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Original Article

Five-year Treatment with Tenofovir Alafenamide Achieves High Rates of Viral Suppression, Alanine Aminotransferase Normalization, and Favorable Bone and Renal Safety in Chinese Chronic Hepatitis B Patients

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Abstract

Background and Aims: After 3-years (144 week) of double-blind treatment in Chinese chronic hepatitis B patients in two ongoing phase 3 studies, tenofovir alafenamide (TAF) showed similar efficacy to tenofovir disoproxil fumarate (TDF), with improved renal and bone safety. In this study, we aimed to report the 5-year results from 2 years into the open-label TAF treatment phase. ***Methods:*** All participants completing the 144-week double-blind treatment were eligible to receive open-label TAF 25 mg once daily up to week 384. Serial analysis of viral suppression (hepatitis B virus DNA <29 IU/mL), alanine aminotransferase normalization, serological responses, and safety outcomes at year 5 (week 240) was performed. ***Results:*** The open-label phase included 93% (311/334) of the enrolled participants, which included 212 who switched from double-blind TAF to open-label TAF (TAF-TAF) and 99 who switched from double-blind TDF to open-label TAF (TDF-TAF). Baseline characteristics were comparable. Week 240 viral suppression rates were similar between groups [93.4% vs. 93.9%; difference: −1.5%, (95% CI: −6.4 to −3.5), p=0.857]. Alanine aminotransferase normalization and serological response rates were higher in the TAF-TAF group than in the TDF-TAF group. The frequencies of adverse events and laboratory abnormalities were low and similar between groups. Both groups had similar small numerical declines from baseline in estimated glomerular filtration rate at year 5 (week 240, −2.85 mL/min vs. −3.29 mL/min, p=0.910). The greater declines in renal and bone parameters in the TDF-TAF group through week 144 improved after switching to TAF. ***Conclusions:*** The 5-year TAF treatment efficacy was high and similar to that of 3-year TDF followed by 2-year TAF in Chinese chronic hepatitis B patients. Favorable effects on bone and renal parameters were sustained with TAF treatment alone and were observed following the switch from TDF to TAF.

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Keywords: Chronic hepatitis B; Antiviral therapy; Bone safety; Renal safety; Tenofovir alafenamide; Tenofovir disoproxil fumarate; Chinese.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AE, adverse event; ALT, alanine aminotransferase; β_2M:Cr, beta 2-microglobulin-to-creatinine ratio; BMD, bone mineral density; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; CKD, chronic kidney disease; DXA, dual energy X-ray absorptiometry; $eGFR_{CG}$, estimated glomerular filtration rate by the Cockcroft-Gault equation; HBV, hepatitis B virus; HDL, high-density-lipoprotein; LDL, low-density lipoprotein; OL FAS, open-label full analysis set; OL SAS, open-label safety analysis set; pol/RT, polymerase/reverse transcriptase; RBP:Cr, retinol binding protein to creatinine ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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Introduction

Hepatitis B virus (HBV) infection remains a major public health problem worldwide. As estimated by the World Health Organization, 296 million people were chronically infected with HBV worldwide in 2019, with 1.5 million new infections each year.[1] With the largest population in the world and a high disease prevalence, there are over 80 million people living with chronic HBV infection in China, accounting for more than one-third of the global disease burden.[2] In the absence of effective treatment, chronic HBV infection can lead to liver fibrosis and cirrhosis, decompensated liver disease, and/or the development of hepatocellular carcinoma.[3] As a major cause of mortality, HBV infection resulted in 820,000 deaths worldwide in 2019,[1] and over 300,000 deaths occur annually in China from HBV-related liver complications.[4]

Tenofovir alafenamide (TAF) is a novel oral prodrug of tenofovir. Compared with tenofovir disoproxil fumarate (TDF), which has been a recommended first-line therapy for chronic hepatitis B (CHB) patients for over a decade,[5,6] the pharmacokinetic/pharmacodynamic profile of TAF allows enhanced hepatic delivery of active drug and thereby reduces systemic exposure to tenofovir relative to TDF, resulting in improved renal and bone safety.[7,8] In two similarly designed, ongoing, pivotal, international (exclusive of China) phase 3 randomized studies involving treatment-naïve and experienced participants with hepatitis B e antigen (HBeAg)-positive (study 110, NCT01940471) or HBeAg-negative (study 108, NCT01940341) CHB, TAF has demonstrated non-inferior efficacy and better renal and bone safety profiles compared with TDF at weeks 48 and 96.[9–11] In a separate cohort of HBeAg-positive and HBeAg-negative CHB patients studied in mainland China (study 108, NCT02836249 and study 110, NCT02836236), results through 3 years (week 144) from the double-blind phase provided efficacy and safety findings to compliment those reported previously for the international cohort.[12] As such, TAF is now recommended as a first-line therapy for CHB alongside TDF in many countries, including China.[13–16]

The TAF registration studies (study 108, HBeAg-negative and study 110, HBeAg-positive) will continue for 8 years (384 weeks) both internationally and within China. Five-year (week 240) results from the international cohort confirm the favorable long-term safety of TAF.[17] Here we report the 5-year (week 240) efficacy and safety results from the China 108 and 110 cohorts. We highlight findings from both studies, including the long-term efficacy and safety of continuous TAF treatment as well as the impact of switching to TAF after receiving 3 years of TDF treatment.

Methods

Participants and study design

Studies 110 and 108 are both phase 3, randomized (2:1) design and conducted in China, enrolling both treatment-naïve and experienced HBeAg-positive and HBeAg-negative CHB participants. Eligible participants were ≥18 years of age, hepatitis B surface antigen (HBsAg)-positive for ≥6 months, with HBV DNA levels ≥20,000 IU/mL, and alanine transaminase (ALT) levels of >60 U/L for men and >38 U/L for women. Participants with an estimated glomerular filtration rate by the Cockcroft-Gault equation ($eGFR_{CG}$), of <50 mL/m, decompensated liver disease, evidence of hepatocellular carcinoma, or coinfection with hepatitis C, hepatitis D, or human immunodeficiency virus were excluded. The complete inclusion and exclusion criteria have been previously described.[12]

As shown in Figure 1, the studies consisted of two phases, a double-blind phase where participants received TAF 25 mg or TDF 300 mg (with a matched placebo for the alternative treatment) once daily through week 144, and an open-label phase in which all participants received TAF 25 mg once daily up to week 384 (i.e. for an additional 5 years after week 144). All participants who completed the double-blind treatment were eligible to enter the open-label extension phase. For the entire duration of the study, participants and investigators remained blinded to the initial treatment assignment. Herein, we present the results at year 5 (week 240), a prespecified time for study endpoint analysis. The two studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocols were approved by the institutional review board or independent ethics committees at all participating sites. All participants provided written informed consent before enrollment. This study was reported following the CONSORT checklist (Supplementary Table 1).

Procedures

Study visits occurred every 4, 8, and 12 weeks in the first, second, and third year of the double-blind phase[12] and every 24 weeks of the open-label phase. Plasma HBV DNA levels, serum ALT, and serum HBV serological markers were assessed at each visit. Other laboratory assessments included serum chemistries, hematological analyses, fasting lipid profile, and measures of renal function and proteinuria including the $eGFR_{CG}$, retinol binding protein to creatinine ratio (RBP:Cr), and the beta 2-microglobulin-to-creatinine ratio (β_2M:Cr), both of which are markers of proximal tubule function. Changes in bone mineral density (BMD) at the lumbar spine and hip were serially assessed by dual energy X-ray absorptiometry (DXA) scans. DXA scans were performed at screening/baseline, every 24 weeks during the double-blind phase and every 48 weeks during the open-label phase in a subset at sites where DXA scanners were available. Fibrosis was assessed using serum FibroTest (BioPredictive SAS, Paris, France) at screen-

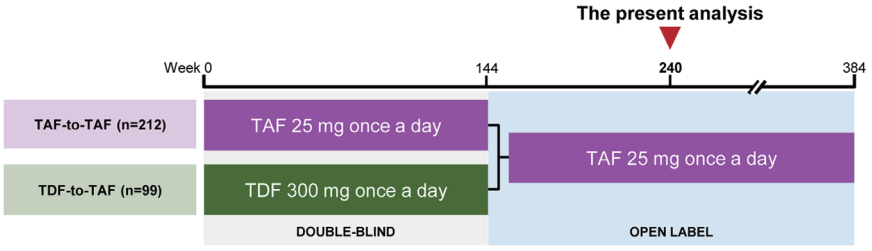

Fig. 1. Study design. Participants were randomized (2:1) to receive either TAF or TDF during the first 144-week, double-blind phase. From week 144 onwards, all participants received open-label TAF treatment. TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

ing and every 48 weeks thereafter. Adverse events (AEs) and graded laboratory abnormalities were cumulatively assessed and summarized. This study was ongoing during the coronavirus disease 2019 (COVID-19) pandemic which had an impact on the conduct of regular visits and, in some cases, resulted in visit disruption. For participants who were unable to attend onsite visits due to COVID-19-related restrictions, a remote study visit was conducted to assess safety. Every effort was made to ensure participants had a continuous supply of study medication during this period.

Outcomes

The primary efficacy endpoint for the 5-year (week 240) analysis was the proportion of participants with HBV DNA <29 IU/mL. Other efficacy endpoints included the proportion of participants with ALT normalization: 40 U/L was chosen as the upper limit of normal (ULN) to reflect the clinical practice in China; a separate analysis using the 2018 American Association for the Study of Liver Diseases (AASLD) criteria (35 U/L for men and 25 U/L for women)[15] was also conducted. As recent studies have suggested that the ULN for ALT should be lower than these,[9–11,18–21] we also conducted additional sensitivity analyses using a lower threshold of 30 U/L for men and 19 U/L for women. The proportion of participants with serological responses, i.e. HBeAg loss with or without seroconversion to antibody to HBeAg (anti-HBe) among those who were HBeAg positive at baseline and HBsAg loss with or without seroconversion to antibody to HBsAg (anti-HBs), and quantitative change in HBsAg, were also reported. Shifts in fibrosis scores from baseline were assessed based on three predefined FibroTest score categories, 0.00 to 0.48 (approximately equivalent to Metavir F0 or F1; no/minimal fibrosis), 0.49 to 0.74 (F2 or F3; moderate to severe fibrosis), and 0.75 to 1.00 (F4; cirrhosis).

AEs and graded laboratory abnormalities were treatment-emergent (i.e. occurring during or after study drug treatment). As AEs and graded laboratory abnormalities that occurred during the double-blind phase have been reported in detail previously,[12] only those occurring during the open-label phase (from the first dose of open-label TAF treatment onward) were included in this analysis. Other safety endpoints included the changes from baseline in $eGFR_{CG}$, spine and hip BMD, fasting lipid parameters, fasting glucose, and body weight, for which serial analyses were performed over 5 years (240 weeks).

Resistance analysis

The resistance analyses have been reported in detail previously.[12] Genotyping of the HBV polymerase/reverse transcriptase (pol/RT) sequence was conducted at baseline for all participants. Phenotyping was performed for participants with virologic breakthrough (defined as HBV DNA ≥69 IU/mL at two consecutive visits if previously confirmed as <69 IU/mL, or confirmed as a ≥1 $\log_{10}$ increase in HBV DNA from nadir) and any pol/RT amino acid change. Additionally, participants were phenotyped if they had a viral blip (defined as HBV DNA ≥69 IU/mL at only one visit) or persistent viremia (defined as HBV DNA ≥69 IU/mL at all scheduled visits) and pol/RT changes in a conserved position or a polymorphic site substitution, provided the latter change was observed in more than one participant. Participants who had early treatment discontinuation were also phenotyped if viremic.

Statistical analysis

Noninferior efficacy of TAF compared with TDF was previously established in the global (non-China) study population;[9–11,22] therefore the representative sample sizes for these two studies in China were determined based on local requirements for demonstrating comparable efficacy and safety for new drug registration in China.[12] Similarly, as the efficacy and safety of TAF have been demonstrated to be generally comparable between HBeAg-positive and HBeAg-negative patient populations in both the global (non-China) and the China cohorts,[9–12] data for the China cohort were pooled for studies 110 and 108 in this analysis. All efficacy endpoints were analyzed in the open-label full analysis set (OL FAS), defined as all randomized participants who received at least one dose of an open-label study drug. Safety endpoints, such as AEs, graded laboratory abnormalities, were analyzed in the open-label safety analysis set (OL SAS), defined as all randomized participants who received at least one dose of an open-label study drug.

The statistical analyses and data reporting methods were consistent with those previously described.[12] A missing-equals-to-failure approach was used for all binary outcomes. For primary efficacy and safety endpoints, exploratory analyses were performed for between-group differences, with two-sided 95% confidence intervals (CIs) and *p*-values reported where appropriate. For HBV DNA <29 IU/mL, p-values were by Cochran-Mantel-Haenszel test stratified by baseline HBV DNA categories and antiviral treatment status (naive vs experienced), and proportional difference between treatments and its 95% confidence intervals by Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and treatment status. AEs were coded using the Medical Dictionary for Regulatory Activities version 23.1, and laboratory abnormalities were reported as participant numbers and percentages. Other study endpoints were summarized using conventional descriptive statistics.

Results

Participant disposition and baseline characteristics

Between June 19, 2015 and March 30, 2016, 336 participants were randomized and 334 received double-blind treatment (TAF: 227; TDF: 107). Of those, 311 completed the 144-week double-blind study treatment and entered the open-label phase (TAF-TAF: 212; TDF-TAF: 99). By year 5 (week 240), nine participants in the TAF-TAF arm and three participants in the TDF-TAF arm discontinued the open-label treatment. A full description of the participant disposition is reported in Supplementary Figure 1.

The mean age of all participants included in the analysis (OL SAS, n=311) was 39 years, 16.7% were ≥50 years of age, and 74.0% were male. The mean HBV DNA was 6.4 $\log_{10}$ IU/mL, the median ALT was 86 U/L, and 53.1% of the participants were HBeAg-positive. The mean (standard deviation) FibroTest score was 0.42 (0.232), with 11.5% (35/304) having a score ≥0.75. Of the participants, 37.9% had prior use of oral nucleos(t)ides and 15.1% had used interferon. The baseline median $eGFR_{CG}$ was 112.4 mL/min. In the hip DXA and spine DXA analysis sets, baseline evidence of bone loss (osteopenia or osteoporosis based on the T-score) was present in 38.2% and 58.4% of participants respectively. Consistent with data from the double-blind phase,[12] baseline characteristics were generally balanced between the two treatment groups (Table 1). A smaller proportion of participants in the TAF-TAF group were ≥50 years of age (13.7% vs. 23.2%, p=0.0358). Where information was available, a history of cirrhosis was present in a larger proportion of participants in the TDF-TAF group than the TAF-TAF group [29.2% (7/24) vs. 9.4% (5/53)].

Table 1. Participant demographics and baseline characteristics (OL SAS)

Characteristic	TAF-TAF (*n*=212)	TDF-TAF (*n*=99)
Age in years, mean (range)	38 (18–69)	40 (20–73)
Age ≥50 years, *n* (%)	29 (13.7)	23 (23.2)[a]
Male sex, *n* (%)	152 (71.7)	78 (78.8)
Asian, n (%)	212 (100.0)	99 (100.0)
Mean BMI, kg/m^2 (SD)	23.7 (3.37)	23.9 (3.08)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)	6.4 (1.87)	6.4 (1.85)
HBV DNA ≥8 $\log_{10}$ IU/mL, *n* (%)	49 (23.1)	22 (22.2)
Median ALT (Q1, Q3)	84 (53, 150)	89 (58, 162)
HBeAg status		
Positive	111 (52.4)	54 (54.5)
Negative	101 (47.6)	45 (45.5)
HBV genotype		
B	85 (40.1)	31 (31.3)
C	122 (57.5)	68 (68.7)
B/C	2 (0.9)	0
D	2 (0.9)	0
Unknown	1 (0.5)	0
History of cirrhosis		
Yes, *n* (%)	5/53 (9.4)	7/24 (29.2)[b]
No, *n* (%)	48/53 (90.6)	17/24 (70.8)
Indeterminate/unknown, *n*	159	75
Mean FibroTest score (SD)[c]	0.41 (0.225)	0.44 (0.247)
FibroTest score ≥0.75, *n* (%)[c]	23/209 (11.0)	12/95 (12.6)
Prior nucleos(t)ide use, *n* (%)	81 (38.2)	37 (37.4)
Prior interferon use, *n* (%)	35 (16.5)	12 (12.1)
Median eGFR by Cockcroft-Gault, mL/m (Q1, Q3)	112.3 (97.6, 127.8)	114.0 (97.5, 125.8)
Diabetes mellitus	20 (9.4)	4 (4.0)
Cardiovascular disease	8 (3.8)	0
Hypertension	18 (8.5)	11 (11.1)
Hyperlipidemia	4 (1.9)	3 (3.0)
Mean hip BMD[d], g/cm^2 (SD)	0.950 (0.120)	0.932 (0.143)
Osteopenia (−2.5≤T-score<−1.0)	30/85 (35.3)	21/51 (41.2)
Osteoporosis (T-score<−2.5)	0/85	1/51 (2.0)
Mean lumbar spine BMD[e], g/cm^2 (SD)	1.035 (0.141)	1.017 (0.124)
Osteopenia (−2.5≤T-score<−1.0)	49/86 (57.0)	23/51 (45.1)
Osteoporosis (T-score<−2.5)	4/86 (4.7)	4/51(7.8)
Median 25-hydroxy vitamin D, ng/mL (Q1, Q3)	18.8 (13.2, 24.4)	18.4 (13.6, 23.6)

[a]p=0.0358; [b]p=0.0280; [c]FibroTest score was missing for three participants in the TAF-TAF group and four participants in the TDF-TAF group; [d]Results from the hip DXA analysis set; [e]Results from the spine DXA analysis set. ALT, alanine aminotransferase; BMD, bone mineral density; BMI, body mass index; DXA, dual energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; OL SAS, open-label safety analysis set; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Efficacy

Antiviral efficacy: At year 5 (week 240), viral suppression rates were similar in the two treatment groups [TAF-TAF: 93.4% (198/212) and TDF-TAF: 93.9% (93/99); a difference of −1.5%, (95% CI: −6.4 to 3.5), p=0.8568)] (Fig. 2A). Only 2.8% (6/212) in the TAF-TAF group and 4.0% (4/99) in the TDF-TAF group had HBV DNA ≥29 IU/mL. Similar proportions in the two groups had missing data

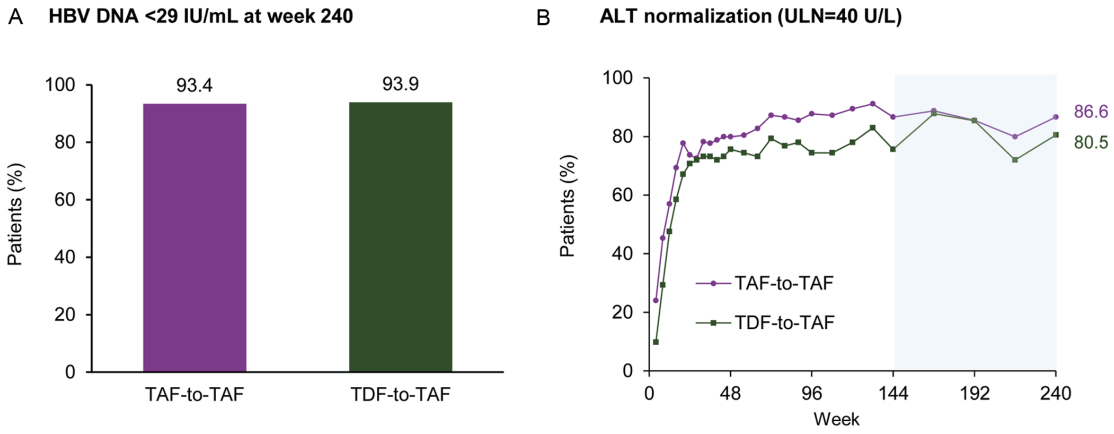

Fig. 2. Antiviral efficacy outcomes (OL FAS). (A) Proportion of participants with HBV DNA <29 IU/mL at year 5 (Week 240). (B) Proportion of participants with ALT normalization through 5 years (240 weeks)*. *In patients with ALT above the China criteria (ULN≤40 U/L) at baseline. ALT, alanine aminotransferase; HBV, hepatitis B virus; OL FAS, open-label full analysis set; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

(TAF-TAF: 3.8% and TDF-TAF: 2.0%). Regardless of treatment group, viral suppression was >90% in most participant subgroups, except those with baseline HBV DNA ≥8 $\log_{10}$ IU/mL, 87.8% of the TAF-TAF group (43/49); and 86.4% of the TDF-TAF group (19/22), and 83.3% of participants with baseline FibroTest scores ≥0.75 in the TDF-TAF group (10/12). Within each study (study 110 and study 108), similar rates of viral suppression were observed between participants in the TAF-TAF and TDF-TAF treatment groups (Supplementary Table 2).

ALT normalization: A higher proportion of participants in the TAF group achieved ALT normalization than in the TDF group at the end of double-blind treatment, with 86.6% at year 3 (week 144) vs. 75.6% (p=0.0207). After 2 years of open-label TAF treatment, the ALT normalization rate (ULN=40 U/L) in the TDF-TAF group increased but remained numerically lower than the TAF-TAF group [year 5 (week 240): 86.6% vs. 80.5%, p=0.2077)] (Fig. 2B). The proportions of patients with ALT normalization by the 2018 AASLD criteria (35 U/L for men and 25 U/L for women),[15] which had a similar trend as when using the 40 U/L ULN, are shown in Supplementary Table 3. When the 2016 AASLD criteria for ALT ULN (30 U/L for men and 19 U/L for women) were used,[19] numerically higher proportions of participants in the TAF group achieved ALT normalization than in the TDF group during the double-blind phase, but the difference diminished after the TDF group switched to TAF during the open-label phase (Supplementary Table 3).

Serological efficacy: At year 5 (week 240), HBeAg loss rates for HBeAg-positive participants in the two groups were 40.0% (44/110) and 31.5% (17/54); while those for HBeAg seroconversion were 25.5% (28/110) and 20.4% (11/54) (Table 2). HBsAg loss and seroconversion occurred in 3.8% (8/212) and 1.9% (4/212) respectively, in the TAF-TAF group, but no participants in the TDF-TAF group had HBsAg loss/seroconversion (Table 2). The mean change from baseline in HBsAg was −0.72 $\log_{10}$ IU/mL in the TAF-TAF group and −0.53 $\log_{10}$ IU/mL in the TDF-TAF group (Table 2). A similar magnitude of HBsAg decline was seen in HBeAg-positive and -negative participants (Supplementary Table 2).

FibroTest changes

At year 5 (week 240), participants in both treatment groups had small mean (standard deviation) decreases in FibroTest scores compared to baseline [TAF-TAF: −0.07 (0.148), TAF-TAF: −0.10 (0.182)] (Table 2). From baseline to year 5 (week 240), the liver fibrosis stage of most participants (~70%) in this study remained unchanged. Improvement in the fibrosis stage occurred in 19.6% and 24.2% of participants in the TAF-TAF and the TDF-TAF groups respectively, while progression in fibrosis stages occurred less frequently, in 4.8% and 5.3% of participants respectively.

Resistance surveillance

Results for resistance surveillance through year 3 (week 144) have been presented previously.[12] Results at years 4 and 5 (weeks 192 and 240) are provided in Supplementary Table 4. At year 4 (week 192), nine (six TAF-TAF and three TDF-TAF) participants had HBV DNA ≥69 IU/mL and qualified for pol/RT sequencing, including three with a viral blip, four with persistent viremia, and two with viral breakthrough. At year 5 (week 240), seven participants, four TAF-TAF and three TDF-TAF, had HBV DNA ≥69 IU/mL and qualified for pol/RT sequencing, including two with a viral blip, two with persistent viremia, and three with viral breakthrough. Of the participants who were successfully sequenced; two at year 4 (week 192) and two at year 5 (week 240) had no sequence changes from baseline, four at year 4 (week 192) and five at year 5 (week 240) had polymorphic substitutions, and two at year 4 (week 192) and none at year 5 (week 240) had conserved site substitutions (Supplementary Table 4). As such, five participants at year 4 (week 192) and two at year 5 (week 240) qualified for phenotype testing, and no pol/RT amino acid substitutions associated with resistance to TAF or tenofovir were detected in either treatment group.

Safety

The incidence of AEs and of laboratory abnormalities during the open-label phase are summarized in Table 3. As shown, the incidence of AEs was similar between the two treatment groups, with 74.5% (158/212) in the TAF-TAF group and 77.8% (77/99) in the TDF-TAF group. Nine participants (4.2%) in the TAF-TAF group and four (4.0%) in the TDF-TAF group experienced grade 3/4 AEs but only one in the TDF-TAF group had a grade 3/4 study drug-related AE (grade 3 chronic gastritis). Serious AEs occurred in 9.0% (19/212) of participants in the TAF-TAF group and 7.1% (7/99) of participants in the TDF-TAF group. However, study drug-related serious AEs were a rare occurrence, occurring only in one participant in the TDF-TAF group (grade 3 chronic gastritis). No

Table 2. Serological responses and changes in FibroTest scores (OL FAS)

Other efficacy endpoints	TAF-TAF (*n*=212)	TDF-TAF (*n*=99)
HBeAg loss, *n*/*N*[a] (%)	44/110 (40.0)	17/54 (31.5)
HBeAg seroconversion, *n*/*N*[a] (%)	28/110 (25.5)	11/54 (20.4)
HBsAg loss, *n*/*N*[b] (%)	8/212 (3.8)	0/99 (0)
HBsAg seroconversion, *n*/*N*[b] (%)	4/212 (1.9)	0/99 (0)
Mean changes from baseline in HBsAg, log_{10}IU/mL (SD)	−0.72 (1.094)	−0.53 (0.884)
Changes in FibroTest score[c] from baseline, mean (SD)		
At week 48	−0.08 (0.134)	−0.07 (0.161)
At week 96	−0.08 (0.130)	−0.07 (0.173)
At week 144	−0.07 (0.139)	−0.06 (0.185)
At week 192	−0.07 (0.153)	−0.08 (0.182)
At week 240	−0.07 (0.148)	−0.10 (0.182)
Change in fibrosis stage from baseline to week 240, *n*/*N*[c] (%)		
Improvement	41/209 (19.6)	23/95 (24.2)
0.49 – 0.74 → 0.00 – 0.48	23/49 (46.9)	16/29 (55.2)
0.75 – 1.00 → 0.49 – 0.74	13/22 (59.1)	3/11 (27.3)
0.75 – 1.00 → 0.00 – 0.48	5/22 (22.7)	4/11 (36.4)
No change	150/209 (71.8)	65/95 (68.4)
0.00 – 0.48 → 0.00 – 0.48	122/130 (93.8)	48/53 (90.6)
0.49 – 0.74 → 0.49 – 0.74	24/49 (49.0)	13/29 (44.8)
0.75 – 1.00 → 0.75 – 1.00	4/22 (18.2)	4/11 (36.4)
Worsening	10/209 (4.8)	5/95 (5.3)
0.00 – 0.48 → 0.49 – 0.74	8/130 (6.2)	4/53 (7.5)
0.00 – 0.48 → 0.75 – 1.00	0	1/53 (1.9)
0.49 – 0.74 → 0.75 – 1.00	2/49 (4.1)	0

[a]In patients who were seropositive for HBeAg and seronegative for anti-HBe at baseline; [b]Among patients who were seropositive for HBsAg and seronegative for anti-HBs at baseline; [c]FibroTest score was missing for three participants in the TAF-TAF group and four participants in the TDF-TAF group at baseline. Anti-HBe, hepatitis B e antibody; Anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; OL FAS, open-label full analysis set; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

participant in either group experienced AEs leading to study drug discontinuation. AEs occurring in >10% of participants during the open-label phase included hepatic steatosis and upper respiratory tract infection, and the other common AEs are shown in Table 3. Grade 3/4 laboratory abnormalities occurred in slightly more participants in the TAF-TAF group than in the TDF-TAF group [9.0% (19/212) vs. 5.1% (5/99)]. The most frequent grade 3/4 laboratory abnormalities were abnormalities in urine glucose, ALT, and gamma glutamyl transferase (Table 3). Grade 3/4 abnormalities of fasting low-density lipoprotein (LDL) cholesterol occurred in four participants (1.9%) in the TAF-TAF group and in one participant (1.0%) in the TDF-TAF group. There were no grade 3/4 abnormalities of the other fasting lipid parameters.

Changes in renal parameters

Changes in renal laboratory parameters are summarized in Figure 3. Participants treated with TDF experienced significantly greater decline in $eGFR_{CG}$ compared with those treated with TAF through the end of the double-blind phase (p=0.0118).[12] However, after 2 years of open-label TAF treatment, the difference between the treatment groups was no longer significant at year 5 (week 240, −2.85 mL/min vs. −3.29 mL/min, p=0.910) (Fig. 3A). When shifts in chronic kidney disease (CKD) stage were assessed, a smaller proportion of TDF-treated participants showed an improvement in CKD stage compared with TAF-treated participants at the end of double-blind treatment, while a greater proportion of TDF-treated participants had CKD stage worsening (week 144: p=0.0522) (Supplementary Table 5). At year 5 (week 240), the differences in CKD stage shifts between the two treatment groups were much smaller (p=0.1731) (Supplementary Table 5).

Significantly greater median percent increases from baseline in the two markers of quantitative proteinuria were experienced by TDF-treated participants than in those receiving TAF at the end of the double-bind phase (RBP:Cr, p=0.0024 and β_2M:Cr, p<0.0001). In the open-label phase, at week 192, the increase in RBP:Cr in the TDF-TAF group was diminished soon after switching, such that in both the TDF-TAF and TAF-TAF groups the changes were comparable to baseline levels; at year 5 (week 240) both groups had comparable median percent increases from baseline in RBP:Cr (p=0.4816) (Fig. 3B). Similar trends were observed for β_2M:Cr, in which the difference between the TDF-TAF and TAF-TAF groups narrowed after switching to open-label TAF (Fig. 3C).

Table 3. Treatment-emergent AEs and laboratory abnormalities (OL SAS)

Parameter	TAF-TAF (*n*=212)	TDF-TAF (*n*=99)
Any AE	158 (74.5)	77 (77.8)
Any study drug-related AE	35 (16.5)	16 (16.2)
Any grade 3 or 4 AEs	9 (4.2)	4 (4.0)
Any grade 3 or 4 study drug-related AEs	0	1 (1.0)
Any SAEs	19 (9.0)	7 (7.1)
Any study drug-related SAEs	0	1 (1.0)
Any AEs leading to study drug discontinuation	0	0
Death	0	0
Common AEs occurring in ≥5% of participants in any treatment group		
Hepatic steatosis	37 (17.5)	16 (16.2)
Upper respiratory tract infection	21 (9.9)	10 (10.1)
Nasopharyngitis	19 (9.0)	8 (8.1)
Gallbladder polyp	9 (4.2)	7 (7.1)
Hypertension	9 (4.2)	5 (5.1)
Cholelithiasis	6 (2.8)	6 (6.1)
Nephrolithiasis	5 (2.4)	6 (6.1)
Any treatment emergent grade 3 or 4 laboratory abnormality	19 (9.0)	5 (5.1)
Treatment emergent grade 3 or 4 laboratory abnormalities occurring in ≥2% of participants in any treatment group		
Urine glucose	5 (2.4)	1 (1.0)
Alanine aminotransferase	2 (0.9)	2 (2.0)
Gamma glutamyl transferase	1 (0.5)	2 (2.0)

AE, adverse event; OL SAS, open-label safety analysis set; SAE, serious adverse event, TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Change in BMD

In the subset of participants with available BMD results, TAF treatment over 5 years showed minimal impact on hip or spine BMD. For participants in the TDF-TAF groups, the small decreases in hip and spine BMD during the double-blind phase improved after switching to TAF (Fig. 4A, B).

Metabolic and anthropometric changes

Changes in fasting lipids during the double-blind phase have been previously reported.[12] As shown in Figure 5A–E, for the TAF-TAF group, the changes in fasting lipid parameters remained relatively stable throughout the double-blind and open-label phases. For the TDF-TAF group, the decreases in fasting lipid parameters, including fasting high-density-lipoprotein (HDL) cholesterol, observed during the double-blind phase were reversed upon switching to open-label TAF. By year 5 (week 240), both groups had comparable changes from baseline in fasting lipid parameters. No significant difference was observed between groups in the median changes in fasting glucose through 5 years (240 weeks) (Fig. 5F).

A small, stable between-group difference was observed in the change of body weight up to week 144. Following switch to open-label TAF, this difference was no longer observed (Fig. 5G). The mean body mass index (BMI) of the TAF-TAF group at baseline was 23.7 kg/m^2 and that of the TDF-TAF group was 23.9 kg/m^2 (Table 1) and was 24.1 kg/m^2 and 24.4 kg/m^2 respectively at year 5 (week 240). The shifts in BMI category from baseline to year 5 (week 240) are provided in Supplementary Table 6. In both groups, the BMI status of most participants remained unchanged at year 5 (week 240). Some participants in the TAF-TAF or TDF-TAF group worsened from normal to overweight (9.2% vs. 16.7% respectively) or overweight to obese (4% vs. 3% respectively) at year 5 (week 240).

Discussion

It has been previously demonstrated that for Chinese participants with HBeAg-positive or -negative CHB, in comparison with TDF, treatment with TAF provides similar antiviral efficacy with improved renal and bone safety at week 144.[12] The results of this analysis provide further evidence for the long-term efficacy and favorable safety of TAF treatment at year 5 (week 240), and the first evidence from randomized, controlled studies in Chinese participants of the effects of switching from TDF treatment to TAF treatment for 96 weeks. Overall, 5-year TAF treatment resulted in high rates of viral suppression and ALT normalization, while important renal and bone parameters remained stable. In addition, the group of participants who were switched from TDF to TAF at week 144 showed improvement in renal and bone safety while a high degree of antiviral efficacy was maintained. The observed benefit of TAF is consistent with the 5-year (week 240) results reported in the study 108 and 110 international cohorts.[17]

In this China cohort, after 3 years of double-blind TDF or TAF treatment followed by 2 years of open-label TAF treatment, similar high proportions of participants achieved and maintained virologic suppression (HBV DNA <29 IU/mL) in

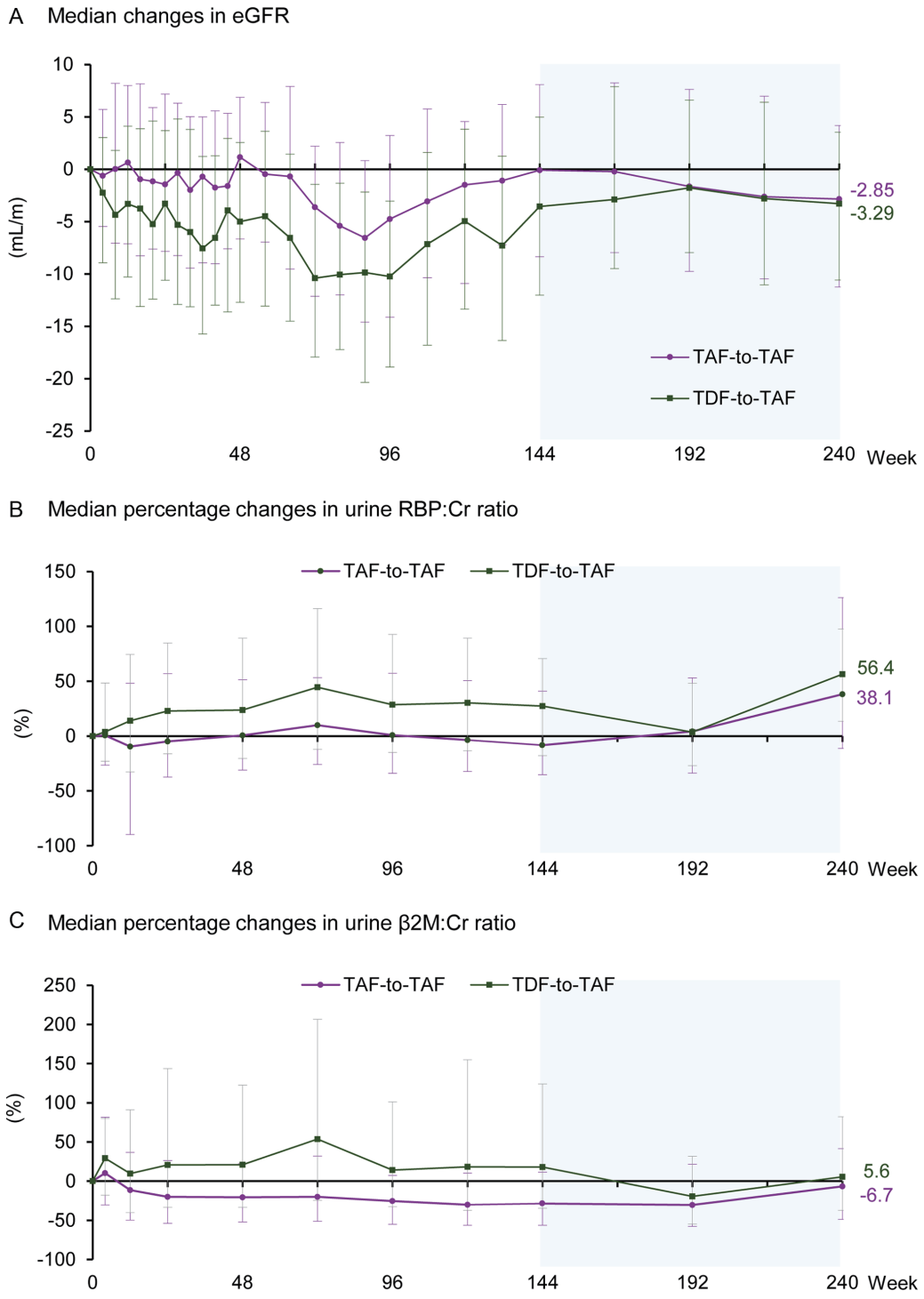

Fig. 3. Change in renal safety parameters from baseline through 5 years (240 weeks, OL SAS). (A) Median (Q1, Q3) changes in eGFR by Cockcroft-Gault. (B) Median (Q1, Q3) percentage changes in urine RBP to creatinine ratio. (C) Median (Q1, Q3) percentage changes in urine β_2M to creatinine ratio. β_2M:Cr, β2-microglobulin to creatinine ratio; eGFR, estimated glomerular filtration rate; RBP:Cr, retinol binding protein to creatinine ratio; OL SAS, open-label safety analysis set; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

both treatment groups, affirming that these two tenofovir prodrugs have similar antiviral activity (Fig. 2A). This was also consistent with previous studies showing that TAF was noninferior to TDF in virologic suppression,[9–12,23] and confirmed the long-term efficacy of TAF in Chinese patients. Similar to results observed in the global cohort,[22] this study also showed that in participants pretreated with TDF, switching to TAF effectively improved or maintained virologic suppression.

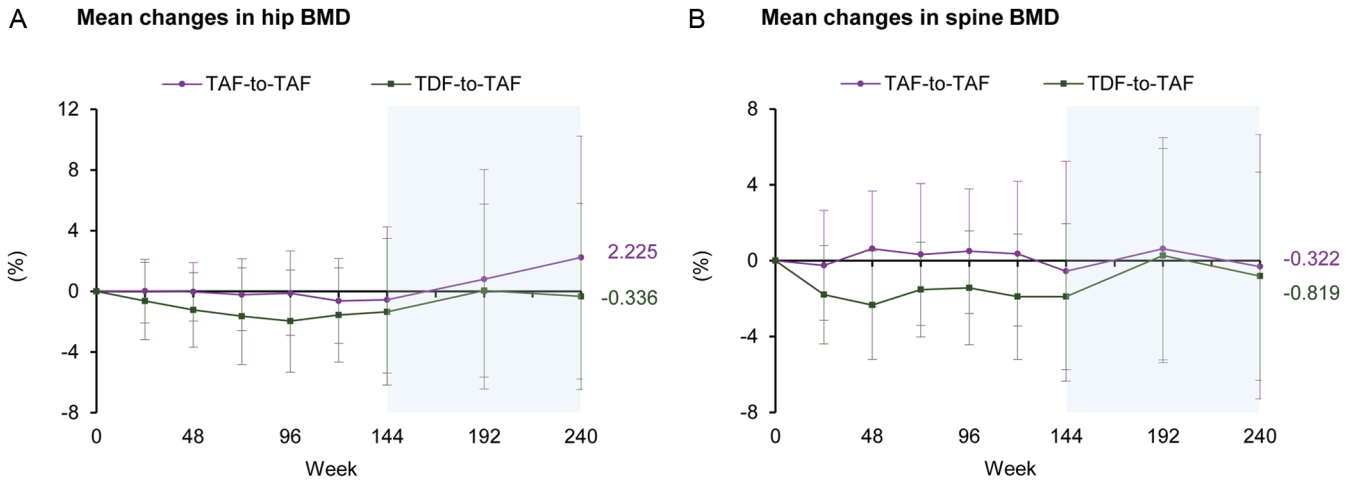

Fig. 4. Mean changes in hip and spine BMD through 5 years (240 weeks). (A) Mean (SD) changes in hip BMD (OL Hip DXA analysis set, TAF-TAF: *n*=85, TDF-TAF: *n*=51). (B) Mean (SD) changes in spine BMD (OL spine DXA analysis set, TAF-TAF: *n*=86, TDF-TAF: *n*=51). BMD, bone mineral density; DXA, dual energy x-ray absorptiometry; OL, open-label; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

In addition, results of resistance surveillance through year 5 (week 240) showed that no Chinese participant in either treatment group had reduced susceptibility to tenofovir after long-term treatment.

As previously reported in both the global and the China cohorts, the proportion of participants with ALT normalization was higher in the TAF than in the TDF group.[9,12] Although it is currently uncertain why elevated ALT levels may persist in some patients despite virologic suppression (possibly associated with HBeAg positivity and hepatic steatosis at baseline),[24] this difference in ALT normalization between TDF and TAF has been consistently observed in studies of both viremic patients treated with TDF or TAF[9] and in virologically suppressed patients switched from TDF to TAF.[22] To further explore these trends we conducted an ALT normalization analysis using the 2016 AASLD criteria (30 U/L for men and 19 U/L for women) (Supplementary Table 3).[19] The use of these more conservative ALT cutoffs in the context of treatment initiation has been recently proposed.[18–21] Even with these more stringent cutoffs, a consistent benefit for TAF versus TDF was observed. As ALT is an established marker of liver injury,[25,26] these results suggest that by effectively maintaining virologic suppression, TAF treatment may result in further improvement of hepatic inflammation compared with TDF; however, this remains to be confirmed by histology and/or other noninvasive means. As measured by FibroTest, the two treatment groups had similar liver fibrosis outcomes at year 5 (week 240). Importantly, by this noninvasive approach, most participants either demonstrated improvement (approximately 20% in both groups) or had no change in their fibrosis stage at year 5 (week 240) compared with baseline, while only approximately 5% had worsening of fibrosis stage (Table 2). These results suggest that the long-term antiviral efficacy of TAF treatment translates into slowing or potentially reversing fibrosis progression, consistent with earlier reports with TDF and entecavir.[27,28]

Regarding serological responses, compared with the TDF-TAF group, the TAF-TAF group had numerically higher rates of HBeAg loss and seroconversion, HBsAg loss and seroconversion, and a numerically larger decrease in HBsAg level from baseline (Table 2), which indicates that TAF and TDF have comparable long-term serologic efficacy. Notably, eight participants (3.8%) in the TAF-TAF group had HBsAg loss; while for reasons that are unclear, this did not occur in any participants in the TDF-TAF group, despite similar demographic and disease characteristics, including HBV genotype. Regardless, the general consensus that loss of HBsAg is an uncommon occurrence with nucleos(t)ide analog monotherapy[29] is further supported by our results in Chinese participants.

Safety results over 5 years (240 weeks) provide further evidence of the excellent long-term safety and tolerability of TAF in Chinese CHB patients. Similar to results from the global cohort and from the double-blind phase,[9–12] long-term TAF treatment was associated with a low incidence of study drug-related AEs and laboratory abnormalities in Chinese participants (Table 3). Of interest, the initial deteriorations in renal and bone parameters observed in TDF-treated participants during the double-blind phase improved in the open-label phase after switching to TAF for 2 years (Figs. 3 and 4), which is also consistent with that observed in the global cohorts of studies 110/108.[30] As these studies will continue through 8 years (week 384), long-term follow-up will confirm if this trend continues.

The observations reported here have some important clinical implications. Firstly, a recent study based on the China Health Insurance Association claims database revealed that the proportion of CHB patients >45 years of age increased from 40% in 2013 to 49% in 2016, accompanied by substantial increases in multiple comorbidities, including renal impairment and osteoporosis and/or pathologic nontraumatic bone fracture.[31] These trends highlight the need to pay close attention to renal function and bone density status in CHB patients, especially those at higher risk of CKD or osteoporosis (note that major guidelines now recommend TAF or entecavir over TDF in these patients).[14,15] Secondly, in addition to confirming the improved renal and bone safety of TAF compared with TDF, the results suggest that the TDF-associated declines in these parameters appear to be reversible after switching to TAF (although this may not be the case for all patients). This is reassuring for patients with declines in renal and bone functions due to prior exposure to TDF and provides evidence favoring a treatment switch to TAF.

The changes in fasting lipids observed in this study provide additional evidence for the effect of TDF on lowering fasting lipids (including HDL cholesterol).[32,33] Thus, it is likely that the increases in fasting lipids observed when switching from

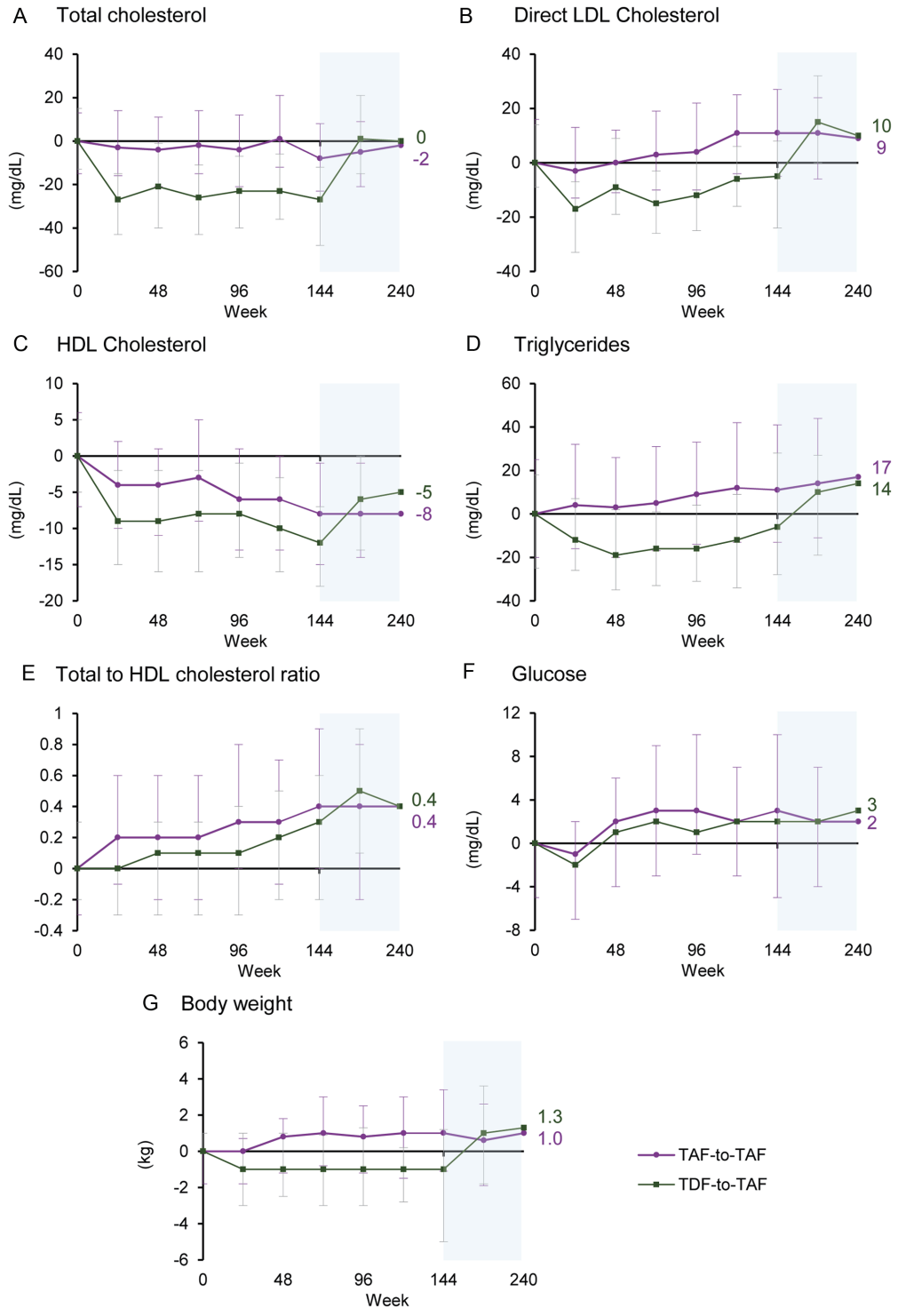

Fig. 5. Median (Q1, Q3) change in fasting blood metabolic parameters and body weight through 5 years (240 weeks, OL SAS). (A) Total cholesterol. (B) Direct LDL cholesterol. (C) HDL cholesterol. (D) Triglycerides. (E) Total to HDL cholesterol ratio. (F) Glucose. (G) Body weight. HDL, high-density-lipoprotein; LDL, low-density-lipoprotein; OL SAS, open-label safety analysis set; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

TDF- to TAF-containing antiviral treatment is due at least in part to the removal of the lipid-suppressing effect of TDF. A recent, larger-scale, cross-sectional study of the general Chinese population showed that LDL cholesterol increases with age in people 20–60 years of age, and triglycerides increase with age in men and women ≤40 and ≤70 years of age respectively.[34] As most of the participants in this study were within this age range, this "natural" increase in LDL choles-

terol and triglycerides with age may account for the small increases in LDL cholesterol and triglycerides observed in the TAF-TAF group (Fig. 5A–E), although a direct effect from TAF cannot be excluded. Of note, similar increases in total cholesterol to HDL cholesterol ratio were observed in both treatment groups at year 5 (week 240) (Fig. 5A–E). Despite the changes in lipid profile seen with long-term TAF, less than 2% of participants in each group had statin therapy initiated during the study. Corroborating evidence from a recent study conducted in Korea showed that TAF may not worsen lipid profiles in CHB patients in the real-world setting.[35]

Over 5 years (240 weeks), body weight remained relatively stable in both groups and similar small increases from baseline were observed (Fig. 5G). Likewise, similar, minimal changes in mean BMI were observed in both treatment groups. Taken together, these results suggest that the small increases in lipid parameters and body weight observed with long-term TAF treatment may not be clinically relevant for most patients. Nevertheless, those with pre-existing hyperlipidemia or other cardiovascular risk factors should be appropriately monitored on TAF treatment. As the study is continuing through 8 years, long-term results may provide further insights into the effect of TAF on metabolic parameters.

There are several limitations to these results that should be addressed. Firstly, due to the study design and smaller sample size than the global cohort, the statistical analysis is considered exploratory in nature. Secondly, compared with the TDF-TAF group, a smaller proportion of participants in the TAF group were ≥50 years of age at baseline. Although the difference was less than 10% and the mean and median ages of the two groups were similar, this could potentially weaken the strength of our findings. Thirdly, a higher proportion in the TDF-TAF group had cirrhosis at baseline, which could have impacted treatment responses to some extent. Finally, reporting of AEs attributed to therapy might have been different during the open-label phase where it was clear that TAF alone was being administered; however, all investigators remained blinded to initial treatment assignment, which helped mitigate the risk of introducing bias between groups. In conclusion, results from this extended analysis at 5 years (week 240) in Chinese participants with CHB confirm the favorable efficacy and safety profile of TAF, both in participants initially randomized to this novel prodrug as well as in those switching from TDF to TAF. Importantly, the results also demonstrate that declines in renal and bone parameters are minimal with TAF, while the TDF-associated effects can be reversed upon switching treatment to TAF.

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Conflict of interest

JH has received consulting fees from Aligos, Assembly, Gilead Sciences, Johnson & Johnson, and Roche; lecturer fees from Gilead Sciences, Johnson & Johnson, and Roche; grants from Bristol Myers Squibb; and has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. QN has served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson, MSD, and Roche, has received research funding from Bristol Myers Squibb, Gilead Sciences, and Roche, and has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2024. QX has served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson, and Roche, and has received grants from Gilead Sciences. SW has served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, GSK, and MSD, and has received research funding from AbbVie, Bristol Myers Squibb, Gilead Sciences, and Roche. HT has served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, GSK, and MSD, and has received research funding from Bristol Myers Squibb, Gilead Sciences, and Roche. JL has served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, GSK, and MSD. YL, SX, HW, RM, TY, FA, LJY, JF are employees and stockholders of Gilead Sciences. CC has served as a consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, GSK, and MSD and received research funding from AbbVie, Bristol Myers Squibb, Gilead Sciences, and Roche. JJ has served as a consultant for Gilead Sciences and GSK; received research funds from Bristol Myers Squibb and Gilead Sciences; and has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Study conceptualization and methodology (JH, SX, JF), investigation (JH, QN, ZD, YC, QX, LZ, SW, HT, JL, FL, YY, GG, RM, TY, CC, YH, MZ, JJ), formal analysis (HW), project administration, supervision, resources, and software (YL, FA, JF, LJY). All authors contributed to data curation, validation, writing original draft, reviewing, and editing. All authors have approved the final manuscript.

Ethics statement

The two studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocols were approved by the institutional review board or independent ethics committees at all participating sites. The trial registration number is Clinicaltrials.gov: NCT02836249 and NCT02836236. All participants provided written informed consent before enrollment.

Data sharing statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

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