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

Eiichi Ogawa1 | Makoto Nakamuta2 | Toshimasa Koyanagi3 | Aritsune Ooho4 | Norihiro Furusyo5 | Eiji Kajiwara6 | Kazufumi Dohmen7 | Akira Kawano8 | Takeki Satoh9 | Kazuhiko 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

1Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan
2Department of Gastroenterology, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan
3Department of Medicine, Fukuoka City Hospital, Fukuoka, Japan
4Department of Hepatology, Steel Memorial Yawata Hospital, Kitakyushu, Japan
5General Internal Medicine, Taihaku Avenue Clinic, Fukuoka, Japan
6Kajiwara Clinic, Kitakyushu, Japan
7Department of Internal Medicine, Chihaya Hospital, Fukuoka, Japan
8Department of Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan
9Center for Liver Disease, Kokura Medical Center, National Hospital Organization, Kitakyushu, Japan
10Department of Medicine, Hamanomachi Hospital, Fukuoka, Japan
11Department of Medicine, Kyushu Central Hospital, Fukuoka, Japan
12The Center for Liver Disease, Shin-Kokura Hospital, Kitakyushu, Japan
13Department of Gastroenterology, Kyushu Cancer Center, Fukuoka, Japan
14Amagase Clinic, Kitakyushu, Japan
15Department of Gastroenterology, Kyushu Rosai Hospital, Kitakyushu, Japan
16Department of Internal Medicine, JCHO Kyushu Hospital, Kitakyushu, Japan
17Department of Internal Medicine, Kyushu Railway Memorial Hospital, Kitakyushu, Japan
18Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
19Graduate School of Nutritional Sciences, Nakamura Gakuen University, Fukuoka, Japan
20Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
21Department of Internal Medicine, Haradoi Hospital, Fukuoka, Japan
22Kyushu University, Fukuoka, Japan
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. 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. 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. 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, 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. TDF causes declines in renal function and gradually reduces bone mineral density. In addition, HBV itself plays a pivotal role in the acquisition and progression of chronic kidney disease (CKD) because of glomerular dysfunction. 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. 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, 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. 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; 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/1.73 m², based on pharmacokinetics data modelling. We have three patterns for switching to TAF. First, patients with older age (>60 years), deteriorating renal function (eGFR<60 ml/min/1.73 m²) 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. 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: for men, eGFR (mL/min/1.73 m²) = 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/1.73 m². 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.

2.4 | 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
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 switching 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...
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/1.73m²) 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 <60ml/min/1.73m²) 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 <20IU/ml (%) | Percentage (%) | p value | Number of ALT<35 (male) / 25 (female) U/L | Percentage (%) | p value |
|--------------|--------|--------------------------------|----------------|---------|------------------------------------------|----------------|---------|
| Overall      | 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 | 387                             | 99.0           | <0.001  | 344                                      | 88.0           | <0.001  |

| Prior ETV    | 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 | 172                             | 98.9           | <0.001  | 155                                      | 89.1           | 0.12    |

| Prior TDF    | 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 | 115                             | 99.1           | 0.10    | 99                                       | 85.3           | 0.016   |

| Prior NA combo | 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 | 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.

*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 viremia 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.
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).
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 20–200 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;\textsuperscript{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,\textsuperscript{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 normalization (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,\textsuperscript{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.\textsuperscript{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\textsuperscript{27} and HBV-infected populations,\textsuperscript{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 j2-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 Nakamura: Data curation (equal). Yoshimasa Koyanagi: Data curation (equal). Aritsune Ooho: Data curation (equal). Norihiro Furusyo: Data curation (equal). Eiji Kajiwara: Data curation (equal). Kazufumi Dojmen: Data curation (equal). Akira Kawano: Data curation (equal). Takeshi Satoh: Data curation (equal). Koichi Azuma: Data curation (equal). Nobuyuki Yamashita: Data curation (equal). Naoki Yamashita: Data curation (equal). Rie Sugimoto: Data curation (equal). Hideyuki Nomura: Data curation (equal). Jun Hayashi: Conceptualization (equal); project administration (equal); supervision (lead).

ACKNOWLEDGEMENTS

Declaration of personal interests: Ogawa E has received research grants from Gilead Sciences and speaker fees from Gilead Sciences and AbbVie. Other authors declare that they have no conflicts of interest.

Declaration of funding interests: This work was funded by Gilead Sciences.

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.

ORCID

Eiichi Ogawa https://orcid.org/0000-0002-5082-3967

REFERENCES

1. World Health Organization. Hepatitis B fact sheet. Published online 27 July, 2021. Accessed 14 February, 2022. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
2. Terrault NA, ASF L, BJ MM, 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;67:1560–99.
3. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–98.
4. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.
5. Baldick CJ, Eggers BJ, Fang J, Levine SM, Pokornowski KA, Rose RE, et al. Hepatitis B virus quasispecies susceptibility to entecavir confirms the relationship between genotypic resistance and patient virologic response. J Hepatol. 2008;48:895–902.
6. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside- naïve patients is rare through 5 years of therapy. Hepatology. 2009;49:1503–14.
7. Gara N, Zhao X, Collins MT, Chong WH, Kleiner DE, Jake Liang T, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. Aliment Pharmacol Ther. 2012;35:1317–25.
8. Gill US, Zissimopoulos A, Al-Shamma S, Burke K, MJ MP, Barr DA, et al. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: can the fracture risk assessment tool identify those at greatest risk? J Infect Dis. 2015;211:374–82.
9. Cacoub P, Asselah T. Hepatitis B virus infection and extra-hepatic manifestations: a systemic disease. Am J Gastroenterol. 2022;117:253–63.
10. Nguyen MH, Lim JK, Burak Ozbay A, Fraysse J, Loui I, Meyer N, et al. Advancing age and comorbidity in a US insured population-based cohort of patients with chronic hepatitis B. Hepatology. 2019;69:597–73.
11. Wong GL, Wong VW, Yuen BW, Tse YK, Luk HW, Yip TC, et al. An aging population of chronic hepatitis B with increasing comorbidities: a territory-wide study from 2000 to 2017. Hepatology. 2020;71:444–55.
12. 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;68:672–81.
13. Ogawa E, Nakamura M, Koyanagi T, Ooho A, Furusyo N, Kajiwara E, et al. Sequential HBV treatment with tenofovir alafenamide for patients with chronic hepatitis B: week 96 results from a real-world, multicenter cohort study. Hepatol Int. 2022;16:282–93.
14. Custodio JM, Fordyce M, Garner W, Vimal M, Ling KHJ, Kearney BP, et al. Pharmacokinetics and safety of tenofovir alafenamide in HIV-infected subjects with severe renal impairment. Antimicrob Agents Chemother. 2016;60:5135–40.
15. Matsuo 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;53:982–92.
16. Lampertico P, Buti M, Fung S, Ahn SH, Chuang WL, Tak WY, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol. 2020;5:441–53.
17. Byun KS, Choi J, Kim JH, Lee YS, Lee HC, Kim YJ, et al. Tenofovir alafenamide for drug-resistant hepatitis B: a randomized trial for switching from tenofovir disoproxil fumarate. Clin Gastroenterol Hepatol. 2022;20:427–37.
18. Fong TL, Lee BT, Tien A, Chang M, Lim C, Ahn A, et al. Improvement of bone mineral density and markers of proximal renal tubular function in chronic hepatitis B patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. J Viral Hepat. 2019;26:561–7.
19. Toyoda H, Leong J, Landis C, Atsukawa M, Watanabe T, Huang DQ, et al. Treatment and renal outcomes up to 96 weeks after tenofovir alafenamide switch from tenofovir disoproxil fumarate in routine practice. Hepatology. 2021;74:656–66.
20. Philips CA, Ahamed R, Abduljaleel JK, Rajesh S, Augustine P. Critical updates on chronic hepatitis B virus infection in 2021. Cureus. 2021;13:e19152.
21. Li ZB, Li L, Niu XX, Chen SH, Fu YM, Wang CY, et al. Switching from entecavir to tenofovir alafenamide for chronic hepatitis B patients with low-level viraemia. Liver Int. 2021;41:1254–64.
22. Uchida Y, Nakao M, Tsuji S, Uemura H, Koyama JI, Naiki K, et al. Significance of switching of the nucleos(t)ide analog used to treat Japanese patients with chronic hepatitis B virus infection from entecavir to tenofovir alafenamide fumarate. J Med Virol. 2020;92:329–38.
23. Hagiwara S, Nishida N, Ueshima K, Yoshida A, Minami Y, Kudo M. Comparison of efficacy and safety of entecavir and switching from entecavir to tenofovir alafenamide fumarate in chronic hepatitis B: long-term effects from a prospective study. Hepatol Res. 2021;51:767–74.
24. Wong G, Kurosaki M, Zur R, Sherman S, Nguyen MH, Yatsuhashi H. Increasing age and comorbidities in 43,316 adult patients with chronic hepatitis B from 2011 to 2016 in Japan: results of a real-world analysis. Hepatol Int. 2018;12(Supple 2):S264–5.
25. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. AIDS Patient Care STDS. 2008;22:99–103.
26. Lee D, Yun BC, Seo KI, Han BH, Lee SU, Park ET, et al. Risk factors associated with hypophosphatemia in chronic hepatitis B patients treated with tenofovir disoproxil fumarate. Medicine (Baltimore). 2019;98:e18351.
27. Gomez M, Seybold U, Roider J, Härtger G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017. Infection. 2019;47:95–102.
28. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients. JGH Open. 2020;5:258–63.
29. Yeh ML, Liang PC, Trinh S, Huang CI, Huang CF, Hsieh MY, et al. Body weight changes in treated hepatitis B patients switching to tenofovir alafenamide. J Formos Med Assoc. 2021;121:1273–82.

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