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# Long-Term Treatment With Tenofovir Alafenamide for Chronic Hepatitis B Results in High Rates of Viral Suppression and Favorable Renal and Bone Safety

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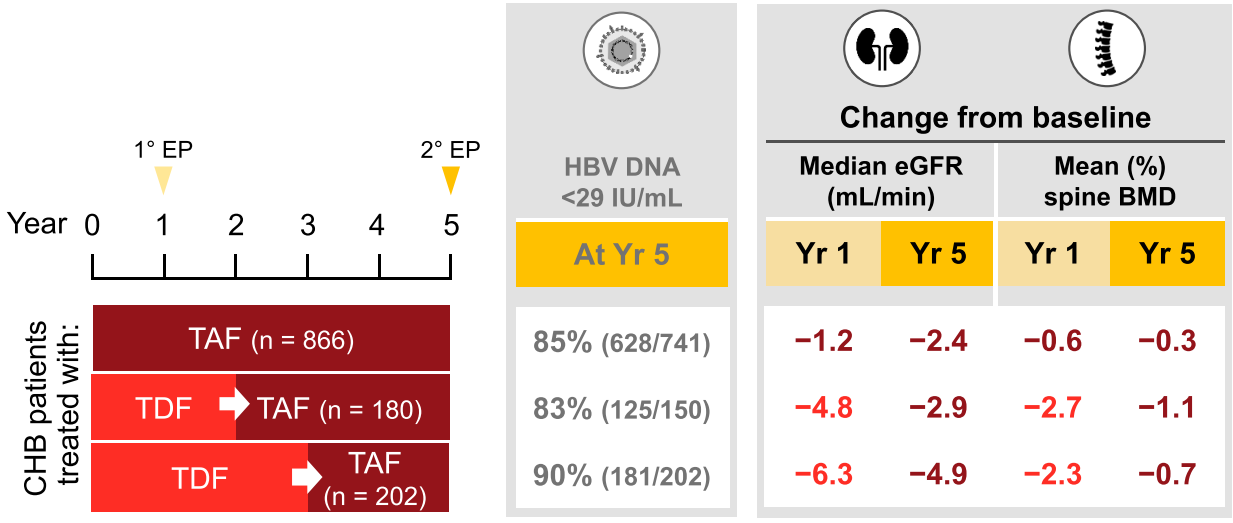


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INTRODUCTION: **The results from 2 phase 3 studies, through 2 years, in chronic hepatitis B infection showed tenofovir alafenamide (TAF) had similar efficacy to tenofovir disoproxil fumarate (TDF) with superior renal and bone safety. We report updated results through 5 years.**

METHODS: **Patients with HBeAg-negative or HBeAg-positive chronic hepatitis B infection with or without compensated cirrhosis were randomized (2:1) to TAF 25 mg or TDF 300 mg once daily in double-blind (DB) fashion for up to 3 years, followed by open-label (OL) TAF up to 8 years. Efficacy (antiviral, biochemical, and serologic), resistance (deep sequencing of polymerase/reverse transcriptase and phenotyping), and safety, including renal and bone parameters, were evaluated by pooled analyses.**

RESULTS: **Of 1,298 randomized and treated patients, 866 receiving TAF (DB and OL) and 432 receiving TDF with rollover to OL TAF at year 2 (n = 180; TDF→TAF3y) or year 3 (n = 202; TDF→TAF2y) were included. Fifty (4%) TDF patients who discontinued during DB were excluded. At year 5, 85%, 83%, and 90% achieved HBV DNA <29 IU/mL (missing = failure) in the TAF, TDF→TAF3y, and TDF→TAF2y groups, respectively; no patient developed TAF or TDF resistance. Median estimated glomerular filtration rate (by using Cockcroft-Gault) declined <2.5 mL/min, and mean declines of <1% in hip and spine bone mineral density were seen at year 5 in the TAF group; patients in the TDF→TAF groups had improvements in these parameters at year 5 after switching to OL TAF.**

DISCUSSION: **Long-term TAF treatment resulted in high rates of viral suppression, no resistance, and favorable renal and bone safety.**

**KEYWORDS:** Chronic hepatitis B virus infection; tenofovir disoproxil fumarate; tenofovir alafenamide; viremia reduction; bone mineral density

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/D18

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## INTRODUCTION

Hepatitis B virus (HBV) infection affects approximately 296 million individuals globally (1,2). Possible sequelae include cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (3). Nucleos(t)ide analogs are the mainstay of anti-HBV therapy and are associated with reversal of fibrosis/cirrhosis and reduction of HCC risk (4). Given the low rate of hepatitis B surface antigen (HBsAg) seroclearance, treatment is often lifelong. As the chronic hepatitis B (CHB) population ages, associated comorbidities, such as renal and bone diseases, highlight the need for optimization of anti-HBV therapies.

Oral administration of tenofovir disoproxil fumarate (TDF), a tenofovir (TFV) prodrug, results in rapid cleavage of the disoproxil component by tissue and plasma esterases' producing high circulating levels of TFV, whereas within hepatocytes, TFV is efficiently converted to TFV-diphosphate, the active form that potently inhibits HBV polymerase/reverse transcriptase (pol/RT) (5,6). TDF has a generally favorable safety profile; however, nephrotoxicity and reductions in bone mineral density (BMD) limit its use in some patients (7).

Tenofovir alafenamide (TAF) is a TFV prodrug with enhanced plasma stability (5). Relative to once-daily 300 mg TDF, once-daily 25 mg TAF has ~90% lower circulating levels of TFV (8), which represents the basis for a more favorable renal and bone safety profile. In 2 similarly designed double-blind (DB), randomized, phase 3 studies conducted in hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients, TAF demonstrated noninferior antiviral efficacy (proportion with HBV DNA <29 IU/mL) vs TDF at weeks 48 and 96, with superior renal and bone safety (9,10). Because these 2 phase 3 studies are ongoing, we report the interim results for treatment through 5 years in patients randomized to receive TAF throughout or DB TDF followed by open-label (OL) TAF.

## METHODS

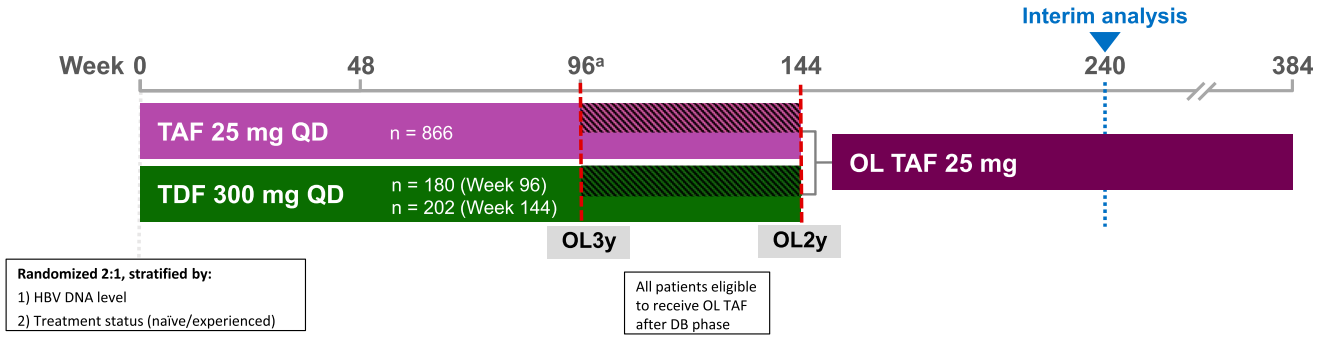
### Study design

The design of phase 3 Studies 108 (NCT01940341) and 110 (NCT01940471) were previously described in detail (9,10). Methodology pertinent to this analysis is included herein.

Adult men and nonpregnant łwomen with HBV DNA ≥20,000 IU/mL, alanine aminotransferase (ALT) >60 U/L (men) or >38 U/L (women), and estimated glomerular filtration rate by using Cockcroft-Gault ($eGFR_{CG}$) ≥50 mL/min were included. Patients were randomized 2:1 to TAF 25 mg or TDF 300 mg (with matching placebo) once daily during the DB phase, followed by OL TAF during the extension phase (Figure 1). Of note, before submission of the New Drug Application for TAF in 2016, the United States Food and Drug Administration requested the DB duration be extended to gain longer-term comparative data. Therefore, the study sponsor implemented an amendment to both protocols that extended the DB phase by 1 year (to week 144), and at the same time, the OL phase was extended to year 8 (week 384). Because the speed of protocol amendment implementation varied widely across study sites, a portion of patients (~50% across both arms) had already rolled over to OL TAF at week 96, whereas the remainder had their DB treatment extended by 1 year.

The protocols were approved by the review board/ethics committee of each institution before study initiation and following any protocol amendments. Studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of




Two phase 3, randomized, DB, active-controlled trials

- Study 108 NCT01940341 (N = 425 originally randomized): HBeAg-negative patients
- Study 110 NCT01940471 (N = 873 originally randomized): HBeAg-positive patients

**Figure 1.** Study design. [a]Amendment 3 enacted to extend DB period to week 144 and OL to week 384 (year 8); shaded areas represent patients who rolled over to OL TAF at week 96 (OL3y) or week 144 (OL2y). DB, double blind; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Helsinki. All patients provided written informed consent before starting study-related procedures.

### Analysis population

The year 5 (week 240) analysis population comprised 3 groups: (i) TAF group, patients who received TAF DB treatment (for 2 or 3 years) followed by OL TAF; (ii) TDF→TAF3y group, patients who received TDF DB treatment for 2 years followed by OL TAF; and (iii) TDF→TAF2y group, patients who received TDF DB treatment for 3 years followed by OL TAF. TDF patients who discontinued during the DB period (ie, those who did not receive any OL TAF) were excluded.

### Study assessments and endpoints

Efficacy was assessed by pooled analysis and by individual study: viral suppression (HBV DNA <29 IU/mL, including proportions with target not detected), ALT normalization (ALT ≤ upper limit of normal in patients with ALT > upper limit of normal at baseline) as determined by both central laboratory (LabCorp., Indianapolis, IN) and 2018 American Association for the Study of Liver Diseases criteria, serologic responses, and fibrosis change by serum FibroTest (BioPredictive, Paris, France). Routine safety assessments and serial changes in renal and bone parameters were assessed by pooled analysis as previously described (11).

Resistance analyses, including deep sequencing of HBV pol/RT (performed at baseline and annually) for those with HBV DNA ≥69 IU/mL (because of virologic breakthrough, persistent viremia, or treatment discontinuation with viremia) along with viral phenotyping, were performed by standardized methods, as previously described (12).

### Statistical analysis

Because the protocol amendments directly affected DB treatment duration and timing of rollover to OL TAF for both treatment groups (TAF and TDF), comparisons between treatment groups were not considered appropriate. Alternatively, within-group treatment outcomes were assessed by descriptive statistics. For patients receiving DB treatment and ≥1 dose of OL TAF, efficacy parameters were assessed using the OL full analysis set (OL FAS). Because 1 center in Asia elected not to participate in the amendment, 69 patients from this site (25 and 44 in Studies 108 and 110, respectively) completed the study at year 3 and thus were excluded from the OL FAS for the 5-year efficacy analysis. For fasting lipids and key renal and bone parameters, by-visit changes over the DB and OL periods were assessed in the safety analysis set, whereas treatment-emergent adverse events (AEs), serious AEs, and graded laboratory abnormalities were assessed cumulatively using the OL safety analysis set, which included all patients who completed DB treatment and received ≥1 dose of study drug in the OL phase. All efficacy endpoints were evaluated as proportions using a missing-equals-failure (M = F) approach. As an additional sensitivity analysis, efficacy was also assessed using missing equals excluded (M = E).

## RESULTS

A total of 1,298 patients, including 439 HBeAg-negative and 859 HBeAg-positive patients, were randomized to receive TAF (n = 866) or TDF (n = 432; Figure 2). Among patients randomized to TAF, 775 (90%) entered the OL phase; by year 5, 70 (9%) had discontinued. Among patients randomized to TDF, 382 (88%) entered the OL TAF phase: 180 and 202 at years 2 (TDF→TAF3y) and 3 (TDF→TAF2y), respectively. Cumulatively, of patients randomized to the TDF→TAF arms, 31 (8%) discontinued study treatment. Of all patients, fewer than 1% discontinued treatment because of an AE. For the OL FAS, 741, 150, and 202 patients were evaluable in the TAF, TDF→TAF3y, and TDF→TAF2y groups, respectively, after excluding the 69 who did not participate in the protocol amendment.

### Patient characteristics

Baseline demographic and disease characteristics are presented in Table 1. In general, characteristics in this analysis are comparable with the overall study population previously described (9–11).

### Efficacy

***Virologic response.*** Rates of viral suppression were most pronounced during years 1–2 and were sustained thereafter (Figure 3), with similar proportions achieving HBV DNA <29 IU/mL at year 5: TAF, 85%; TDF→TAF3y, 83%; and TDF→TAF2y, 90% (Table 2). Comparable results were observed by M = E and when evaluated by

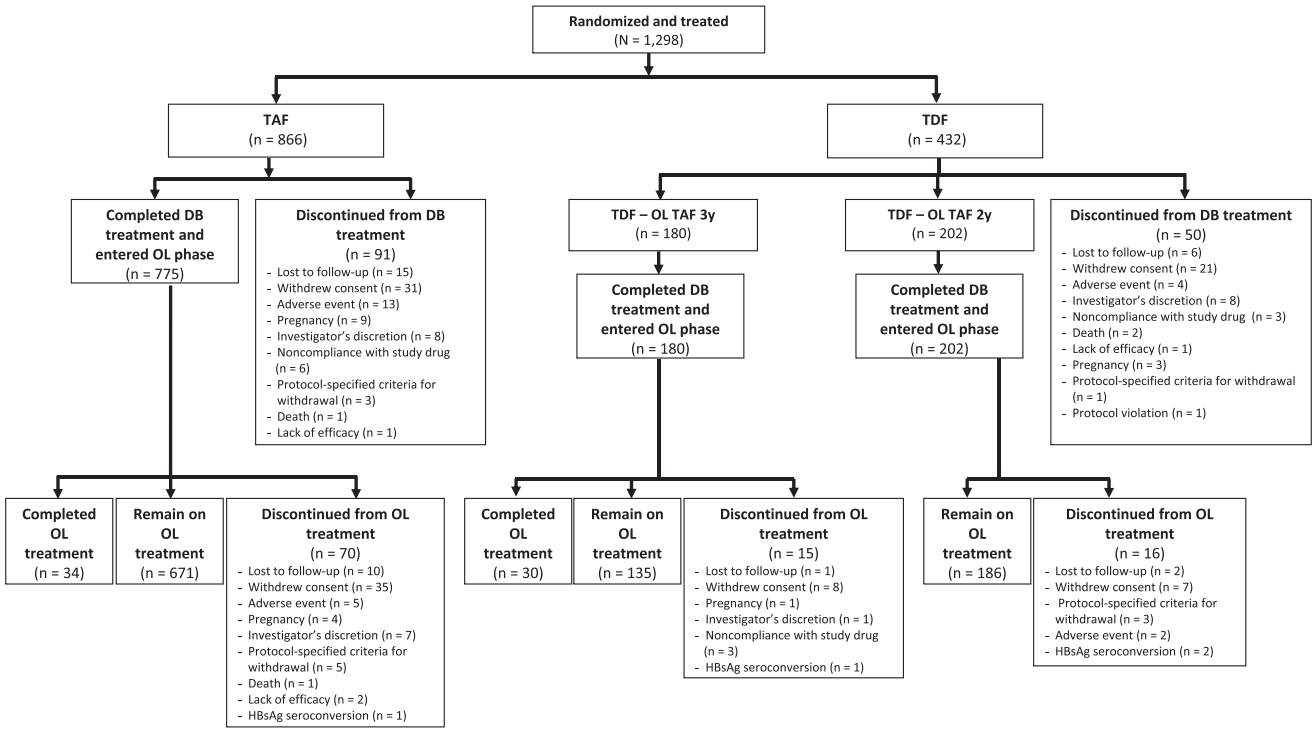



**Figure 2.** Patient disposition at week 240. DB, double blind; HBsAg, hepatitis B surface antigen; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

individual study (see Supplementary Tables 1 and 2, http://links.lww.com/AJG/D18).

***Biochemical and serologic responses.*** A higher proportion of TAF than TDF patients experienced ALT normalization (by each criterion) during DB treatment. Increases in ALT normalization rates were observed after TDF to OL TAF switch (Figure 3; see Supplementary Figures 2 and 3, http://links.lww.com/AJG/D18). ALT normalization rates were generally comparable across groups, ranging from 66%–70% and 77%–78%, by the American Association for the Study of Liver Diseases and central laboratory criteria, respectively (Table 2; see Supplementary Tables 1 and 2, http://links.lww.com/AJG/D18).

The proportions who achieved HBeAg loss were similar and progressively increased across treatment groups over time (Figure 3; Table 2; see Supplementary Tables 1 and 2, http://links.lww.com/AJG/D18); the rates of HBeAg seroconversion were also similar across groups (Table 2; see Supplementary Tables 1 and 2; see Supplementary Figure 4, http://links.lww.com/AJG/D18). Over the 5-year period, mean HBsAg declines ranged from $-0.53$ to $-0.72$ $\log_{10}$ IU/mL (see Supplementary Figure 5, http://links.lww.com/AJG/D18), with ≤1.2% (n = 13) of total patients achieving HBsAg loss or HBsAg seroconversion (n = 8; 1%).

***Fibrosis change.*** Mean FibroTest scores and fibrosis categories were similar among treatment groups at baseline (Table 1). After 5 years of treatment, mean decreases in scores were observed in all groups (see Supplementary Table 3, http://links.lww.com/AJG/D18). When evaluated by categorical shifts from baseline to year 5, most patients with moderate-severe fibrosis or cirrhosis by FibroTest had improvements in status, whereas few with mild fibrosis showed progression at year 5 (see Supplementary Table 4, http://links.lww.com/AJG/D18).

## Resistance

Forty-four of 1,298 patients (3%) met the criteria for sequencing at year 5 (26 for virologic breakthrough, 9 for viral blip, 9 for persistent viremia). Sequencing and phenotyping results for the 39 successfully sequenced patients are summarized in Supplementary Digital Content (see Supplementary Table 5, http://links.lww.com/AJG/D18). Overall, the TAF half-maximal effective concentration of baseline and postbaseline sample pairs showed no substitutions conferring reduced susceptibility to TAF. Overall, no HBV pol/RT amino acid substitutions associated with resistance to TAF were detected through year 5. Resistance analyses at weeks 144 and 192 are summarized in Supplementary Digital Content (see Supplementary Tables 6 and 7, http://links.lww.com/AJG/D18).

## Safety

***Adverse events.*** The safety of TAF during the OL phase was comparable across the 3 treatment groups (Table 3). Most AEs were mild, with 3.5%–6.7% of patients across the 3 groups experiencing treatment-emergent AEs of ≥ grade 3 severity. Serious AEs occurred in <10% of patients, with 4 (all in the TAF group) judged related to study treatment. Few patients (≤1%) discontinued treatment because of AEs. Over the course of the study, there were 6 deaths (3 TAF; 3 TDF); the only death occurring during the OL phase was from pancreatic adenocarcinoma. The most common AEs (≥5%) were upper respiratory tract infection, nasopharyngitis, cough, and headache, and incidence rates were similar across groups.

***Hepatocellular carcinoma.*** Given the longer-term duration for this analysis, AEs of HCC were carefully assessed. Over the 5-year

**Table 1. Baseline demographic and disease characteristics**

| | TAF n = 866 | TDF→TAF3y n = 180 | TDF→TAF2y n = 202 |
|---|---|---|---|
| Male, n (%) | 544 (62.8) | 111 (61.7) | 132 (65.3) |
| Age, mean (SD) | 40 (11.8) | 42 (12.1) | 42 (12.3) |
| Asian, n (%) | 687 (79.3) | 146 (81.1) | 149 (73.8) |
| HBeAg-positive, n (%) | 569 (65.7) | 114 (63.3) | 137 (67.8) |
| HBV genotype, n (%) | | | |
| A | 54 (6.2) | 11 (6.1) | 16 (7.9) |
| B | 160 (18.5) | 49 (27.2) | 30 (14.9) |
| C | 418 (48.3) | 80 (44.4) | 100 (49.5) |
| D | 224 (25.9) | 36 (20.0) | 53 (26.2) |
| E | 7 (0.8) | 2 (1.1) | 0 |
| F | 3 (0.3) | 1 (0.6) | 1 (0.5) |
| H | 0 | 0 | 2 (1.0) |
| Unknown | 0 | 1 (0.6) | 0 |
| HBV DNA, log IU/mL, mean (SD) | 7.0 (1.59) | 7.0 (1.64) | 7.0 (1.63) |
| ALT, U/L, mean (SD) | 109 (100.4) | 117 (110.2) | 104 (92.4) |
| Previous treatment, n (%) | | | |
| Oral nucleoside/nucleotide | 211 (24.4) | 43 (23.9) | 51 (25.2) |
| Interferon | 107 (12.4) | 19 (10.6) | 23 (11.4) |
| Cirrhosis history, n (%) | 65 (10.2) | 16 (12.2) | 13 (8.3) |
| FibroTest, mean (SD) | 0.37 (0.230) | 0.36 (0.222) | 0.37 (0.229) |
| FibroTest stage, n (%) | | | |
| 0.00–0.48 | 601 (71.0) | 128 (72.3) | 142 (71.4) |
| 0.49–0.74 | 169 (20.0) | 37 (20.9) | 34 (17.1) |
| 0.75–1.00 | 76 (9.0) | 12 (6.8) | 23 (11.6) |
| Missing | 20 | 3 | 3 |
| $eGFR_{CG}$, mL/min, median (Q1–Q3) | 106.2 (91.0–125.4) | 104.4 (86.1–124.8) | 103.2 (92.4–118.8) |
| Diabetes, n (%) | 57 (6.6) | 9 (5.0) | 19 (9.4) |
| CVD, n (%) | 26 (3.0) | 4 (2.2) | 7 (3.5) |
| Hypertension, n (%) | 99 (11.4) | 29 (16.1) | 31 (15.3) |
| Hyperlipidemia, n (%) | 76 (8.8) | 18 (10.0) | 21 (10.4) |
| Hip BMD, n (%) | | | |
| Normal | 570 (67.0) | 112 (62.6) | 138 (69.7) |
| Osteopenia | 256 (30.1) | 62 (34.6) | 57 (28.8) |
| Osteoporosis | 12 (1.4) | 2 (1.1) | 0 |
| Spine BMD, n (%) | | | |
| Normal | 477 (55.7) | 93 (51.7) | 112 (56.6) |
| Osteopenia | 309 (36.1) | 66 (36.7) | 75 (37.9) |
| Osteoporosis | 57 (6.7) | 18 (10.0) | 8 (4.0) |

ALT, alanine aminotransferase; BMD, bone mineral density; CVD, cardiovascular disease; $eGFR_{CG}$, estimated glomerular filtration rate by using Cockcroft-Gault method; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; Q1, first quartile; Q3, third quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

analysis period, 19 patients (TAF, 10/866 [1.2%]; TDF, 9/432 [2.1%]; $P = 0.18$) developed HCC (see Supplementary Figure 6, http://links.lww.com/AJG/D18). Among 11 cases (5 TAF; 6 TDF groups) identified during the DB phase, 5 discontinued early, 5 remained on study, and 1 completed the study at the data cutoff date. Among 8 cases (5 TAF; 3 TDF→TAF groups) identified during the OL phase, 2 discontinued early, 5 remained on study, and 1 completed the study.

**Table 2. Efficacy results at year 5**

| | TAF n = 866 | TDF→TAF3y n = 180 | TDF→TAF2y n = 202 |
|---|---|---|---|
| Pooled analysis | | | |
| HBV DNA <29 IU/mL | 628/741 (84.8) | 125/150 (83.3) | 181/202 (89.6) |
| HBV DNA <29 IU/mL w/TND | 312/741 (42.1) | 71/150 (47.3) | 83/202 (41.1) |
| HBV DNA ≥29 IU/mL (nonmissing) | 47/741 (6.3) | 11/150 (7.3) | 7/202 (3.5) |
| Normalized ALT (central lab)[a] | 507/659 (76.9) | 106/136 (77.9) | 139/181 (76.8) |
| Normalized ALT (2018 AASLD)[b] | 484/708 (68.4) | 95/144 (66.0) | 138/196 (70.4) |
| HBeAg loss[c] | 164/485 (33.8) | 30/93 (32.3) | 48/136 (35.3) |
| HBeAg seroconversion[c] | 114/485 (23.5) | 17/93 (18.3) | 28/136 (20.6) |
| HBsAg loss | 7/735 (1.0) | 1/146 (0.7) | 5/202 (2.5) |
| HBsAg seroconversion | 5/735 (0.7) | 1/146 (0.7) | 2/202 (1.0) |
| FibroTest, mean change from baseline (SD) | −0.06 (0.141) | −0.03 (0.151) | −0.02 (0.137) |

M = F analysis. Data presented as n/N (%) unless otherwise indicated.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; M = F, missing equals failure; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, target not detected; ULN, upper limit of normal.
[a]Central laboratory ULN: males ≤43 U/L, females ≤34 U/L (≥69 years, males ≤35 U/L, females ≤32 U/L).
[b]AASLD ULN: 25 U/L for females and 35 U/L for males.
[c]Data are from Study 110 only.

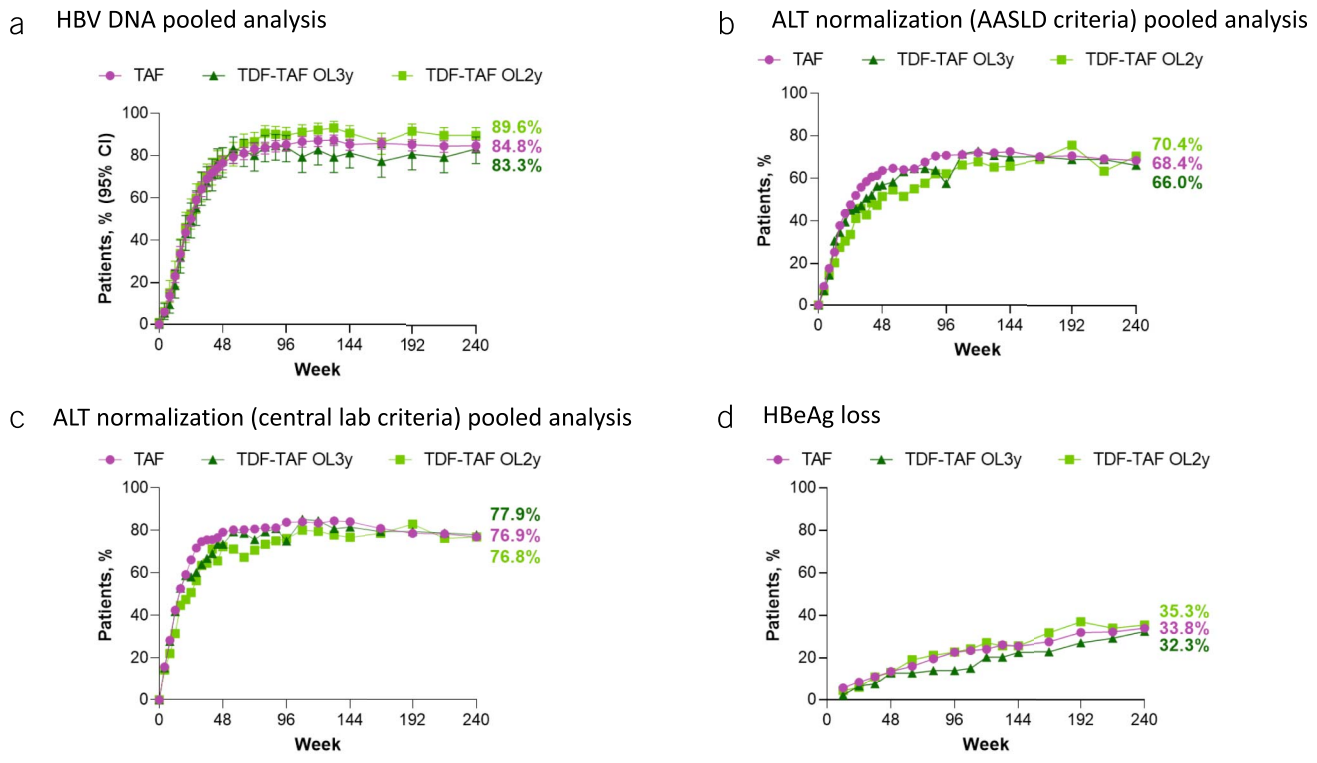



**Figure 3.** Efficacy results over time to 5 years (240 weeks), M = F analysis. (**a**) Proportion of patients with HBV DNA <29 IU/mL by study week. Bars are 95% CIs. (**b**) Proportion of patients achieving ALT normalization by central laboratory criteria (≤43 U/L for men and ≤34 U/L for women <69 years of age; ≤35 U/L for men and ≤32 U/L for women ≥69 years of age) by study week. (**c**) Proportion of patients achieving ALT normalization by AASLD criteria (≤19 U/L for women and ≤30 U/L for men) by study week. (**d**) Proportion of patients with HBeAg loss by study week, Study 110 patients only. AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; M = F, missing equals failure; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

**Table 3. Safety results during the OL period**

| | TAF n = 775 | TDF→TAF3y n = 180 | TDF→TAF2y n = 202 |
|---|---|---|---|
| AE | 444 (57.3) | 111 (61.7) | 103 (51.0) |
| Study drug–related AE | 25 (3.2) | 9 (5.0) | 2 (1.0) |
| Grade ≥3 AE | 42 (5.4) | 12 (6.7) | 7 (3.5) |
| Study drug–related grade ≥3 AE | 2 (0.3) | 0 | 0 |
| SAE | 66 (8.5) | 14 (7.8) | 14 (6.9) |
| Study drug–related SAE | 4 (0.5) | 0 | 0 |
| AE leading to discontinuation | 6 (0.8) | 0 | 2 (1.0) |
| TE death | 0 | 0 | 0 |
| Common AE (≥5%) | | | |
| Nasopharyngitis | 46 (5.9) | 6 (3.3) | 10 (5.0) |
| Upper respiratory tract infection | 47 (6.1) | 16 (8.9) | 10 (5.0) |
| Headache | 44 (5.7) | 11 (6.1) | 10 (5.0) |
| Cough | 21 (2.7) | 12 (6.7) | 4 (2.0) |
| Grade ≥3 laboratory abnormalities | 124 (16.1) | 40 (22.6) | 25 (12.5) |
| Common grade 3 or 4 laboratory abnormality (≥2%) | | | |
| Amylase | 9/768 (1.2) | 5/177 (2.8) | 3/199 (1.5) |
| Fasting LDL cholesterol (>190 mg/dL) | 26/748 (3.5) | 11/169 (6.5) | 8/197 (4.1) |
| Urinalysis, occult blood | 13/768 (1.7) | 5/177 (2.8) | 0 |
| Urine erythrocytes | 24/548 (4.4) | 7/149 (4.7) | 3/134 (2.2) |
| Urine glucose | 28/768 (3.6) | 4/177 (2.3) | 4/199 (2.0) |

All data are presented as n (%).
AE, adverse event; LDL, low-density lipoprotein; OL, open label; SAE, serious adverse event; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, treatment-emergent.

***Laboratory abnormalities.*** Grade 3 or 4 laboratory abnormalities occurred during the OL phase in 16%, 23%, and 12.5% of patients in the TAF, TDF→TAF3y, and TDF→TAF2y groups, respectively. Elevated amylase, fasting low-density lipoprotein (LDL) cholesterol, glycosuria, and occult blood (or erythrocytes) in urine were most common (≥2% in any group; Table 3).

***Fasting lipid and metabolic changes.*** Among patients on TAF, total cholesterol (TC) levels were essentially unchanged at year 5 (median change 1 mg/dL), whereas high-density lipoprotein (HDL) cholesterol decreased (median change −6 mg/dL), such that the TC:HDL ratio increased (median change 0.4) by year 5 (Figure 4). Progressive increases in LDL cholesterol (median change 24 mg/dL) and triglycerides (median change 13 mg/dL) were observed at year 5. After switching from DB TDF to OL TAF, median increases were seen in all fasting lipids, including HDL (Figure 4). Fewer than 4% of patients were taking lipid-lowering medications at study entry; fewer than 3% during DB phase, and fewer than 5% of patients during OL phase initiated lipid-lowering medications.

***Bone mineral density.*** During the DB period, greater declines were observed in hip and spine BMD in the TDF groups compared with the TAF group (Figure 5). In the TAF group, mean declines from baseline in hip and spine BMD remained <1% in the OL period: −0.87% and −0.26%, respectively, at year 5. After switching from TDF to TAF, progressive increases in BMD were observed. In general, changes in biomarkers of bone resorption (carboxy-terminal crosslinked telopeptide of type 1 collagen) and formation (procollagen type 1 N-terminal propeptide) were reflective of the smaller impact on BMD decline with TAF (see Supplementary Table 8, http://links.lww.com/AJG/D18).

***Renal parameters.*** Key renal laboratory parameters (serum creatinine, serum phosphorus, and $eGFR_{CG}$) remained stable in the TAF group (see Supplementary Table 9, http://links.lww.com/AJG/D18) over the 5-year period. In the 2 TDF→TAF groups, median declines in $eGFR_{CG}$ occurred during DB TDF treatment, which improved after switching to OL TAF (Figure 5). Shifts from baseline in chronic kidney disease (CKD) stage at year 5 support stable or improved renal function for most of the TAF-treated patients, with most improving by 1 CKD stage (ie, stage 2→1 or stage 3→2). Similarly, after switching from TDF to TAF, shifts in CKD stage supporting improved renal function were seen in both groups (see Supplementary Table 10, http://links.lww.com/AJG/D18).

Serial assessment of tubular markers of proteinuria in the TAF group revealed a small median percent decrease at week 48 followed by gradual increases through week 240. With DB TDF treatment, progressive median percent increases in tubular markers were seen at week 48, peaking at the time of switching to OL TAF, with improvement after switching to OL TAF such that results similar to the TAF group were seen at week 240 (see Supplementary Table 11, http://links.lww.com/AJG/D18).

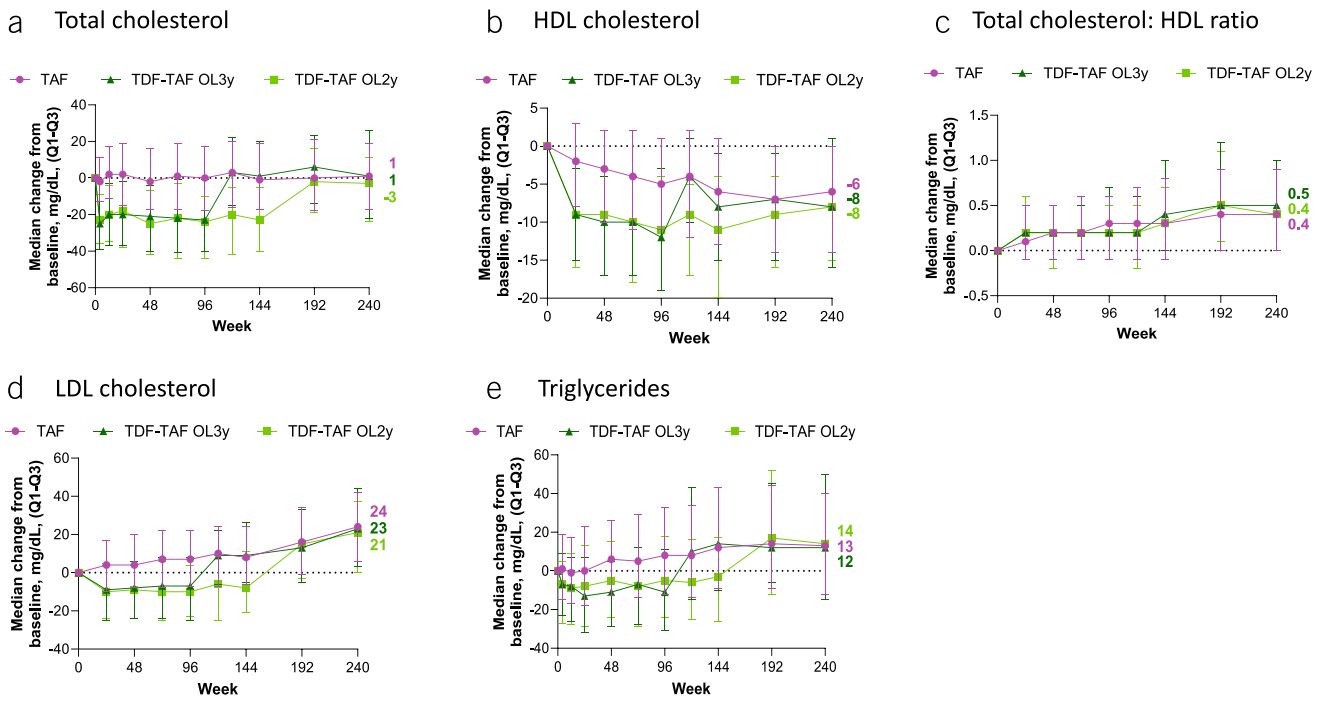



**Figure 4.** Fasting lipid changes over time to 5 years (240 weeks). HDL, high-density lipoprotein; LDL, low-density lipoprotein; OL, open label; Q1, first quartile; Q3, third quartile; TAF, tenofovir alafenamide; TC, total cholesterol; TDF, tenofovir disoproxil fumarate.

## DISCUSSION

The necessity of long-term antiviral therapy for CHB underscores the need for therapies that are not just effective but safe and well tolerated, particularly in the context of an aging HBV population. We present the results from the longest analysis to date of TAF efficacy and safety in patients with CHB. Building on previous published results from these 2 large phase 3 studies (9–11), 5-year findings show continued high rates of viral suppression among those randomized to receive TAF and among those randomized to receive TDF who were subsequently switched to TAF for the OL phase. Importantly, the improved bone and renal safety parameters initially reported with TAF were maintained through 5

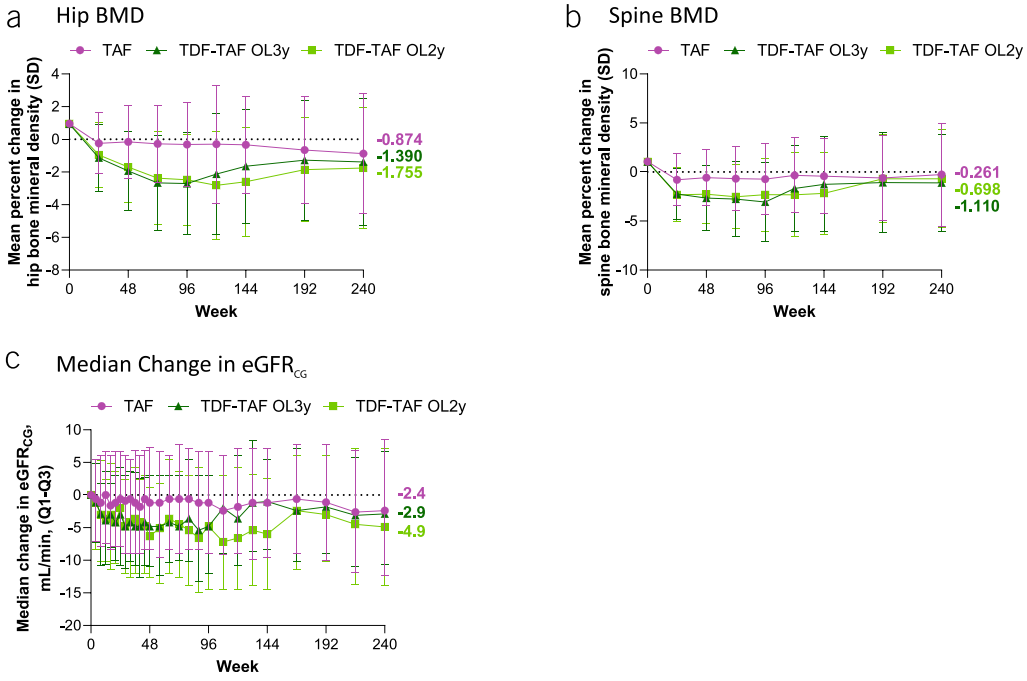



**Figure 5.** Bone and renal parameters over time to 5 years (240 weeks). BMD, bone mineral density; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; OL, open label; Q1, first quartile; Q3, third quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

years, and no resistance has been identified to date (9–12). Real-world evidence up to 144 weeks regarding patients who switched to TAF support these findings (13).

In this analysis of HBeAg-positive and HBeAg-negative patients, the proportions with HBV DNA <29 IU/mL at year 5 ranged from 83%–90% across the 3 groups, which is comparable with the previously reported long-term data for TDF (14). Consistent with our previously published report at year 2 (12), no HBV pol/RT amino acid substitutions associated with resistance were detected through year 5. Although liver biopsies were not performed in these studies, most patients in the highest baseline FibroTest category (0.75 or greater, consistent with F4 cirrhosis) shifted to a lower category, with ≤10% of those in the mild or moderate-severe categories showing worsening of fibrosis. These data are generally aligned with the 5-year results with TDF, which included change in histology, and support the widely accepted concept that long-term viral suppression results in improved liver outcomes in patients with compensated disease (14).

In these 2 registration studies (Studies 108 and 110), in addition to meeting the primary endpoint of noninferior antiviral efficacy of TAF compared with TDF in the proportion with HBV DNA <29 IU/mL at week 48, we also noted at that time point that the normalization of serum ALT occurred at higher rates in the TAF groups in both studies (9,10). These results were confirmed at week 96 (11). Although the reason for greater ALT normalization with TAF vs TDF remains unknown, this finding was seen consistently and was also noted at week 48 in a phase 3, DB, randomized, noninferiority study, wherein virally suppressed patients with CHB taking TDF were randomized to switch to TAF or continue taking TDF for an additional year (15). Approximately 74% of TAF patients in this analysis achieved ALT normalization at week 240 by M = F analysis; ALT normalization rates also increased in the TDF→TAF groups after switching over to TAF during the OL phases. The consistency of higher ALT normalization rates in TAF- vs TDF-treated patients across multiple studies suggests that this is not occurring by chance and rather represents a clinical benefit because the early and sustained achievement of ALT normalization (along with improved necroinflammation by histology) is associated with a reduced risk of disease progression and lower incidence of HCC development and may contribute to cirrhosis reversal (14,16,17). The observed and sustained high rates of ALT normalization with TAF during the OL extension phases of these 2 studies support this assertion of treatment benefit. Although the mechanism of greater ALT normalization with TAF is unclear, in a previous report of 5-year TDF treatment, we demonstrated that metabolic factors and hepatic steatosis (ie, nonviral etiologies) often account for a lack of ALT normalization (18).

Approximately one-third of HBeAg-positive patients had achieved HBeAg loss by year 5, and the rates generally increased with time. Not surprisingly, the proportions with HBsAg loss were relatively low (≤2.5%). Similar to previous reports of long-term TDF, HBsAg loss was more frequent in HBeAg-positive patients (19). The relatively low frequency of HBsAg loss/seroconversion may be explained by most of our patients being Asian and infected with genotypes C or B; a previous analysis suggests that Caucasian race and HBV genotypes A and D are independent predictors of HBsAg loss with TDF treatment (19).

We continued to observe excellent safety and tolerability with TAF over 5 years. Median eGFR declines were small among patients treated only with TAF, and few of these patients had worsening of CKD stage from baseline. Notably, when TDF-treated patients switched to OL TAF, TDF-induced reductions in eGFR were reversible, a finding that is consistent with a previous report in virally suppressed patients with CHB (15). Improved markers of proximal tubular function (urine beta-2-microglobulin to creatinine ratio and urine retinol-binding protein to creatinine ratio), although exploratory, provide corroboration of improved renal safety with TAF vs TDF. In a similar manner, TDF-associated decreases in BMD—which are thought to be due in part to upregulation of bone turnover (20)—improved with TAF treatment, whereas treatment solely with TAF showed minimal impact on hip and spine BMD over 5 years, as previously reported (9–11). The results for median percent changes in markers of resorption and bone formation (carboxy-terminal crosslinked telopeptide of type 1 collagen and pro-collagen type 1 N-terminal propeptide, respectively) provide further evidence that TAF has minimal impact on bone turnover. The data for TDF-treated patients switching to TAF support that this mechanism may be reversible in many patients.

A longitudinal analysis of fasting lipid changes showed small, yet progressive, increases in fasting LDL and triglycerides in the TAF group, whereas the decreases in fasting lipids occurring with DB TDF treatment showed similar increases in groups switched to TAF at either 96 or 144 weeks. The effects seen in TDF patients switched to TAF are due at least in part to the removal of the known lipid-lowering effect of TDF (21). Importantly, in our analysis, the TC: HDL ratio, an accepted measure of cardiovascular risk, was similar and within the normal range at baseline in all 3 treatment groups and increased only slightly by year 5 (median increase ~0.5). Our findings are similar to those from a study showing an increase in TC, HDL, and LDL in patients who switched to TAF for 6 months. Of note, the change in lipid profile did not result in a significant change in cardiovascular risk (22). In addition, only a few patients required initiation of lipid-lowering therapy during the study. Collectively, these results suggest the changes with TAF treatment in fasting lipid profile, although modest, may be of particular importance for a subset of patients with dyslipidemias or those with risk factors for cardiovascular disease. Careful monitoring of fasting lipids during TAF therapy would be prudent in such individuals.

The differential timing of implementation of the protocol amendment extending DB treatment across multiple study centers globally does impart an important limitation to our study by dividing the TDF-treated group into 2 subgroups based on when the switch to TAF occurred. However, taken together, the 5-year efficacy and safety data for TAF treatment remain relatively consistent across all treatment groups.

In summary, the results from 2 large phase 3 trials evaluating long-term treatment of CHB confirm TAF to have efficacy comparable with TDF (or TDF switched to TAF) with improved renal and bone safety. These findings, coupled with the absence of documented resistance, provide continued support for TAF as a preferred treatment for CHB infection.

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## CONFLICTS OF INTEREST

**Guarantor of the article:** Henry L.Y. Chan, MD.

**Specific author contributions:** H.L.Y.C., M.B., Y.S.L., K.A., P.M., M.B., W.L.C., H.L.A.J., S.F., N.I., D.A., F.C., M.K.C., X.M., C.Q.P., S., W.K.S., E.G., M.J., J.F.F., F.A., A.O.: conception, planning, or conducting the study. All authors: collecting or interpreting data. All authors: drafting or critically revising the article. All authors approved the final version of this manuscript for submission to *Am J Gastroenterol*.

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**Data sharing:** Gilead Sciences, Inc, shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting no conflict of interest. The request proposal must also include a statistician. Approval of such requests is at the discretion of Gilead Science and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.



## Study Highlights

### WHAT IS KNOWN

- ✓ Tenofovir disoproxil fumarate (TDF) effectively treats hepatitis B virus (HBV) infection and has a generally favorable safety profile.
- ✓ Nephrotoxicity and reductions in bone mineral density limit the use of TDF in some patients.
- ✓ Tenofovir alafenamide (TAF) demonstrated noninferior antiviral efficacy vs TDF at weeks 48 and 96, with superior renal and bone safety.

### WHAT IS NEW HERE

- ✓ Among 1,248 patients with chronic HBV treated for up to 5 years with TAF or for 2–3 years after switching from TDF to TAF, ≥83% of patients achieved HBV DNA <29 IU/mL.
- ✓ Over 5 years of treatment, no patient developed resistance to TDF or TAF.
- ✓ Improved renal and bone safety profiles were observed for patients treated with TAF vs TDF and among TDF-treated patients who switched to TAF: TDF-induced reductions in estimated glomerular filtration rate were reversible, with improvements in renal function and bone mineral density seen with TAF treatment.

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