Safety and Efficacy of Long-Term Tenofovir Alafenamide Treatment in Patients Aged 60 Years and Older With Chronic Hepatitis B: Experience From Two Phase 3 Clinical Trials

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Viral Hepatitis B and D: Current Therapies

Conclusions

- Tenofovir alafenamide (TAF) is highly effective and well tolerated in older patients (≥60 years) with chronic hepatitis B (CHB) and a high burden of comorbidities followed for up to 8 years
- High rates of virologic suppression were maintained through 8 years of TAF treatment across age groups, with differences in suppression rates by age at earlier time points likely reflecting baseline hepatitis B e antigen (HBeAg) status and hepatitis B virus (HBV) DNA levels
- Improved renal and bone safety profiles were seen in patients treated with TAF vs tenofovir disoproxil fumarate (TDF) across both age groups
- Switching from TDF to TAF led to stabilisation of or modest improvements in both renal function and bone mineral density (BMD), particularly in older patients
- These findings support the use of TAF as the preferred treatment option in older adults and those at risk for renal and bone complications, in alignment with current guideline recommendations

Plain Language Summary

- Chronic hepatitis B is a serious global health issue, especially in older adults, who often have other health problems like kidney and bone complications
- This analysis looked at how 2 antiviral medicines—tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF)—worked in people aged 60 years and older, compared with younger adult patients, for up to 8 years in 2 large clinical studies
- TAF was highly effective and well tolerated in older adults with chronic hepatitis B, many of whom had higher rates of comorbidities, including reduced kidney function and bone loss, at the start of treatment
- While older patients experienced some decline in kidney and bone health over time, patients treated with TAF consistently showed better safety outcomes across all age groups compared with those treated with TDF
- People who switched from TDF to TAF experienced stabilisation of or modest improvements in kidney function and bone parameters, especially in the spine
- These results support using TAF as a preferred treatment option for older adults and people at risk for kidney or bone complications, in line with current medical guidelines

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Introduction

- CHB is a major global health problem, with approximately 250 million individuals worldwide living with CHB[1]
- The population with CHB is ageing and increasingly presents with comorbidities, including renal and bone disorders[2,3]
- Nucleos(t)ide analogues, such as TAF and TDF, are recommended as first-line antiviral treatments for CHB[4-6]
- In two randomised Phase 3 studies (Studies 108 and 110), TAF demonstrated noninferior efficacy compared with TDF, with improved renal and bone safety profiles,[7-10] and switching treatment from TDF to TAF was associated with improvements in renal and bone parameters[11-14]
- Major clinical guidelines recommend the use of TAF or entecavir over TDF for patients with risk factors for TDF-associated renal and bone toxicities and for those over 60 years of age[4,5]

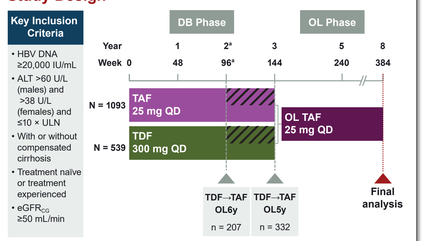
Objective

- To evaluate the long-term safety and efficacy outcomes of TAF in patients aged 60 years and older with CHB enrolled in two 8-year clinical trials

Methods

- Patients in this pooled analysis were enrolled in two Phase 3 trials with similar designs:
  - Study 108: HBeAg-negative patients (global and China cohorts: NCT01940341 and NCT02836236)[7,8,10]
  - Study 110: HBeAg-positive patients (global and China cohorts: NCT01940471 and NCT02836249)[7,9,10]
- Patients were randomised 2:1 to the following treatment groups:
  - TAF 25 mg once daily (QD) for up to 144 weeks (3 years) followed by open-label (OL) TAF
  - TDF 300 mg QD for up to 3 years followed by OL TAF
- All patients then received OL TAF through 384 weeks (8 years)

Study Design



[a]Amendment 3 was enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded/slashed areas represent patients who rolled over to OL TAF at week 96 (OL6y).
TDF→TAF OL6y, patients received DB TDF for 2 years (96 weeks), then OL TAF for 6 years; and TDF→TAF OL5y, patients received DB TDF for 3 years (144 weeks), then OL TAF for 5 years.
ALT, alanine aminotransferase; DB, double-blind; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; HBV, hepatitis B virus; OL, open-label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; y, year.

- Efficacy and safety were assessed for older (≥60 years) vs younger (<60 years) adult patients
  - Efficacy
    - HBV DNA <29 IU/mL
  - Safety
    - Adverse events (AEs), serious AEs, and Grade 3 or 4 laboratory abnormalities during the OL phase
    - Changes in estimated glomerular filtration rate (Cockcroft-Gault method; eGFR$_{CG}$) and quantitative urinary biomarkers of tubular function (ratio of retinol-binding protein [RBP] to creatinine [Cr] and ratio of beta-2 microglobulin [β2M] to Cr)
    - Changes in BMD based on dual-energy X-ray absorptiometry (DXA) scans at hip and spine, and changes in serum biomarkers of bone formation and resorption (procollagen type 1 N-terminal propeptide [P1NP] and C-type collagen sequence [CTX], respectively)

Results

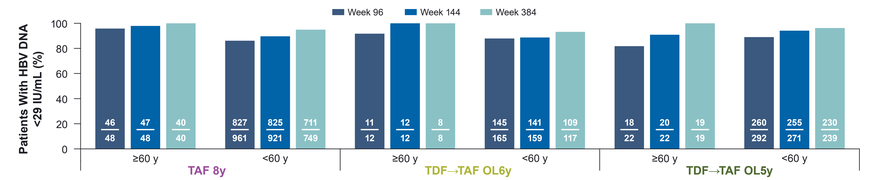
Baseline Demographics and Disease Characteristics

		TAF 8y		TDF→TAF OL6y		TDF→TAF OL5y	
		≥60 y n = 55	<60 y n = 1038	≥60 y n = 12	<60 y n = 195	≥60 y n = 24	<60 y n = 308
Demographics	Age, y, median (range)	62 (60–80)	38 (18–59)	64 (60–67)	39 (18–59)	63 (60–73)	38 (18–59)
	Male, n (%)	30 (55)	676 (65)	5 (42)	121 (62)	12 (50)	219 (71)
	Asian, n (%)	47 (86)	867 (84)	11 (92)	156 (80)	16 (67)	257 (83)
	BMI ≥25 kg/m^2, n (%)	24 (44)	385 (37)	3 (25)	79 (41)	12 (50)	109 (35)
Disease characteristics	HBeAg negative, n (%)	37 (67)	366 (35)	8 (67)	66 (34)	17 (71)	99 (32)
	HBV DNA, log$_{10}$ IU/mL, median (Q1, Q3)	6.5 (5.3, 7.2)	7.4 (5.6, 8.2)	6.3 (4.9, 7.8)	7.5 (6.0, 8.3)	6.3 (5.5, 8.2)	7.2 (5.5, 8.2)
	ALT, U/L, median (Q1, Q3)	72 (53, 138)	82 (56, 128)	74 (47, 95)	82 (53, 137)	87 (50, 171)	84 (54, 129)
	FibroTest score ≥0.75, n (%)	16 (30)	84 (8)	2 (17)	14 (7)	8 (33)	31 (10)
	Cirrhosis history, n (%)	6 (18)	64 (10)	1 (9)	21 (15)	3 (17)	20 (11)
Comorbidities	Hypertension, n (%)	22 (40)	95 (9)	6 (50)	24 (12)	13 (54)	32 (10)
	Cardiovascular disease, n (%)	4 (7)	32 (3)	1 (8)	4 (2)	1 (4)	9 (3)
	Diabetes, n (%)	9 (16)	69 (7)	0	9 (5)	7 (29)	18 (6)
	Hyperlipidaemia, n (%)	7 (13)	73 (7)	3 (25)	18 (9)	4 (17)	22 (7)
Renal parameter	eGFR$_{CG}$, mL/min, median (Q1, Q3)	80 (67, 91)	110 (95, 128)	67 (64, 77)	107 (90, 126)	85 (73, 97)	109 (95, 125)
Bone parameters	Osteopenia by hip BMD T-score,[a] n (%)	23 (46)	265 (30)	7 (58)	64 (33)	8 (44)	74 (29)
	Osteoporosis by hip BMD T-score,[a] n (%)	3 (6)	9 (1)	0	2 (1)	0	1 (<1)
	Osteopenia by spine BMD T-score,[a] n (%)	21 (41)	339 (38)	2 (17)	69 (36)	8 (44)	99 (39)
	Osteoporosis by spine BMD T-score,[a] n (%)	11 (22)	50 (6)	7 (58)	14 (7)	2 (11)	10 (4)
	Vitamin D level, ng/mL, median (Q1, Q3)	18 (14, 24)	17 (13, 23)	20 (18, 25)	18 (13, 23)	18 (12, 23)	17 (13, 22)

[a]T-score ≥−2.5 and <−1 based on DXA scan. [b]T-score <−2.5 based on DXA scan.
TAF 8y, patients received TAF throughout the study; TDF→TAF OL6y, patients received TDF for 2 years (96 weeks), then OL TAF for 6 years; and TDF→TAF OL5y, patients received TDF for 3 years (144 weeks), then OL TAF for 5 years.
ALT, alanine aminotransferase; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open-label; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Only 6% (91/1632) of patients were aged ≥60 years, yet this group had notably higher rates of comorbidities, including hypertension, cardiovascular disease, hyperlipidaemia, and diabetes
- Compared with younger patients, those aged ≥60 years had lower baseline renal function and a greater prevalence of bone loss (osteopenia and osteoporosis), and were more likely to have a history of cirrhosis or a FibroTest score ≥0.75 (suggestive of cirrhosis; Metavir F4)

Proportion of Patients With HBV DNA <29 IU/mL



Missing values were excluded from the analysis; the top number within the bar represents the number of patients with HBV DNA <29 IU/mL, and the bottom number represents the group n value.
HBV, hepatitis B virus; OL, open-label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- High rates of virologic suppression were observed across both age groups throughout long-term TAF treatment
- Numerically higher proportions of patients aged ≥60 years with HBV DNA <29 IU/mL were observed at earlier time points, likely reflecting differences in baseline disease characteristics, including a lower proportion of HBeAg-positive patients and lower baseline HBV DNA levels, compared with those aged <60 years
- At week 384, nearly all patients had achieved virologic suppression regardless of age

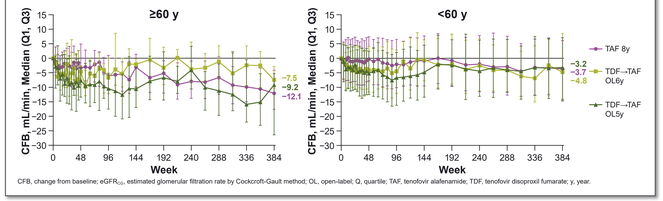
OL Safety Summary[a]

	TAF 8y		TDF→TAF OL6y		TDF→TAF OL5y	
	≥60 y n = 48	<60 y n = 939	≥60 y n = 12	<60 y n = 168	≥60 y n = 22	<60 y n = 279
Any AE, n (%)	35 (73)	676 (72)	10 (83)	123 (73)	18 (82)	214 (77)
Grade 3 or 4 AE	7 (15)	65 (7)	4 (33)	11 (7)	4 (18)	14 (5)
Study drug–related Grade 3 or 4 AE	0	2 (<1)	0	0	1 (5)	0
SAE	17 (35)	107 (11)	2 (17)	22 (13)	5 (23)	31 (11)
Study drug–related SAE[b]	0	4 (<1)	0	0	1 (5)	0
D/C due to AE, n (%)	1 (2)	8 (1)	0	0	1 (5)	2 (1)
Grade 3 or 4 laboratory abnormalities, n/N (%)	6/48 (13)	213/936 (23)	1/12 (8)	47/165 (28)	3/22 (14)	54/278 (19)
ALT	0/48	18/936 (2)	0/12	2/165 (1)	1/22 (5)	6/278 (2)
LDL cholesterol, fasting	0/48	50/923 (5)	0/12	15/161 (9)	0/22	17/276 (6)
Total cholesterol, fasting	0/48	15/930 (2)	1/12 (8)	1/161 (1)	0/22	9/277 (3)
Urine erythrocytes	2/36 (6)	36/664 (5)	0/10	7/144 (5)	0/17	5/168 (3)
Urine glucose	2/48 (4)	46/936 (5)	0/12	5/165 (3)	0/22	8/276 (3)
Treatment-emergent death,[c] n (%)	0	2 (<1)	0	0	0	1 (<1)

[a]Among patients in the OL safety analysis who received ≥1 dose of OL study drug (OL safety analysis set). [b]Study drug–related SAEs were as follows: TAF 8y, renal neoplasm, cerebrovascular accident (stroke), ALT increased, and osteonecrosis (n = 1 each); TDF→TAF OL5y, chronic gastritis (n = 1). [c]Deaths were as follows: TAF 8y, liver cancer and pancreatic adenocarcinoma (n = 1 each); TDF→TAF OL5y, small cell carcinoma (n = 1).
AE, adverse event; ALT, alanine aminotransferase; D/C, discontinuation; LDL, low-density lipoprotein; OL, open-label; SAE, serious adverse event; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Across both age groups, TAF treatment demonstrated a consistent and favourable long-term safety profile, with low rates of severe or treatment-related AEs

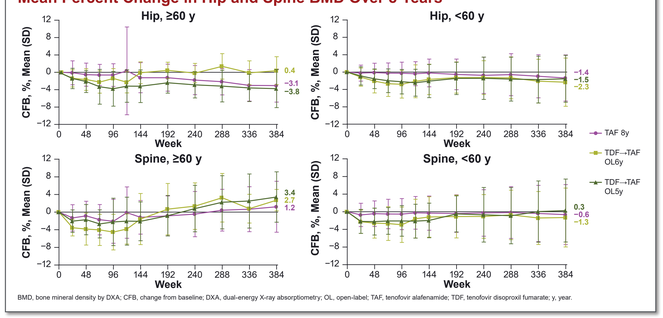
Median Change in eGFR$_{CG}$ Over 8 Years



CFB, change from baseline; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; OL, open-label; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Older patients (≥60 years) experienced greater declines in eGFR$_{CG}$ than younger patients across all treatment groups, with TAF treatment showing smaller reductions compared with TDF
- Switching from TDF to TAF led to modest improvements in or stabilisation of eGFR$_{CG}$

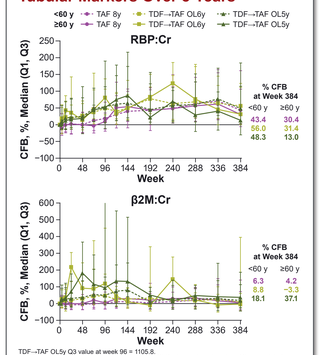
Mean Percent Change in Hip and Spine BMD Over 8 Years



BMD, bone mineral density by DXA; CFB, change from baseline; DXA, dual-energy X-ray absorptiometry; OL, open-label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Compared with TDF, TAF treatment resulted in smaller BMD declines across both age groups, and switching from TDF to TAF led to modest improvements in hip BMD and notable improvements in spine BMD, particularly in older patients

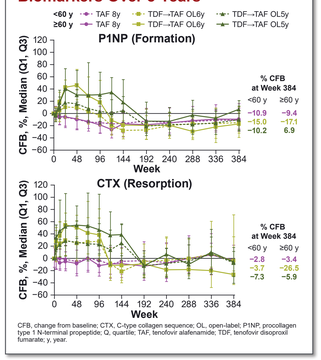
Median Percent Change in Renal Tubular Markers Over 8 Years



TDF→TAF OL5y Q3 value at week 96 = 1105.8.
β2M:Cr, beta-2 microglobulin to creatinine ratio; CFB, change from baseline; OL, open-label; Q, quartile; RBP:Cr, retinol-binding protein to creatinine ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Early TDF-associated increases in renal tubular markers were more pronounced in patients aged ≥60 years vs those <60 years; stabilisation was observed across age groups after switching to TAF

Median Percent Change in Bone Biomarkers Over 8 Years



CFB, change from baseline; CTX, C-type collagen sequence; OL, open-label; P1NP; procollagen type 1 N-terminal propeptide; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Serum markers of bone turnover remained stable over 8 years among patients receiving TAF
- In the TDF→TAF groups, changes in serum bone turnover markers were greater in patients aged ≥60 years vs those <60 years, with improvements observed across both age groups after switching to TAF