy. Drug Des Devel Ther. 2017;11:3197–3204
9. Lok AS, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology. 2016;63:284–306
10. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology. 2010;139:1218–1229
11. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: a review. JAMA. 2018;319:1802–1813
12. Casado JL. Renal and bone toxicity with the use of tenofovir: understanding at the end. AIDS Rev. 2016;18:59–68
13. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci. 2015;60:1457–1464
14. Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:185–195
15. Buti M, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:196–206
16. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68:672–681
17. Ogawa E, Nomura H, Nakamuta M, Furusyo N, Koyanagi T, Dohmen K, et al. Tenofovir alafenamide after switching from entecavir or nucleos(t)ide combination therapy for patients with chronic hepatitis B. Liver Int. 2020;40:1578–1589
18. Matsu S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–992
19. Ogawa E, Furusyo N, Murata M, Ohnishi H, Toyoda K, Tanai H, et al. Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with nucleoside analog. Hepatol Res. 2011;41:1178–1188
20. Uchida Y, Nakao M, Tsuji S, Uemura H, Koyama JI, Naiki K, et al. Significance of switching of the nucleos(t)ide analog used
Authors and Affiliations

Eiichi Ogawa · Makoto Nakamuta · Toshimasa Koyanagi · Aritsune Ooho · Norihiro Furusyo · Eiji Kajiwara · Kazufumi Dohmen · Akira Kawano · Takeaki Satoh · Kazuhiro Takahashi · Koichi Azuma · Nobuyuki Yamashita · Naoki Yamashita · Rie Sugimoto · Hiromasa Amagase · Masami Kuniyoshi · Yasunori Ichiki · Chie Morita · Masaki Kato · Shinji Shimoda · Hideyuki Nomura · Jun Hayashi · The Kyushu University Liver Disease Study (KULDS) Group

1 Department of General Internal Medicine, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
2 Department of Gastroenterology, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan
3 Department of Medicine, Fukuoka City Hospital, Fukuoka, Japan
4 Department of Hepatology, Steel Memorial Yawata Hospital, Kitakyushu, Japan
5 General Internal Medicine, Taihaku Avenue Clinic, Fukuoka, Japan
6 Kajiwara Clinic, Kitakyushu, Japan
7 Department of Internal Medicine, Chihaya Hospital, Fukuoka, Japan
8 Department of Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan
9 Center for Liver Disease, Kokura Medical Center, National Hospital Organization, Kitakyushu, Japan
10 Department of Medicine, Hamanomachi Hospital, Fukuoka, Japan
11 Department of Medicine, Kyushu Central Hospital, Fukuoka, Japan
12 The Center for Liver Disease, Shin-Kokura Hospital, Kitakyushu, Japan
13 Department of Gastroenterology, Kyushu Cancer Center, Fukuoka, Japan
14 Amagase Clinic, Kitakyushu, Japan
15 Department of Gastroenterology, Kyushu Rosai Hospital, Kitakyushu, Japan
16 Department of Internal Medicine, JCHO Kyushu Hospital, Kitakyushu, Japan
17 Department of Internal Medicine, Kyushu Railway Memorial Hospital, Kitakyushu, Japan
18 Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
19 Graduate School of Nutritional Sciences, Nakamura Gakuen University, Fukuoka, Japan
20 Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
21 Department of Internal Medicine, Haradoi Hospital, Fukuoka, Japan
22 Kyushu General Internal Medicine Center, Haradoi Hospital, Fukuoka, Japan