Journal of Clinical and Translational Hepatology **2026** vol. 14(2) | 146–158
DOI: 10.14218/JCTH.2025.00438

Original Article

Eight-year Results from Two Randomized Phase 3 Trials of Tenofovir Alafenamide for Chronic Hepatitis B Virus Infection in China

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Received: August 26, 2025 | **Revised:** November 27, 2025 | **Accepted:** December 08, 2025 | **Published online:** February 04, 2026

Abstract

Background and Aims: Tenofovir alafenamide (TAF) has demonstrated comparable efficacy to tenofovir disoproxil fumarate (TDF), with improved renal and bone safety, in Chinese participants with chronic hepatitis B enrolled in two Phase 3 trials. This study aimed to evaluate the long-term virologic efficacy, serological and biochemical responses, resistance, and renal and bone safety of TAF over eight years in this population. ***Methods:*** Participants completing the three-year double-blind phase were eligible to receive open-label TAF 25 mg/day for up to an additional five years (totaling eight years). Analyses of viral suppression (HBV DNA < 29 IU/mL), alanine aminotransferase normalization, serological responses, resistance surveillance, and safety outcomes were conducted. ***Results:*** Among 334 enrolled participants, 212 of 227 participants randomized to TAF continued open-label TAF (TAF-TAF), and 99 of 107 participants on TDF switched to open-label TAF (TDF-TAF). At Year 8, 79.3% (180/227) and 78.5% (84/107) of participants in the TAF-TAF and TDF-TAF groups, respectively, achieved viral suppression (missing = failure); rates increased to 95.2% (180/189) and 95.5% (84/88) when excluding missing data. Alanine aminotransferase normalization rates remained high and comparable between groups. Serologic response rates continued to increase over time, with higher rates observed in the TAF-TAF group. Estimated glomerular filtration rate (by Cockcroft-Gault) and hip/spine bone mineral density remained stable in the TAF-TAF group through eight years; the small declines in these renal and bone parameters observed during double-blind TDF treatment improved after switching to open-label TAF. No resistance to TAF was detected. ***Conclusions:*** Long-term TAF treatment demonstrated durable virologic efficacy, sustained biochemical and serological responses, and favorable renal and bone safety over eight years in Chinese participants with chronic hepatitis B.

Citation of this article: Hou J, Ning Q, Duan Z, Chen Y, Xie Q, Zhang L, *et al*. Eight-year Results from Two Randomized Phase 3 Trials of Tenofovir Alafenamide for Chronic Hepatitis B Virus Infection in China. J Clin Transl Hepatol 2026; 14(2):146–158. doi: 10.14218/JCTH.2025.00438.

Introduction

Hepatitis B virus (HBV) infection is a major global health burden, especially in highly endemic countries such as China. According to the World Health Organization, 254 million people were living with chronic HBV infection in 2022.[1] In China alone, approximately 80 million people are chronically infected with HBV, representing the largest HBV-infected population worldwide.[1] Chronic hepatitis B (CHB) can lead to cirrhosis and hepatocellular carcinoma (HCC) and is a major cause of liver disease-related mortality.[1,2] Notably, HBV-

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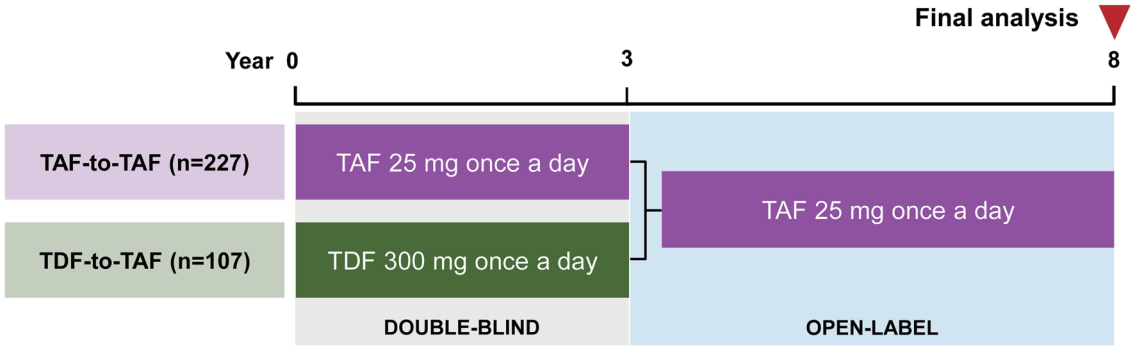

Fig. 1. Study design. Participants were randomized (2:1) to receive either TAF or TDF during the three-year double-blind phase. From Year 3 onwards, all participants received open-label TAF treatment up to Year 8. TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

related deaths rose from 0.82 million in 2019 to 1.10 million in 2022 despite a decline in new HBV infections during the same period, likely due to an aging HBV-infected population and treatment scale-up disruptions caused by the COVID-19 pandemic.[1]

Treatment with nucleos(t)ide analogues has been shown to reduce the risk of progression to cirrhosis, decompensated liver disease, and HCC in individuals with CHB.[3] Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), both prodrugs of tenofovir, are recommended as first-line therapies.[4] TAF is more stable in plasma and provides enhanced hepatic delivery of the active metabolite, resulting in reduced systemic exposure and improved renal and bone safety profiles compared with TDF when used at approved doses.[4]

Two similarly designed, pivotal, international phase 3 randomized studies of participants with hepatitis B e antigen (HBeAg)-positive (Study 110, NCT01940471) or HBeAg-negative (Study 108, NCT01940341) CHB conducted outside of China demonstrated that TAF has non-inferior efficacy and improved renal and bone safety profiles compared with TDF at Years 1 and 2.[5–7] After completing the double-blind phase, participants across both studies continued in an open-label TAF extension phase for up to eight years. Importantly, the five-year and eight-year results of these two studies confirmed that long-term treatment with TAF maintains high rates of viral suppression with renal and bone safety profiles that remained stable and favorable through Year 8 in this large, international cohort of participants with CHB.[8,9]

Although the two international phase 3 studies planned to enroll participants globally, including in China, due to differences in review timelines, full enrollment was reached before any Chinese participants could be included. As such, a separate cohort of participants with HBeAg-positive (Study 110, NCT02836249) and HBeAg-negative CHB (Study 108, NCT02836236) was enrolled in China. Similar to the findings from the global cohorts, the three-year double-blind results from the China cohort showed comparable efficacy between TAF and TDF, with TAF demonstrating improved renal and bone safety.[10] Additionally, interim five-year results from the China cohort confirmed that the favorable bone and renal safety profile was maintained over five years of continuous TAF treatment, with improvements observed in participants who switched from TDF to TAF.[11]

We present the final eight-year efficacy and safety results of the China cohort from these two studies, which inform the long-term efficacy and safety of continuous TAF treatment, including in patients who were previously treated with TDF.

Methods

Study design and participants

Studies 108 and 110 were both phase 3, randomized studies enrolling treatment-naive or -experienced participants with CHB. The design and methodology of these studies were previously described in detail.[6,7,10,11] In China, Study 108 enrolled participants with HBeAg-negative CHB from 27 sites, and Study 110 enrolled participants with HBeAg-positive CHB from 23 sites. For both studies, eligible participants were ≥18 years old, hepatitis B surface antigen (HBsAg)-positive for ≥6 months, and had a HBV DNA level of ≥20,000 IU/mL, an alanine aminotransferase (ALT) level of >60 U/L for men and >38 U/L for women, and an estimated glomerular filtration rate by Cockcroft-Gault equation ($eGFR_{CG}$) of ≥50 mL/m. Detailed inclusion and exclusion criteria were previously reported.[6,7]

In both studies, participants first completed a three-year (144-week) double-blind phase, during which they were randomized (2:1) to receive TAF 25 mg or TDF 300 mg once daily (Fig. 1). Those who completed the double-blind treatment were eligible to enter the five-year (240-week) open-label extension phase, in which all participants received TAF 25 mg once daily. Study visits occurred every four, eight, and 12 weeks in the first, second, and third year, respectively, during the double-blind phase,[10] and every 24 weeks during the open-label phase to assess efficacy and safety.[11] As the studies were ongoing during the COVID-19 pandemic, every effort was made to ensure that participants had a continuous supply of the study medication. Remote safety visits were conducted for participants who were unable to attend onsite visits due to COVID-19-related restrictions.

The studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and 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).

Study assessment and outcomes

Efficacy endpoints of this analysis included the proportion of participants with viral suppression (HBV DNA <29 IU/mL, target detected or target not detected (TND)) at Year 8 (Week 384), ALT normalization (defined as upper limit of normal (ULN) ≤ 40 U/L for both males and females, reflective of clinical practice in China), serological responses (HBeAg and HBsAg loss/seroconversion), quantitative change in HBsAg, and shifts in fibrosis stage by FibroTest. Treatment-emergent

adverse events (AEs) and graded laboratory abnormalities were reported. As AEs and laboratory abnormalities occurring during the double-blind phase were reported in detail previously,[10] only those occurring during the open-label phase (from the first dose of open-label TAF treatment onward) are reported here. Serial changes in renal and bone parameters, including $eGFR_{CG}$, urine retinol-binding protein to creatinine (hereinafter referred to as RBP:Cr) ratio, urine β_2-microglobulin to creatinine (hereinafter referred to as β_2M:Cr) ratio, and bone mineral densities (BMDs) at the lumbar spine and hip, as well as changes in fasting lipids through eight years, were also reported. Finally, as previously described, resistance analyses, including genotyping of the HBV polymerase/reverse transcriptase (pol/RT) sequence for all participants at baseline and subsequently for those with HBV DNA ≥69 IU/mL, and phenotyping for those meeting prespecified conditions (such as virologic breakthrough), were conducted using standardized methods.[10,11]

Statistical analysis

As the non-inferior efficacy of TAF versus TDF was established in the global cohorts,[5–7,12] the sample sizes for the two pivotal studies conducted in China were calculated based on local requirements for demonstrating comparable efficacy and safety for new drug registration. As previously mentioned, given that the efficacy and safety of TAF are generally comparable between HBeAg-positive and HBeAg-negative populations,[5–7,10] data from Studies 110 and 108 were pooled for the China cohort analysis.[10,11]

For this analysis, most efficacy endpoints were analyzed using the full analysis set, which included all randomized participants who received ≥1 dose of the study drug. Safety was analyzed in the open-label safety analysis set, defined as all randomized participants who received ≥1 dose of open-label study drug. Hip and spine BMD were analyzed in the hip and spine dual-energy x-ray absorptiometry analysis set, which included all randomized and treated participants who had non-missing baseline hip and spine BMD values, respectively. Efficacy endpoints reported as proportions were analyzed using both the missing-equals-to-failure (M=F) approach and the missing-equals-to-excluded (M=E) approach. The statistical analyses and data reporting methods were consistent with those previously described, and more details can be found in previous reports.[10,11]

Results

Participant disposition and baseline characteristics

From June 19, 2015, to September 18, 2023, 334 participants received double-blind treatment (TAF: 227; TDF: 107), 311 (93.1%) completed the double-blind phase and entered the open-label phase (TAF-TAF: 212; TDF-TAF: 99), and 279 (83.5%) completed the open-label study treatment (TAF-TAF: 188; TDF-TAF: 91). Complete participant dispositions are provided in Supplementary Fig. 1.

Baseline characteristics are summarized in Table 1. Overall, the mean (range) age was 38 (18–73) years, and 73.1% were male. The mean (standard deviation (SD)) HBV DNA level was 6.4 (1.9) $\log_{10}$ IU/mL, the median (Q1, Q3) ALT was 88 (56, 165) U/L, and 53.9% of participants were HBeAg-positive. The mean (SD) FibroTest score was 0.42 (0.23). Among participants with a baseline FibroTest score, 11.3% (37/327) had a score of ≥0.75, suggestive of cirrhosis. For prior treatment, 37.1% and 15.9% of participants had received nucleos(t)ide and interferon, respectively. The median (Q1, Q3) $eGFR_{CG}$ was 112.8 (97.2, 128.4) mL/m. Among participants with available baseline hip and spine BMD data, 38.1% and 56.8% had evidence of bone loss (T-score < −1) in the hip and spine, respectively. Baseline characteristics were generally balanced between the two treatment groups. However, a smaller proportion of participants in the TAF-TAF group, compared with the TDF-TAF group, were ≥50 years old (13.7% vs. 22.4%, P = 0.044). Among participants with available information, a smaller proportion had a history of cirrhosis in the TAF-TAF group than in the TDF-TAF group (8.9% [5/56] vs. 28.0% [7/25], P = 0.0265).

Efficacy

Virologic response: The high rates of viral suppression achieved during the double-blind phase were maintained during the open-label phase through Year 8. Similar proportions of participants in the two treatment groups achieved HBV DNA < 29 IU/mL, regardless of the analysis approach. At Year 8, by the M=F approach, the proportion of participants with HBV DNA < 29 IU/mL was 79.3% (180/227) and 78.5% (84/107) in the TAF-TAF and TDF-TAF groups, respectively (Fig. 2A), with the difference in proportion being 0.9% (95% confidence interval −8.8% to 10.6%, P = 0.8517); the proportion of participants achieving HBV DNA < 29 IU/mL with TND was 55.9% (127/227) and 51.4% (55/107), respectively. By the M=E approach, the proportion of participants with HBV DNA < 29 IU/mL was 95.2% (180/189) and 95.5% (84/88) in the TAF-TAF and TDF-TAF groups, respectively (Fig. 2B), with the difference in proportions being −0.2% (95% confidence interval −6.4% to 6.0%, P = 0.9407); the proportion of participants achieving HBV DNA < 29 IU/mL with TND was 67.2% (127/189) and 62.5% (55/88), respectively. In both HBeAg-negative and HBeAg-positive participants, similar rates of viral suppression were achieved in the TAF-TAF and TDF-TAF groups (Supplementary Table 2).

Biochemical response: During the double-blind phase, a higher proportion of participants in the TAF-TAF group achieved ALT normalization (ULN ≤ 40 U/L) compared with the TDF-TAF group, as demonstrated by both the M=F and M=E approaches (Fig. 2C and D). At Years 5 and 8, two and five years into the open-label phase, numerical differences in the proportion of participants with ALT normalization between the two groups persisted (Year 5: 80.8% vs. 73.3%, P = 0.1457; Year 8: 72.5% vs. 64.4%, P = 0.1457) by the M=F analysis (Fig. 2C). Consistent results were observed using the M=E approach (Fig. 2D). Similar trends were seen in the proportion of participants with ALT normalization by 2018 AASLD criteria (ULN ≤ 25 U/L for females and ≤35 U/L for males) (Supplementary Table 3).

Serological responses: By M=F analysis, among participants who were HBeAg-positive at baseline, the proportion with HBeAg loss at Year 8 was 40.8% (49/120) in the TAF-TAF group and 33.9% (20/59) in the TDF-TAF group; the proportion with HBeAg seroconversion at Year 8 was 27.5% (33/120) and 15.3% (9/59) in the two groups, respectively (Table 2). HBsAg loss and seroconversion occurred in 4.8% (11/229) and 2.6% (6/227), respectively, in the TAF-TAF group, while no participants in the TDF-TAF group achieved HBsAg loss or seroconversion (Table 2). Consistent results were observed by M=E analysis (Table 2). The mean change in HBsAg from baseline was −1.01 $\log_{10}$ IU/mL in the TAF-TAF group and −0.77 $\log_{10}$ IU/mL in the TDF-TAF group (Table 2). Similar magnitudes of HBsAg decline were observed in HBeAg-positive and -negative participants (Supplementary Table 2).

FibroTest changes

Participants in both treatment groups had small mean (SD) decreases from baseline in FibroTest scores at Year 8 (TAF-

Table 1. Participant demographics and baseline characteristics (FAS)

Characteristic	TAF-TAF (N = 227)	TDF-TAF (N = 107)	Total (N = 334)
Mean age, years (range)	38 (18–69)	40 (20–73)	38 (18–73)
Age ≥ 50 years, n (%)	31 (13.7)	24 (22.4)[a]	55 (16.5)
Male sex, n (%)	162 (71.4)	82 (76.6)	244 (73.1)
Asian, n (%)	227 (100.0)	107 (100.0)	334 (100.0)
Mean BMI, kg/m^2 (SD)	23.7 (3.37)	23.8 (3.06)	23.7 (3.27)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)	6.4 (1.87)	6.4 (1.81)	6.4 (1.85)
HBV DNA ≥ 8 $\log_{10}$ IU/mL, n (%)	55 (24.2)	22 (20.6)	77 (23.1)
Median ALT (Q1, Q3)	85 (53, 160)	90 (63, 185)	88 (56, 165)
HBeAg status, n (%)			
Positive	121 (53.3)	59 (55.1)	180 (53.9)
Negative	106 (46.7)	48 (44.9)	154 (46.1)
HBV genotype, n (%)			
B	90 (39.6)	33 (30.8)	123 (36.8)
B/C	2 (0.9)	0	2 (0.6)
C	131 (57.7)	74 (69.2)	205 (61.4)
D	2 (0.9)	0	2 (0.6)
Unknown	2 (0.9)	0	2 (0.6)
History of cirrhosis			
Yes, n (%)	5 (8.9)	7 (28.0)[b]	12 (14.8)
No, n (%)	51 (91.1)	18 (72.0)	69 (85.2)
Indeterminate/unknown, n	171	82	253
Mean FibroTest score (range) [c]	0.41 (0.04–0.98)	0.44 (0.06–0.96)	0.42 (0.04–0.98)
FibroTest score ≥ 0.75, n (%)[c]	24 (10.7)	13 (12.6)	37 (11.3)
Prior nucleos(t)ide use, n (%)	86 (37.9)	38 (35.5)	124 (37.1)
Prior interferon use, n (%)	38 (16.7)	15 (14.0)	53 (15.9)
Median $eGFR_{CG}$, mL/m (Q1, Q3)	112.8 (97.8, 129.0)	112.8 (96.6, 125.4)	112.8 (97.2, 128.4)
Diabetes mellitus, n (%)	21 (9.3)	5 (4.7)	26 (7.8)
Cardiovascular disease, n (%)	8 (3.5)	1 (0.9)	9 (2.7)
Hypertension, n (%)	18 (7.9)	13 (12.1)	31 (9.3)
Hyperlipidemia, n (%)	4 (1.8)	3 (2.8)	7 (2.1)
Total hip BMD status[d], n (%)			
Normal (T-score ≥ −1)	59 (63.4)	31 (57.4)	90 (61.2)
Osteopenia (−2.5 ≤ T-score < −1.0)	33 (35.5)	22 (40.7)	55 (37.4)
Osteoporosis (T-score < −2.5)	0	1 (1.9)	1 (0.7)
Status undetermined	1 (1.1)	0	1 (0.7)
Total lumbar spine BMD status[e], n (%)			
Normal (T-score ≥ −1)	38 (40.4)	25 (46.3)	63 (42.6)
Osteopenia (−2.5 ≤ T-score < −1.0)	51 (54.3)	25 (46.3)	76 (51.4)
Osteoporosis (T-score < −2.5)	4 (4.3)	4 (7.4)	8 (5.4)
Status undetermined	1 (1.1)	0	1 (0.7)
Median vitamin D, ng/mL (Q1, Q3)	18.8 (13.2, 24.4)	18.4 (14.0, 23.6)	18.8 (13.6, 24.4)

[a]P = 0.0440; [b]P = 0.0265; [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 (N = 147); [e]Results from the Spine DXA analysis set (N = 148). ALT, alanine aminotransferase; BMD, bone mineral density; BMI, body mass index; DNA, deoxyribonucleic acid; DXA, dual-energy x-ray absorptiometry; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; FAS, full analysis set; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; Q, quartile; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

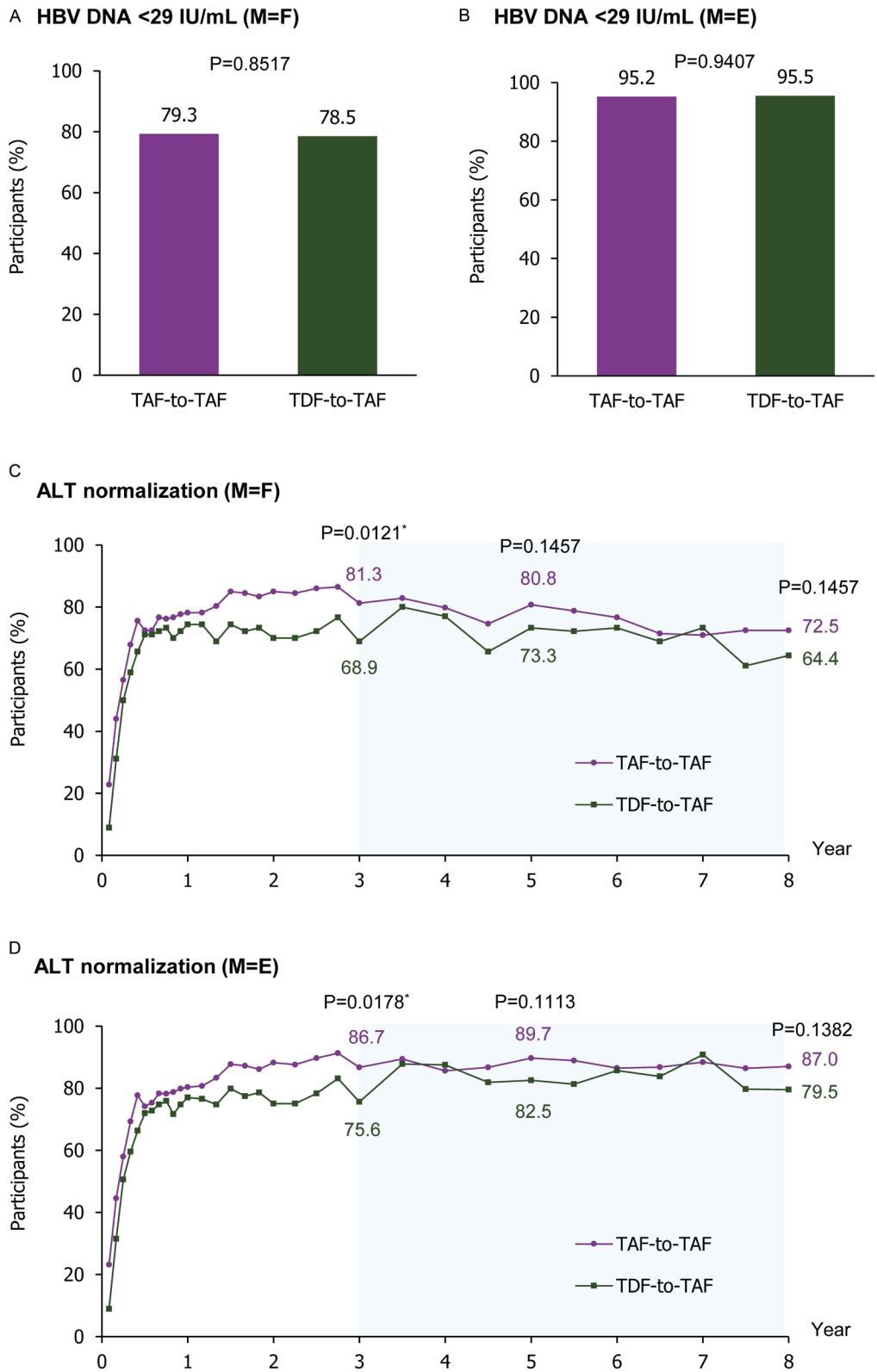

Fig. 2. Key efficacy outcomes (FAS). A–B. Proportions of participants with HBV DNA <29 IU/mL at Year 8. C–D. Proportions of participants with ALT normalization through eight years†. *$P < 0.05$; †Among participants with ALT above the China criteria (ULN ≤ 40 U/L for both males and females) at baseline. ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; FAS, full analysis set; HBV, hepatitis B virus; M=E, missing=excluded; M=F, missing=failure; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

Table 2. Serological responses at Year 8 (FAS)

Other efficacy endpoints	M=F		M=E	
	TAF-TAF (N = 227)	TDF-TAF (N = 107)	TAF-TAF (N = 189)	TDF-TAF (N = 87)
Serological Response				
HBeAg loss, n/N[a] (%)	49/120 (40.8)	20/59 (33.9)	49/94 (52.1)	20/46 (43.5)
HBeAg seroconversion, n/N[a] (%)	33/120 (27.5)	9/59 (15.3)	33/94 (35.1)	9/46 (19.6)
HBsAg loss, n/N[b] (%)	11/227 (4.8)	0/107 (0)	11/189 (5.8)	0/87 (0)
HBsAg seroconversion, n/N[b] (%)	6/227 (2.6)	0/107 (0)	6/189 (3.2)	0/87 (0)
Mean changes from baseline in HBsAg, log_{10}IU/mL (SD)	NA	NA	−1.01 (1.224)	−0.77 (1.123)

[a]Among participants who were seropositive for HBeAg and negative for anti-HBe at baseline; [b]Among participants who were seropositive for HBsAg and negative for anti-HBs at baseline; Anti-HBe, hepatitis B e antibody; Anti-HBs, hepatitis B surface antibody; FAS, full analysis set; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

TAF: −0.1 [0.154]; TDF-TAF: −0.1 [0.209]) (Supplementary Table 4). Among participants with FibroTest scores at both baseline and Year 8, the proportions with improvement, no change, and worsening of fibrosis stage were 26.1%, 71.7%, and 2.2%, respectively, in the TAF-TAF group; and 28.9%, 61.4%, and 9.6%, respectively, in the TDF-TAF group. Notably, among participants with a baseline FibroTest score ≥ 0.75 (suggestive of cirrhosis), 18 of 19 (94.7%) in the TAF-TAF group and six of nine (66.7%) in the TDF-TAF group had scores < 0.75 at Year 8, indicating a reversal of cirrhosis.

Resistance surveillance

Prior reports showed no TAF resistance through Year 5.[10,11] For annual resistance surveillance at Years 6, 7, and 8, five (TAF-TAF: 4; TDF-TAF: 1), seven (TAF-TAF: 5; TDF-TAF: 2), and 12 (TAF-TAF: 9; TDF-TAF: 3) participants had HBV DNA ≥ 69 IU/mL at these timepoints, respectively, and qualified for pol/RT sequencing. Among them, most had viremia in the absence of virologic breakthrough. At Year 6 (n = 5), three participants experienced a viral blip, one experienced a virologic breakthrough, and one had persistent viremia (in Study 110). At Year 7 (n = 7), five participants experienced a viral blip, one experienced a virologic breakthrough, and one had persistent viremia (in Study 110). At Year 8 (n = 12), nine participants experienced a viral blip, three experienced a virologic breakthrough, and no participant had persistent viremia. Sequencing results of these participants are provided in Supplementary Table 5. Overall, no pol/RT amino acid substitutions associated with resistance to TAF or tenofovir were identified in either treatment group.

Safety

The incidences of AEs and laboratory abnormalities during the five-year open-label phase in the open-label safety analysis set are summarized in Table 3. Overall, 87.7% (186/212) of the TAF-TAF group and 94.9% (94/99) of the TDF-TAF group experienced treatment-emergent AEs, and 5.7% (12/212) and 6.1% (6/99), respectively, experienced grade 3/4 AEs. Up to 27.4% (58/212) of the TAF-TAF group and 30.3% (30/99) of the TDF-TAF group experienced study drug-related AEs. All study drug-related AEs were grade ≤ 2, except for one Grade 3 AE of chronic gastritis in the TDF-TAF group, which was also the only study drug-related serious AE reported. No AEs led to study drug discontinuation. Two deaths, one in each group, occurred during the open-label phase, and both were considered unrelated to study drug.

AEs occurring in ≥5% of participants in either group during the open-label phase are also provided in Table 3. COVID-19 (TAF-TAF: 39.6%; TDF-TAF: 28.3%), hepatic steatosis (TAF-TAF: 25.0%; TDF-TAF: 27.3%), and upper respiratory tract infection (TAF-TAF: 18.9%; TDF-TAF: 16.2%) were the top three most common AEs. The higher incidence of hepatic steatosis AEs reported during the open-label phase was likely due to the introduction of hepatic ultrasounds at Year 2 following a protocol amendment (conducted for HCC surveillance every six months). Two participants (0.9%) in the TAF-TAF group and three (3.0%) in the TDF-TAF group developed HCC.

Grade ≥ 3 laboratory abnormalities occurred in 16.0% (34/212) of the TAF-TAF group and 12.1% (12/99) of the TDF-TAF group (Table 3). Grade ≥ 3 laboratory abnormalities in ≥2% of participants in either group included occult blood, urine glucose, fasting low-density lipoprotein (LDL) cholesterol, ALT, and gamma-glutamyl transferase. Detailed frequencies of these laboratory abnormalities are provided in Table 3.

Changes in renal parameters: Serial changes in renal function parameters are summarized in Figure 3. Participants treated with TAF experienced a significantly smaller decline from baseline in median $eGFR_{CG}$ compared with those treated with TDF during the double-blind phase (Year 3: −0.1 mL/m vs. −3.6 mL/m, P = 0.0120). After both groups entered the open-label phase, $eGFR_{CG}$ increases were observed in the TDF-TAF group. At Year 8, the median change from baseline in $eGFR_{CG}$ was −1.3 mL/m and −2.0 mL/m in the TAF-TAF and TDF-TAF groups, respectively, and the difference between the two groups was no longer statistically significant (Fig. 3A). Similarly, the median percent changes from baseline in RBP:Cr and β_2M:Cr were significantly different between the two treatment groups during the double-blind phase, but no longer so at Year 8 (Fig. 3B and C).

Shifts in chronic kidney disease (CKD) stage versus baseline are provided in Supplementary Table 6. At the end of the double-blind phase, the TAF-treated group had a larger proportion of participants with an improved CKD stage and a smaller proportion with a worsening CKD stage than the TDF-treated group. However, at Year 8, the shifts in CKD stages from baseline were similar across the two groups (TAF-TAF: 3.8% improved, 89.2% remained the same, 7.0% worsened; TDF-TAF: 3.4% improved, 88.5% remained the same, 8.0% worsened; P = 0.7230).

Changes in BMD: For participants with available hip and spine BMD data, the mean percentage changes through eight years are presented in Fig. 4. TAF treatment over eight years showed minimal impact on hip or spine BMD. For participants

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

n, (%)	TAF-TAF (N = 212)	TDF-TAF (N = 99)
Any AEs	186 (87.7)	94 (94.9)
Any study drug-related AEs	58 (27.4)	30 (30.3)
Any grade 3 or 4 AEs	12 (5.7)	6 (6.1)
Any study drug-related grade 3 or 4 AEs	0	1 (1.0)*
Any SAEs	27 (12.7)	11 (11.1)
Any study drug-related SAEs	0	1 (1.0)*
Any AEs leading to study drug discontinuation	0	0
Death	1 (0.5)†	1 (1.0)‡
AEs occurring in ≥5% of participants in either group		
COVID-19	84 (39.6)	28 (28.3)
Hepatic steatosis	53 (25.0)	27 (27.3)
Upper respiratory tract infection	40 (18.9)	16 (16.2)
Hyperlipidemia	27 (12.7)	7 (7.1)
Nasopharyngitis	24 (11.3)	10 (10.1)
Hypertension	19 (9.0)	12 (12.1)
Gallbladder polyp	15 (7.1)	7 (7.1)
Diarrhea	14 (6.6)	2 (2.0)
Cough	12 (5.7)	3 (3.0)
Renal cyst	11 (5.2)	0
Nephrolithiasis	8 (3.8)	6 (6.1)
Cholelithiasis	6 (2.8)	6 (6.1)
Any treatment-emergent grade 3 or 4 laboratory abnormality	34 (16.0)	12 (12.1)
Treatment-emergent grade 3 or 4 laboratory abnormalities occurring in ≥2% of participants in either group		
Occult blood	13 (6.1)	4 (4.1)
Urine glucose	8 (3.8)	3 (3.1)
Fasting LDL cholesterol	5 (2.4)	2 (2.0)
Alanine aminotransferase	3 (1.4)	4 (4.0)
Gamma-glutamyl transferase	1 (0.5)	2 (2.0)

*Grade 3 (SAE) of chronic gastritis; †Liver cancer; ‡Small cell carcinoma. AE, adverse event; SAE, serious adverse event; LDL, low-density lipoprotein; OL SAS, open-label safety analysis set; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

who were initially randomized to TDF, small mean percentage decreases from baseline in hip and spine BMD were observed during the double-blind phase; improvements in both hip and spine BMD were observed following the switch to open-label TAF.

Metabolic changes: As shown in Fig. 5A–D, median declines in fasting lipid parameters from baseline were observed during the double-blind phase in the TDF group. After switching from TDF to TAF at Year 3, median increases in lipid parameters were observed. These increases generally plateaued after Year 5, and at Year 8, both groups had small and similar increases in median total cholesterol (TAF-TAF: 6 mg/dL; TDF-TAF: 11 mg/dL; $P = 0.2175$), direct LDL cholesterol (TAF-TAF: 11 mg/dL; TDF-TAF: 16 mg/dL; $P = 0.1937$), and triglycerides (TAF-TAF: 24 mg/dL; TDF-TAF: 12 mg/dL; $P = 0.3441$), and small decreases from baseline in median high-density lipoprotein (HDL) cholesterol (TAF-TAF: −8 mg/dL; TDF-TAF: −6 mg/dL; $P = 0.5124$). Both groups had a similar median increase of 0.7 in the total cholesterol to HDL cholesterol (hereinafter referred to as TC:HDL) ratio, a marker of cardiovascular risk. No significant difference was observed between the two groups in median changes from baseline in fasting glucose during both the double-blind and open-label phases (Fig. 5F).

As previously reported, small between-group differences were observed in the changes in body weight up to Year 3 (small median increases from baseline in the TAF-TAF group and small median decreases in the TDF-TAF group). Following the switch to open-label TAF, similar small median increases were observed in both groups.[11] At Year 8, the median change from baseline in body weight in the TAF-TAF and TDF-TAF groups was 1.8 kg and 2.3 kg, respectively (Fig. 5G), and the median change (Q1, Q3) in body mass index (BMI) was 0.6 (−0.4, 1.7) and 0.8 (−0.7, 1.9), respectively. The shifts in BMI category are provided in Supplementary Table 7. Most participants maintained their original BMI category

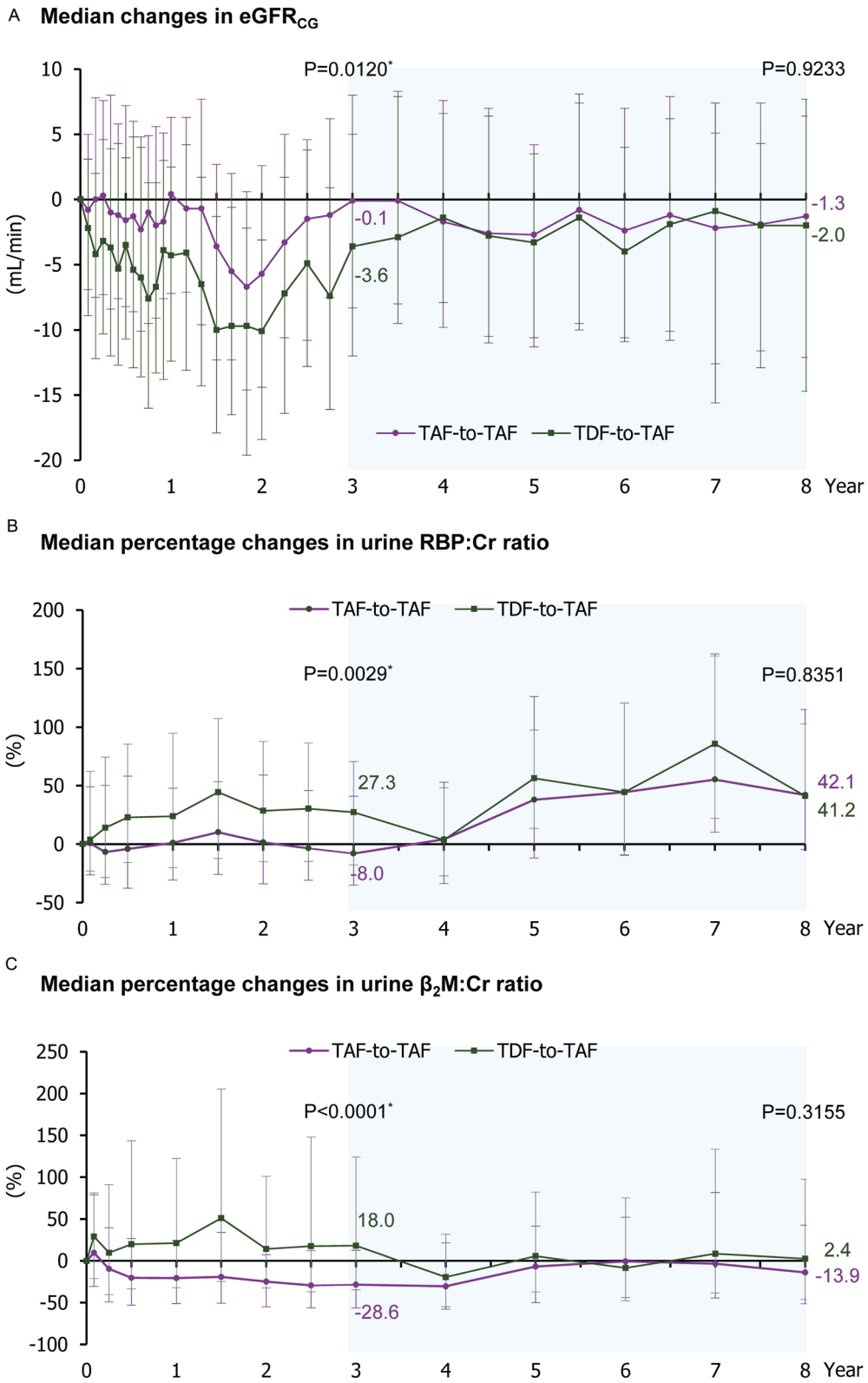

Fig. 3. Changes in renal safety parameters from baseline through eight years (FAS). A. Median (Q1, Q3) changes in eGFR$_{CG}$. B. Median (Q1, Q3) percentage changes in urine RBP:Cr ratio. C. Median (Q1, Q3) percentage changes in urine β_2M:Cr ratio. *P < 0.05; β_2M:Cr, β_2-microglobulin to creatinine; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; FAS, full analysis set; Q, quartile; RBP:Cr, retinol binding protein to creatinine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

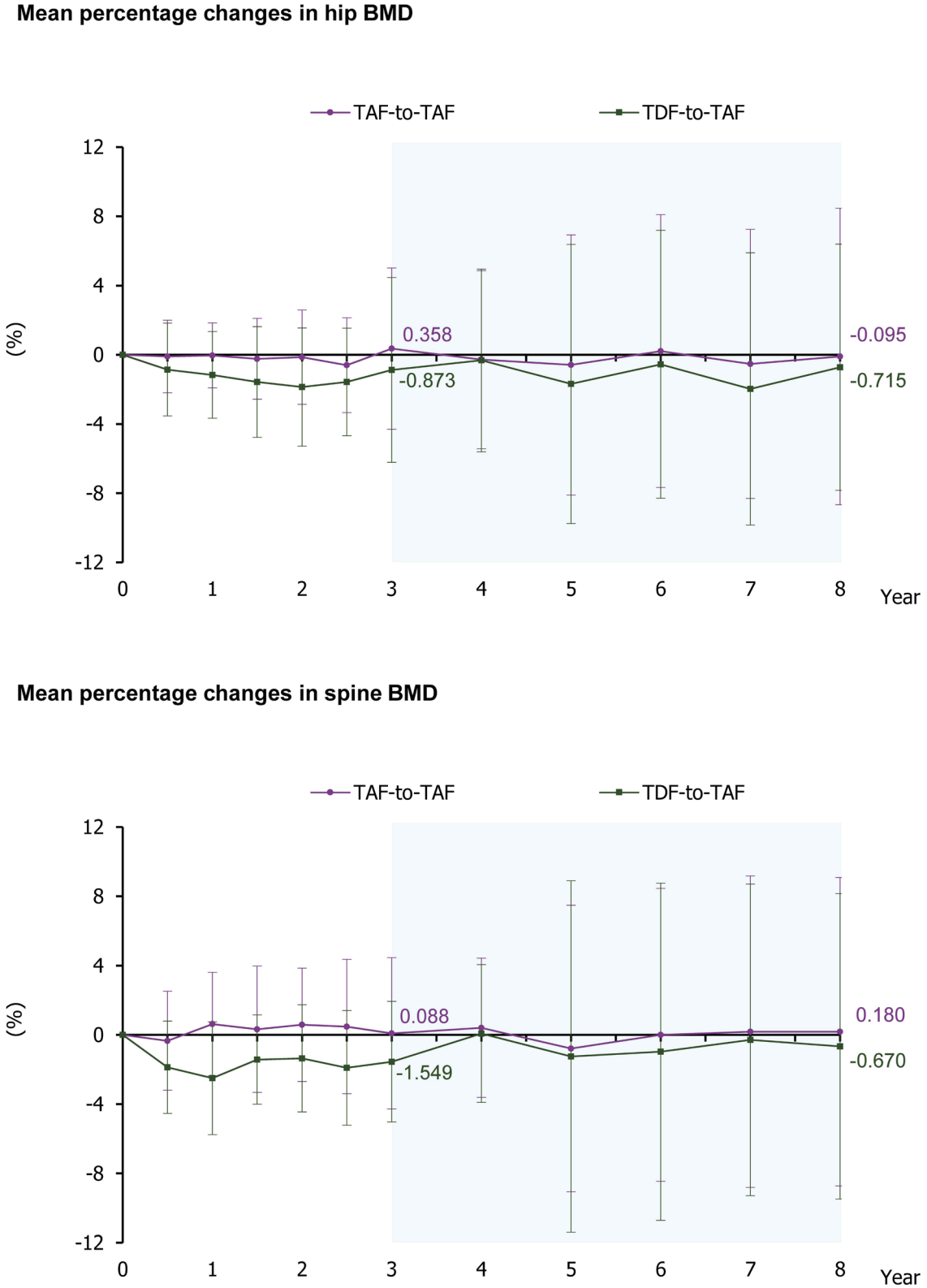

Fig. 4. Mean (SD) percentage changes from baseline in hip and spine bone mineral density through eight years[*] (DXA analysis sets). A. Mean percentage changes in hip BMD (Hip DXA analysis set, TAF-TAF: N = 93, TDF-TAF: N = 54). B. Mean percentage changes in spine BMD (Spine DXA analysis set, TAF-TAF: N = 94, TDF-TAF: N = 54). [*]Results from the open-label Hip DXA and Spine DXA analysis sets. BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

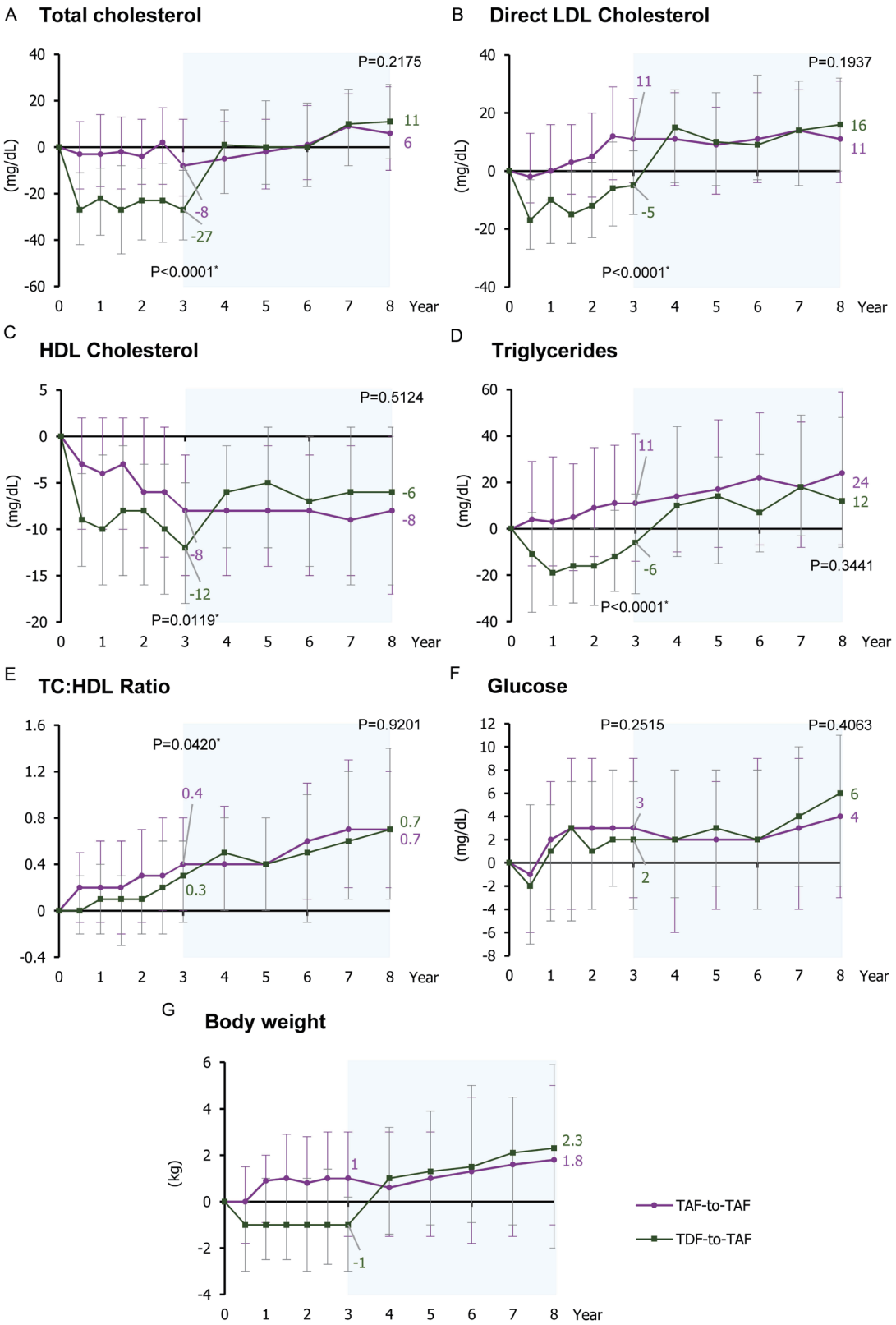

Fig. 5. Median (Q1, Q3) changes from baseline in fasting blood metabolic parameters and body weight through eight years (FAS). A. Total cholesterol. B. Direct LDL cholesterol. C. HDL cholesterol. D. Triglycerides. E. TC:HDL ratio. F. Glucose. G. Body weight. FAS, full analysis set; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quartile; TAF, tenofovir alafenamide; TC:HDL, total cholesterol to high-density lipoprotein cholesterol; TDF, tenofovir disoproxil fumarate.

after eight years of TAF treatment, with only modest shifts observed—primarily among those who were overweight or obese at baseline.

Discussion

Studies 108 and 110 represent the longest evaluation of TAF in people living with CHB. This final, eight-year analysis of the China cohort confirmed that TAF maintained potent antiviral efficacy, with high rates of viral suppression and ALT normalization. These outcomes were consistent across both the TAF-TAF and TDF-TAF groups, aligning with the data generated in global cohorts. Notably, no resistance to TAF was detected over the entire study period.

The primary endpoint of Studies 108 and 110 was the proportion of participants with HBV DNA < 29 IU/mL. At Year 8, approximately 80% of participants in both groups achieved HBV DNA < 29 IU/mL by the M=F approach, increasing to 95% with the M=E approach (Fig. 2A and B). This high viral suppression rate is consistent with the global eight-year results as well as the previous five-year China report.[9,11] These findings reaffirm TAF's non-inferiority to TDF in antiviral efficacy and its ability to maintain long-term viral suppression in Chinese patients with CHB.

ALT normalization occurred rapidly and remained high throughout treatment. During the double-blind phase, TAF-treated participants had higher normalization rates than those on TDF. Although this difference narrowed after the switch to open-label TAF, the trend persisted (Fig. 2C and D). These results are consistent with trends observed in the global cohort and real-world studies, which have also linked early and sustained ALT normalization to improved clinical outcomes, including reduced HCC risk.[6,7,9,13–17] For instance, Choi et al. showed that delayed ALT normalization at 6–12, 12–24, and >24 months was associated with incrementally higher risks of HCC (adjusted hazard ratio = 1.40, 1.74, and 2.45, respectively, $P < 0.001$) versus early ALT normalization within six months.[14]

Serological responses, including HBeAg loss and seroconversion, were numerically higher in the TAF-TAF group at Year 8 (Table 2). A real-world study in China similarly reported superior ALT normalization and HBeAg seroconversion with TAF compared with TDF or entecavir (ETV) in treatment-naive patients.[18] However, HBsAg loss and seroconversion remained uncommon, occurring in less than 5% of participants after eight years. These findings are consistent with global eight-year data and other long-term studies of potent nucleos(t)ide analogues, which typically report HBsAg loss rates of 2–5% over similar durations.[9,19–22] As HBsAg loss is considered a surrogate for functional cure, these results highlight a critical unmet need for novel therapies that can significantly increase HBsAg clearance. Additionally, fewer participants in the TAF-TAF group experienced fibrosis progression at Year 8 (2.2% vs. 9.6%), suggesting potential long-term histologic benefits. The observation that many participants with baseline evidence of cirrhosis no longer met the FibroTest threshold for cirrhosis at Year 8 suggests that long-term TAF treatment may not only prevent fibrosis progression but also promote histologic regression—an outcome with meaningful implications for reducing long-term liver-related morbidity and mortality.

As the CHB population ages and comorbidities become more prevalent, ensuring the long-term safety of antiviral treatment is of growing importance. Safety outcomes over eight years were favorable. The incidences of grade 3/4 AEs (~6%) and serious AEs(~12%) remained low, with only one study drug-related serious AE reported. These results reinforce the long-term tolerability of TAF in this population.

The favorable renal and bone safety of TAF in CHB patients, demonstrated in both randomized controlled trials and real-world studies, remains a key strength of TAF.[6–8,10,11,23–26] Consistent with past studies and the global eight-year results, $eGFR_{CG}$, tubular markers, and BMD of the TAF-TAF group were stable over the course of TAF treatment through eight years (Figs. 3 and 4), and most of the TAF-TAF group retained their baseline CKD stage at Year 8 (Supplementary Table 7). More importantly, declines in renal and bone parameters observed in TDF-treated participants during the double-blind phase improved following the switch to open-label TAF at Year 3. Similar trends have been observed in prior clinical trials and real-world studies evaluating the switch from TDF to TAF.[9,27–30] These results support the renal and bone safety advantages of TAF, particularly in aging populations or those at risk of renal impairment or bone loss.

Consistent with global eight-year findings,[9] modest changes in lipid parameters were observed in the China cohort. During the double-blind phase, TDF-treated participants experienced early decreases in total cholesterol, LDL-cholesterol, and triglycerides, reflecting the known lipid-lowering effect of TDF.[27,31] After switching to TAF at Year 3, these parameters increased, reaching levels similar to those observed in participants receiving continuous TAF from baseline, and then stabilized through Year 8. Among participants treated with TAF throughout, small median changes were observed in fasting total cholesterol and HDL cholesterol (6 mg/dL and −8 mg/dL, respectively), and a slightly greater median increase in LDL cholesterol (11 mg/dL). Importantly, the TC:HDL ratio, a marker of cardiovascular risk, increased only minimally over eight years in both groups (Fig. 5). These findings align with global trial results, ASCVD risk analyses, and real-world studies, all of which confirm neutral long-term cardiovascular effects for both TDF and TAF despite differing lipid profiles.[9,32–34] Nevertheless, as in the general population, comprehensive baseline cardiovascular risk assessment and routine lipid monitoring remain advisable, particularly for patients with pre-existing risk factors.[9,27,29,33,34]

Beyond comparisons with TDF, real-world studies have also evaluated TAF versus ETV, another recommended first-line nucleos(t)ide analogue for CHB. These studies, including those conducted in China, consistently show comparable antiviral efficacy in the general CHB population and advantages of TAF in specific subgroups.[35–41] For example, retrospective and prospective cohorts have reported that switching from ETV to TAF improves virologic response and ALT normalization in patients with suboptimal ETV response, while maintaining favorable bone and renal safety profiles.[36,38–40] These findings, together with the established safety benefits of TAF, support its role as a potent and safer alternative to both TDF and ETV, particularly for patients with compromised renal or bone health, or inadequate response to ETV.

The limitations of the China cohort in Studies 108 and 110, such as the exploratory nature of statistical analysis and differences in certain baseline characteristics, have been previously acknowledged.[11] To mitigate bias, both the M=F and M=E approaches were applied in efficacy analyses, and outcomes were interpreted in the context of these limitations. Additionally, the consistency of findings with global cohorts strengthens the generalizability and robustness of the conclusions. For the current analysis, we note that by Year 8, a total of 55 (16.5%) participants prematurely discontinued the study. Although this rate is not unexpected for a long-term trial, attrition may introduce bias. For example, discontinuations could lead to underestimation of treatment efficacy if participants with sustained viral suppression were

less motivated to return for study visits, or underestimation of long-term safety events if participants with subclinical AEs were lost. Most discontinuations during the open-label phase were due to administrative reasons, and none were attributable to AEs. The use of both M=E and M=F analyses helps further mitigate potential bias in efficacy analyses. Additionally, the COVID-19 pandemic may have contributed to loss to follow-up during the open-label phase. Notably, the attrition rate observed in this China cohort was lower than that reported in the global eight-year studies, further supporting the robustness of these findings.

Conclusions

This eight-year analysis provides robust evidence supporting the long-term efficacy and safety of TAF in Chinese patients with CHB. As the longest investigation of TAF in this population, our study not only supports the favorable long-term renal and bone safety of TAF but also demonstrates that declines in renal and bone parameters associated with TDF may be reversible after switching to TAF. These findings are particularly relevant for the aging CHB population in China and reinforce the role of TAF as the preferred long-term treatment option.

Acknowledgments

The authors thank the participants and the study staff for participating in this study. The authors acknowledge Ruilin Chen (Costello Medical, Singapore, sponsored by Gilead Sciences) for medical writing and editorial assistance in preparing this manuscript for publication, based on the authors' input and direction.

Funding

This study was funded by Gilead Sciences, Inc.

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; and grants from Bristol Myers Squibb. QN has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Johnson & Johnson, MSD, and Roche, and has received research funding from Bristol-Myers Squibb, Gilead Sciences, and Roche. 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, YaC, FA, LJY, HW, RM, TY, and IB are employees and stockholders of Gilead Sciences. CC 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. JJ has served as a consultant for Gilead Sciences and GSK, and has received research funds from Bristol-Myers Squibb and Gilead Sciences. JH and JJ have been Executive Associate Editors of *Journal of Clinical and Translational Hepatology* since 2013, QN has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2024. The other authors have no other conflict of interests related to this publication.

Author contributions

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

Ethical statement

Trial Registration: Clinicaltrials.gov numbers: NCT02836249 and NCT02836236. The two studies were conducted in accordance with the Declaration of Helsinki (as revised in 2024) and Good Clinical Practice. The study protocols were approved by the institutional review board or independent ethics committees at all participating sites (approval numbers of the leading site: NFEC-2015-047 and NFEC-2015-048). 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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