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Vemlidy® (tenofovir alafenamide) Comparison With TDF

This document is in response to your request for information regarding Vemlidy® (tenofovir alafenamide [TAF]) compared with tenofovir disoproxil fumarate (TDF) for use in patients with chronic HBV (CHB). This response was developed according to principles of evidence-based medicine and only contains prospective clinical trials or retrospective studies (N≥5000).

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Summary

Clinical Data on TAF vs TDF in Participants With CHB

Phase 3 Studies 108 and 110 compared the efficacy and safety of TAF with TDF in participants with CHB. Participants received DB TAF or TDF for 2 or 3 years, followed by OL TAF for up to 6 years.[1,23]

Week 48 Primary Endpoint:

- TAF was non-inferior to TDF in virologic suppression at Week 48 in both TN and TE participants.[1,2]
- The majority of AEs were mild to moderate in severity through Week 48.[1,2]

Year 8 Final Analysis:

- Rates of virologic suppression (HBV DNA <29 IU/mL) ranged from 91% to 98% across TAF8y and TDF→TAF treatment arms through Year 8. ALT normalization rates increased after switching from TDF to TAF and were comparable across treatment groups and by HBeAg status.[4]
- HBeAg loss and seroconversion rates progressively increased through Year 8 and were similar in the TAF8y and TDF→TAF arms.[4]
- A pooled analysis found higher baseline BMI (AASLD and central laboratory criteria, *P*<0.0001), younger age (AASLD and central laboratory criteria, *P*<0.0001), HBV GT A (AASLD criteria; *P*=0.0053), and male sex (central laboratory criteria; *P*=0.0131) were significantly associated with persistently elevated ALT levels at Year 8.[5]
- In resistance testing, 2% of participants (n=29) qualified for sequence analysis. No amino acid substitutions that reduced susceptibility to TAF were detected at Year 8.[4]
- TAF was generally well tolerated, with Grade ≥3 AEs occurring in 8% of participants in the TAF8y arm, 8% in the TDF2y→TAF6y arm, and 6% in the TDF3y→TAF5y arm. Improvements in $eGFR_{CG}$ and changes in BMD and lipid profiles are provided below.[4]

- A subanalysis of bone and renal safety outcomes according to the presence or absence of risk factors for TDF-related toxicities demonstrated stable renal and bone safety findings after treatment with TAF through Year 8.[6]

Real-World Data on TAF vs TDF in Patients With CHB

In a Korean nationwide health insurance claims database, the incidence of HCC was compared between PS-matched cohorts who received TAF and those who received TDF as initial treatment for CHB (each, n=19,013). The cumulative incidence of HCC was significantly more reduced with TAF treatment than with TDF treatment: 7.5 vs 9.9 per 1000 PY (SHR, 0.77; 95% CI: 0.67–0.87; *P*<0.0001). Treatment with TDF, older age, male sex, and presence of cirrhosis were among factors that were significantly associated with a higher risk of HCC development.[7]

Clinical Data on TAF vs TDF in Participants With CHB

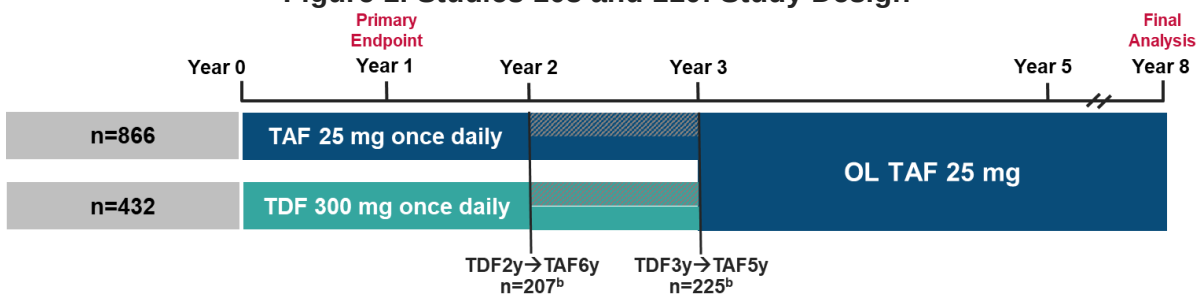
Studies 108 and 110

Study design and demographics

Studies 108 and 110 were phase 3 clinical trials that compared the efficacy and safety of TAF with TDF in predominantly NUC-naive participants with CHB. A total of 1298 adult, monoinfected participants with compensated liver function were randomly assigned in a 2:1 ratio to receive either DB TAF 25 mg or TDF 300 mg, followed by OL TAF for up to 6 years. Upon completion of the blinded phase, eligible participants from both arms were enrolled into an OL phase and received one of the following: DB then OL TAF for a total of 8 years (TAF8y), DB TDF for 2 years then OL TAF for 6 years (TDF2y→TAF6y), or DB TDF for 3 years then OL TAF for 5 years (TDF3y→TAF5y; Figure 1).[4]

The primary endpoint was the proportion of participants with undetectable HBV DNA (<29 IU/mL) at Week 48. Secondary endpoints included changes in hip and spine BMD, changes in SCr levels, dipstick proteinuria, biochemical response (ALT normalization), serologic response (HBsAg seroconversion), and change in fibrosis measured by FibroTest.[1,2]

Figure 1. Studies 108 and 110: Study Design[4,8a]



[a]Shaded areas represent participants who entered the OL phase of TAF treatment at Year 2 or Year 3.
[b]Number of participants who received DB TDF and switched to TAF.

Table 1. Studies 108 and 110: Baseline Demographics and Disease Characteristics[4]

Key Demographics and Characteristics	TAF (n=866)	Combined TDF→TAF Arms (n=432)
Age, mean ± SD, years	40±11.8	41±12.3
Male, n (%)	544 (63)	275 (64)

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Key Demographics and Characteristics		TAF (n=866)	Combined TDF→TAF Arms (n=432)
Race, n (%)	Asian	687 (79)	333 (77)
	White	167 (19)	87 (20)
BMI, mean ± SD, kg/m^2		24±4.13	24.4±3.95
HBeAg+, n (%)		569 (66)	290 (67)
ALT, median (Q1, Q3), U/L		80 (56, 123)	80 (53, 130)
Prior NUC treatment, n (%)		211 (24)	108 (25)
FibroTest score, n/N (%)	0–0.48 (no/mild)	601/846 (71)	297/421 (71)
	0.49–0.74 (moderate/severe)	169/846 (20)	82/421 (19)
	0.75–1 (cirrhosis)	76/846 (9)	42/421 (10)
$eGFR_{CG}$, median (Q1, Q3), mL/min		106 (91, 125)	104.5 (90, 124)
Osteoporosis by hip BMD T-score,[a] n (%)		12 (1)	2 (<1)
Osteoporosis by spine BMD T-score,[a] n (%)		57 (7)	29 (7)
Hyperlipidemia, n (%)		76 (9)	44 (10)

Abbreviation: Q=quartile.
[a]T-score less than -2.5.

Efficacy results through Week 48 (primary endpoint)

TAF 25 mg demonstrated non-inferiority to TDF in viral suppression at Week 48 in both TN and TE adults.[1,2]

Table 2. Studies 108 and 110: Summary of Efficacy Results at Week 48[1,2]

n/N (%) or %	Study 108 (HBeAg-; N=425)			Study 110 (HBeAg+; N=873)		
	TAF (n=285)	TDF (n=140)	*P*-Value	TAF (n=581)	TDF (n=292)	*P*-Value
HBV DNA <29 IU/mL	268/285 (94)[a]	130/140 (92.9)[a]	0.47	371/581 (63.9)[b]	195/292 (66.8)[b]	0.25
Baseline HBV DNA thresholds						
<7 log_{10} IU/mL	221/230 (96)	107/116 (92)	-	-	-	-
≥7 log_{10} IU/mL	47/55 (85)	23/24 (96)	-	-	-	-
<8 log_{10} IU/mL	-	-	-	254/309 (82)	123/150 (82)	-
≥8 log_{10} IU/mL	-	-	-	117/272 (43)	72/142 (51)	-
NUC naive	212/225 (94)	102/110 (93)	-	302/444 (68)	156/223 (70)	-
NUC experienced	56/60 (93)	28/30 (93)	-	69/137 (50)	39/69 (57)	-
ALT normalization[c]	50	32	<0.001	45	36	0.014
HBeAg loss	-	-	-	78/565 (14)	34/285 (12)	0.47
HBeAg seroconversion	-	-	-	58/565 (10)	23/285 (8)	0.32
HBsAg loss	-	-	-	4/576 (<1)	1/288 (<1)	0.52
HBsAg seroconversion	-	-	-	3/576 (<1)	0	0.22

[a]Reasons for failure: HBV DNA ≥29 IU/mL (2% TAF, 3% TDF); missing data (<1% TAF, 1% TDF); discontinuation due to AE (1% TAF, 1% TDF); discontinuation for other reasons (2% TAF, 3% TDF).
[b]Reasons for failure: HBV DNA ≥29 IU/mL (31% TAF, 30% TDF); missing data (<1% TAF, 0 TDF); discontinuation due to AE or death (1% TAF, 1% TDF); discontinuation due to any other reason (3% TAF, 2% TDF).
[c]ULN=30 IU/L for males and 19 IU/mL for females.

Safety results through Week 48[1,2]

The majority of AEs in Studies 108 and 110 were mild or moderate in severity. None of the SAEs that occurred were considered to be treatment-related, and study drug discontinuations due to AEs were 1% in both TAF and TDF arms of Studies 108 and 110.

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Table 3. Studies 108 and 110: Overall Safety Through Week 48[1,2]

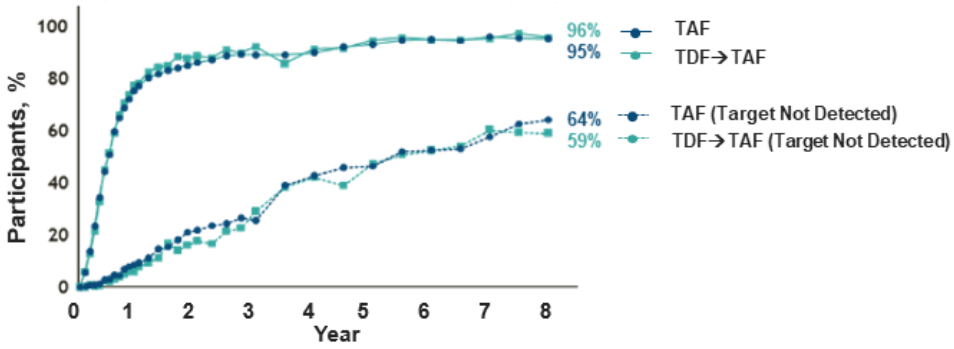
Safety Outcomes, n (%) or n/N (%)		Study 108 (HBeAg-)		Study 110 (HBeAg+)	
		TAF (n=285)	TDF (n=140)	TAF (n=581)	TDF (n=292)
Any AE		210 (74)	99 (71)	398 (69)	192 (66)
Grade 3/4 AE		12 (4)	6 (4)	27 (5)	11 (4)
SAE		14 (5)	9 (6)	22 (4)	12 (4)
Discontinuation due to AE		3 (1)	2 (1)	6 (1)	3 (1)
Death		0	1 (<1)[a]	1 (<1)[b]	0
AEs in ≥5% of participants in either treatment group	Headache	40 (14)	14 (10)	42 (7)	22 (8)
	URTI	35 (12)	10 (7)	51 (9)	22 (8)
	Nasopharyngitis	30 (11)	15 (11)	56 (10)	16 (5)
	Cough	18 (6)	8 (6)	37 (6)	19 (7)
	Fatigue	16 (6)	9 (6)	33 (6)	14 (5)
	Nausea	15 (5)	9 (6)	NR	NR
	Back pain	14 (5)	7 (5)	NR	NR
	Arthralgia	11 (4)	10 (7)	NR	NR
	Diarrhea	NR	NR	27 (5)	15 (5)
	Upper abdominal pain	NR	NR	19 (3)	15 (5)
Grade 3/4 laboratory abnormalities[c]		82/282 (29)	30/140 (21)	187 (32)	96 (33)
Grade 3/4 laboratory abnormalities in ≥1% of participants in either treatment group[c]	Urine erythrocytes	17/252 (7)	9/127 (7)	42/516 (8)	26/259 (10)
	Occult blood	17 (6)	7 (5)	49 (8)	23/286 (8)
	Urine glucose	15 (5)	2 (1)	26 (5)	3/286 (1)
	Fasting LDL cholesterol >300 mg/dL	14/277 (5)	1/135 (1)	23/560 (4)	0/282
	Amylase >2 × ULN	14 (5)	3 (2)	9 (2)	7/287 (2)
	Non-fasting glucose >250 mg/dL	10 (4)	2 (1)	16/574 (3)	5/287 (2)
	ALT/AST >5 × ULN	8 (3)/8 (3)	4 (3)/4 (3)	62 (11)/20 (3)	36 (13)/19 (7)
	Creatine kinase ≥10 × ULN	7 (2)	3 (2)	18 (3)	10 (3)
	Fasting glucose >250 mg/dL	4/280 (1)	0	NR	NR
	TC >300 mg/dL	3/280 (1)	0	NR	NR
	GGT >5 × ULN	0	3 (2)	3 (1)	3 (1)
	ANC <750 cells/mcL	NR	NR	7 (1)	1/286 (<1)

Abbreviations: ANC=absolute neutrophil count; NR=not reported.
[a]A 51-year-old, male, Asian participant with cirrhosis died due to HCC at Week 56 (non-treatment-emergent).
[b]A 54-year-old, female, Asian participant died due to H1N1 influenza at Week 14 (non-treatment-emergent).
[c]Laboratory abnormality results were based on data from the following number of participants per study, unless otherwise indicated: Study 108, TAF=282 and TDF=140; Study 110, TAF=577 and TDF=288.

Efficacy results through Year 8 (final analysis)

In both studies, rates of viral suppression were high during the DB phase and continued through Year 8 across all treatment arms (Figure 2).[4]

Figure 2. Studies 108 and 110: HBV DNA <29 IU/mL Through Year 8 (M=E Analysis)[4,8]



Through Year 8, the rates of HBeAg loss and seroconversion progressively increased and were similar among treatment arms (Figure 3). HBsAg loss with or without seroconversion occurred at low rates (2–3%), and 0.9% of participants (12/1298) overall discontinued due to achieving HBsAg seroconversion.[4]

Figure 3. Studies 108 and 110: HBeAg Loss and Seroconversion Through Year 8 (M=E Analysis)[4,8]

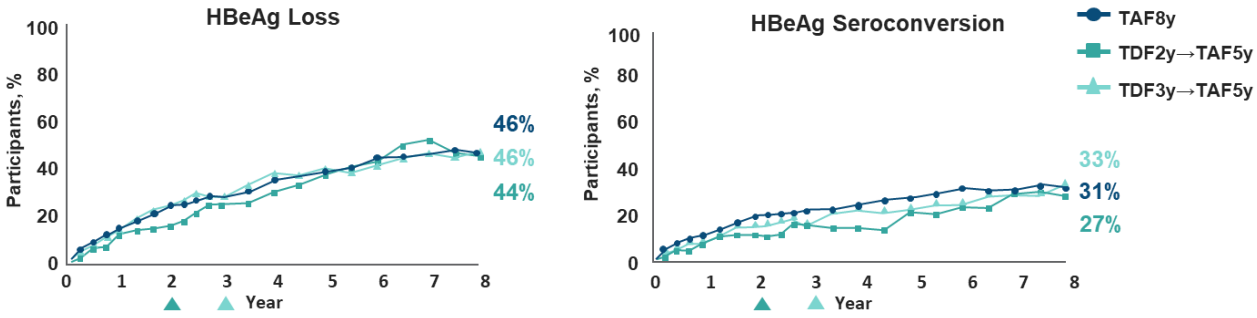


Table 4. Studies 108 and 110: HBsAg Loss and Seroconversion at Year 8 (M=E Analysis)[4,8]

	TAF8y		TDF2y→TAF6y		TDF3y→TAF5y	
	HBeAg-	HBeAg+	HBeAg-	HBeAg+	HBeAg-	HBeAg+
HBsAg loss, n/N (%)	8/199 (4)	9/384 (2)	0/41	4/76 (5)	1/58 (2)	3/109 (3)
HBsAg seroconversion, n/N (%)	6/199 (3)	6/384 (2)	0/41	4/76 (5)	0/58	3/109 (3)
HBsAg mean change ± SD, log_{10} IU/mL	-0.62±0.924	-0.89±1.211	-0.5±0.526	-1.09±1.424	-0.61±0.758	-1.09±1.268

High rates of ALT normalization were observed in the TAF8y arm, regardless of HBeAg status. ALT normalization rates increased after switching to TAF in participants randomly assigned to TDF in the DB period before switching to OL TAF at Year 2 or 3.[4]

At Year 8, approximately 30% of all participants with baseline cirrhosis (ie, FibroTest score ≥0.75) continued to show evidence of cirrhosis, but most participants had improved to a lower FibroTest category.[4]

Factors associated with lack of ALT normalization through Year 8[5]

A pooled analysis of participants in Studies 108 and 110 categorized by ALT status at Year 8 found that most participants achieved ALT normalization (n/N=907/1159 [78%]) with TAF or TDF→TAF after 8 years of treatment. Approximately 20% had persistently elevated

ALT levels based on AASLD criteria (ALT ULN of 25 U/L for females and 35 U/L for males), with 13% (n/N=148/1159) meeting the definition of persistent ALT elevation using the central laboratory cutoff (ULN of 34 U/L for females and 43 U/L for males [age ≥69 years, ULN of 32 U/L and 35 U/L, respectively]). No significant differences in baseline comorbidities were observed between participants with persistent elevation in ALT levels and those with normal ALT levels at Year 8. Most participants achieved HBV DNA suppression regardless of biochemical response, with suppression observed in 88% of participants with persistently elevated ALT levels and in 97% of participants with normal ALT levels, according to the AASLD criteria. Participants with normal ALT levels at Year 8 had higher rates of HBeAg loss and seroconversion, although meaningful virological responses were also observed in participants with persistent elevation in ALT levels. On multivariable analysis, higher baseline BMI (AASLD and central laboratory criteria, *P*<0.0001), younger age (AASLD and central laboratory criteria, *P*<0.0001), HBV GT A (AASLD criteria; *P*=0.0053), and male sex (central laboratory criteria; *P*=0.0131) were significantly associated with persistently elevated ALT levels at Year 8.

Resistance results at Year 8[4]

A total of 2% of participants (n=29) met the criteria for a sequence analysis of HBV polymerase-reverse transcriptase to scan for potential resistance mutations: viral blip, n=17 (59%); virologic breakthrough, n=9 (31%); and persistent viremia, n=3 (10%). No amino acid substitutions that reduced susceptibility to TAF were detected at Year 8.

Safety results through Year 8[4]

The OL safety analysis included data from any participant who received ≥1 dose of OL TAF (Table 5).

Table 5. Studies 108 and 110: Safety Results Through Year 8 (OL Safety Analysis Set)[4]

Safety Outcomes, n or n/N (%)		TAF8y (n=775)	Combined TDF→TAF Arms (n=382)
Any AE		525 (68)	271 (71)
Any study drug-related AEs		43 (6)	18 (5)
Grade ≥3 AEs		60 (8)	27 (7)
Study drug-related Grade ≥3 AEs		2 (<1)[a]	0
SAEs		97 (13)	49 (13)
Study drug-related SAEs		4 (1)[b]	0
AEs that led to discontinuation		9 (1)[c]	3 (<1)[d]
Deaths[e]		3/866 (<1)	3/432 (<1)
HCC[f]		7 (<1)	3 (<1)
AEs occurring in ≥5% of participants	Headache	59 (8)	30 (8)
	URTI	55 (7)	27 (7)
	Nasopharyngitis	52 (7)	23 (6)
	Arthralgia	41 (5)	23 (6)
	Hypertension	37 (5)	26 (7)
	Back pain	34 (4)	23 (6)
	Cough	28 (4)	27 (7)

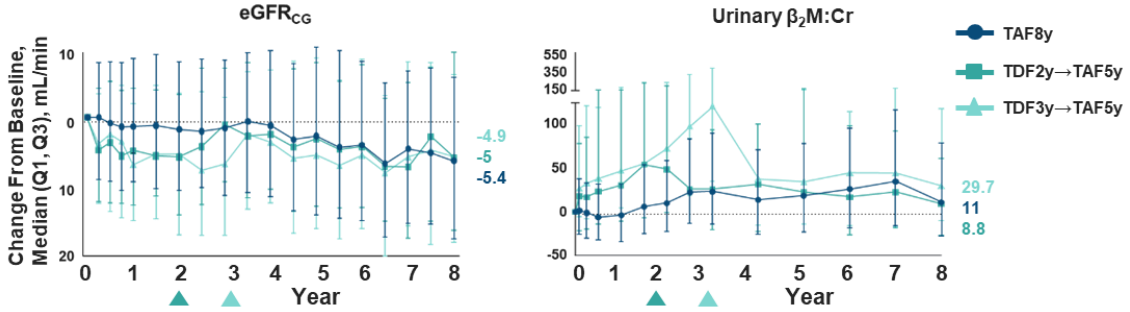
[a]Cerebrovascular accident, renal neoplasm (each, n=1).
[b]ALT increase, cerebrovascular accident, osteonecrosis, renal neoplasm (each, n=1).
[c]Cardiopulmonary failure, cerebrovascular accident, GGT increased, HCC, myelodysplastic syndrome, osteonecrosis, osteoporosis, pancreatic carcinoma, proteinuria (each, n=1).
[d]Ascites, pemphigoid, tuberculosis (each, n=1). All occurred in the TDF3y→TAF5y arm.
[e]TAF: HCC, H1N1 influenza, pancreatic cancer (each, n=1). TDF: cardiopulmonary arrest, HCC, bilateral pneumonia (each, n=1).
[f]Over the course of the entire study, 21 participants developed HCC.

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Renal safety through Year 8

From baseline to Year 8, the median $eGFR_{CG}$ decreased in all treatment arms (Figure 4). Participants in the TDF→TAF arms demonstrated improvements in $eGFR_{CG}$ and urinary β_2:Cr after switching to TAF (Figure 4).

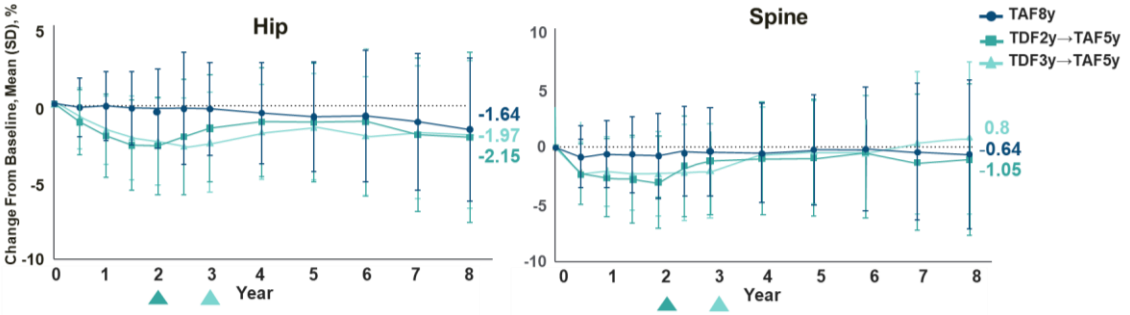
Figure 4. Studies 108 and 110: Renal Parameter Changes Through Year 8 (M=E Analysis)[4]



Bone safety through Year 8

At Year 8, changes in BMD from baseline in the TAF8y arm were minimal, with mean percentage decreases from baseline of <2% in hip and spine BMD (Figure 5). Among participants in the TDF→TAF arms, early decreases in hip and spine BMD that occurred during TDF treatment improved over time after participants switched to TAF at Year 2 or 3.

Figure 5. Studies 108 and 110: Mean Changes in BMD from Baseline to Year 8 (M=E Analysis)[4]



In the TAF8y arm at Year 8, the median percentage decrease in bone biomarkers from baseline was 2.7% for CTX resorption and 9.03% for P1NP formation. Compared with the TAF8y arm, larger decreases in hip and spine BMD and larger increases in CTX P1NP were seen in the TDF→TAF arms during the DB phase; switching to TAF resulted in increased BMD and smaller increases in CTX and P1NP.

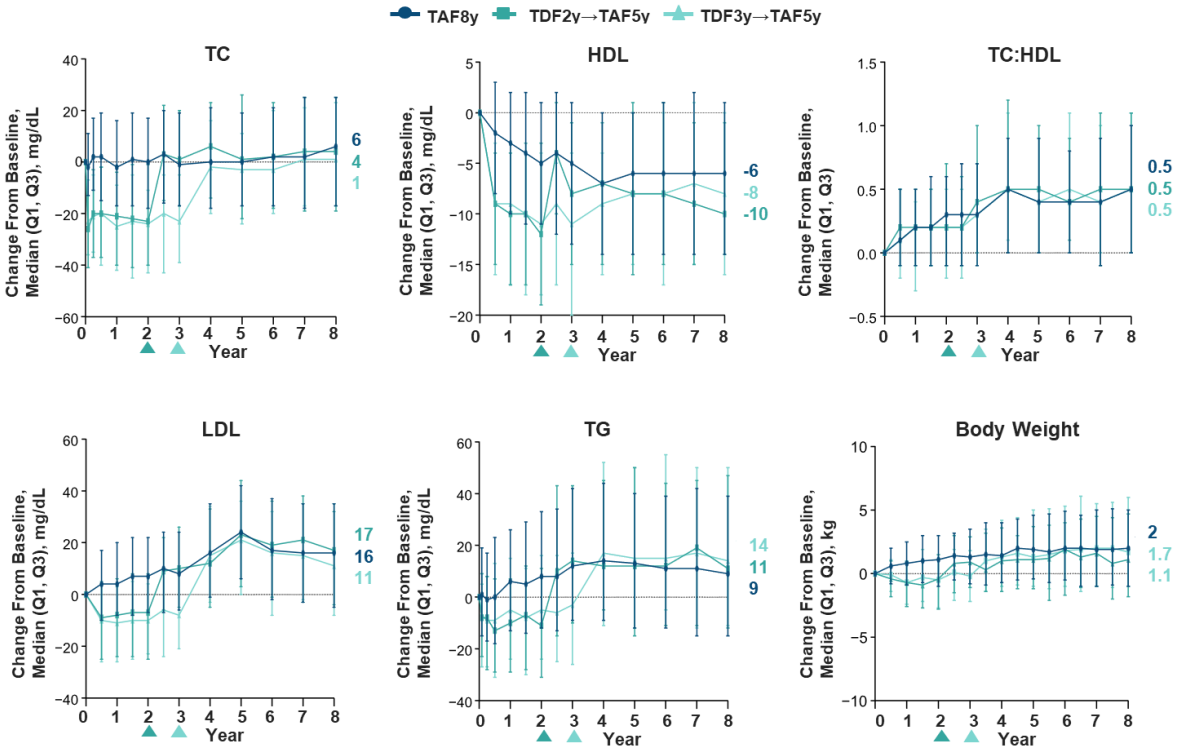
Lipid changes through Year 8

In the TAF8y treatment arm, median TC, LDL, and TG levels increased, and median HDL levels decreased at Year 8. In the TDF→TAF treatment arms, modest decreases in TC, LDL, HDL, and TG levels were observed during the DB phase of TDF treatment, and increases in these parameters similar to levels seen in the TAF8y group were observed once participants were switched to TAF. The median change in TC:HDL from baseline to Year 8 was 0.5 in all treatment arms (Figure 6).

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During the OL phase, Grade ≥3 abnormalities in fasting LDL levels were noted in 6% (45/760) of participants in the TAF8y treatment arm, 9% (15/173) in the TDF2y→TAF6y arm, and 8% (15/200) in the TDF3y→TAF5y arm. Grade ≥3 abnormalities in fasting cholesterol levels were noted in 1% (11/767) of participants in the TAF8y treatment arm, 1% (2/173) in the TDF2y→TAF6y arm, and 5% (9/200) in the TDF3y→TAF5y arm.

Figure 6. Studies 108 and 110: Median Changes in Fasting Lipid Panel and Body Weight Through Year 8[4]



Renal and bone safety subanalysis according to risk factors[6]

Study design and demographics

A pooled subanalysis of Studies 108 and 110 evaluated the long-term renal and bone safety of TAF in participants with ≥1 risk factor for TDF-associated renal and bone toxicities (eg, age >60 years, T-score less than -2.5 on DXA of hip and/or spine, $eGFR_{CG}$ <60 mL/min, UA:Cr >30 mg/g, and serum phosphorus level <2.5 mg/dL). Hip and spine DXA scans, serum bone biomarkers, $eGFR_{CG}$, and biomarkers of renal tubular function through Year 8 of treatment were compared between those with and those without risk factors. A total of 1059 participants did not have risk factors, and 239 (18%) had ≥1 risk factor in the TAF8y and TDF→TAF arms (Table 6).

Table 6. Subanalysis of Studies 108 and 110: Baseline Demographics and Disease Characteristics Among Participants With ≥1 Risk Factor for Renal and Bone Toxicities[6]

Key Demographics and Characteristics	Participants With ≥1 Risk Factor	
	TAF8y (n=151)	TDF→TAF (n=88)
Male, n (%)	91 (60)	53 (60)
Race, Asian/White/Native Hawaiian or Pacific Islander/ Black or African American, %	81/17/1/1	80/20/0/0

Key Demographics and Characteristics		Participants With ≥1 Risk Factor	
		TAF8y (n=151)	TDF→TAF (n=88)
HBeAg-, n (%)		73 (48)	40 (46)
FibroTest score ≥0.75, n/N (%)		26/145 (18)	14/87 (16)
Risk factors for TDF-associated renal and bone toxicities, n or n (%)	Number of risk factors, 1/2/≥3	133/17/1	75/12/1
	Osteoporosis by hip/spine	60 (40)	30 (34)
	UA:Cr >30 mg/g	44 (29)	28 (32)
	Age >60 years	42 (28)	28 (32)
	Serum phosphorus level <2.5 mg/dL	19 (13)	12 (14)
	$eGFR_{CG}$ <60 mL/min	5 (3)	4 (5)

Results

Among those in the TAF8y arm who had ≥1 TDF risk factor (median changes: -8.3, -5.8, and -10.6 mL/min in the TAF8y, TDF2y→TAF6y, and TDF3y→TAF5y arms, respectively) or no risk factors (-4.6, -5, and -3.1 mL/min in the TAF8y, TDF2y→TAF6y, and TDF3y→TAF5y arms), small decreases from baseline in $eGFR_{CG}$ were observed and were consistent with age-related decreases. Improvements in $eGFR_{CG}$ were noted after participants switched from TDF to TAF in both those with and those without risk factors; a greater recovery in eGFR was noted among those in the TDF2y→TAF6y arm than among those in the TDF3y→TAF5y arm. β_2:Cr and RBP:Cr remained stable, and tubular protein levels recovered among participants who switched from TDF to TAF and had ≥1 risk factor.

Regardless of the presence or absence of risk factors, mean percent changes from baseline in hip and spine BMD were small in those in the TAF8y arm. Serum levels of markers of bone turnover were stable among those with ≥1 risk factor. Recovery in hip and spine BMD measurements occurred after participants switched from TDF to TAF in both those with and those without risk factors; serum markers of bone turnover decreased after switching and eventually stabilized in participants with as well those without risk factors.

Among those with ≥1 TDF risk factor, 68% and 74% of participants in the TAF8y and TDF→TAF arms experienced any AEs. No participants in either group experienced a study drug-related Grade 3 or 4 AE or study drug-related SAE.

Real-World Data on TAF vs TDF in Patients With CHB

PS-Matched Cohort Analysis of HCC Risk[7]

Study design and demographics

Data from a nationwide health insurance claims database in Korea were analyzed to compare the incidence of HCC between patients who received TAF and those who received TDF as initial treatment of CHB. Eligible patients who received ≥6 months of TAF (n=20,994) or TDF (n=33,191) between 2017 and 2022 were PS-matched 1:1 (each, n=19,013) to minimize confounding effects. Liver transplantation and death were considered competing events.

Table 7. PS-Matched Cohorts: Baseline Demographics and Disease Characteristics[7]

Key Demographics and Characteristics	TAF (n=19,013)	TDF (n=19,013)	*P*-Value
Duration of antiviral treatment, mean ± SD, years	2.7±1.3	3±1.6	<0.001

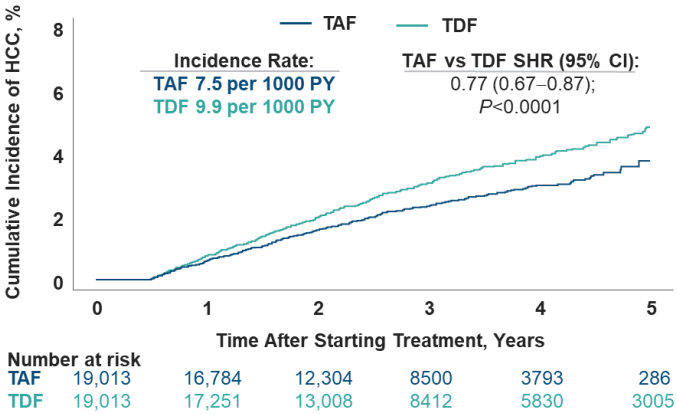
Key Demographics and Characteristics		TAF (n=19,013)	TDF (n=19,013)	*P*-Value
Age, mean ± SD, years		48±12	48±12	0.484
Male, %		57	58	0.401
Cirrhosis, %		18	18	0.729
ALT (U/L), <40/≥40/not available, %		21/25/54	21/25/54	0.696
CCI, 0/1/2/≥3, %		1/31/25/43	2/31/25/43	0.876
Alcohol consumption,[a] %	None	19	19	0.929
	Mild	24	24	
	Increased	2	2	
	Excessive	1	1	
	Not available	54	54	
Comorbidities, %	Dyslipidemia	62	62	0.547
	DM	25	25	0.822
	Hypertension	22	22	0.509
	Stroke	2	2	0.876
	CKD	1	1	0.956

[a]Alcohol consumption was categorized by the maximum amount consumed: mild, <210 g/week and <140 g/week for males and females, respectively; increased, 210 to <420 g/week and 140 to <350 g/week, respectively; excessive, ≥420 g/week and ≥350 g/week.

Results

After PS-matching was performed, the cumulative incidence of HCC was significantly more reduced with TAF treatment than with TDF treatment (*P*<0.0001; Figure 7).

Figure 7. PS-Matched Cohorts: Cumulative Incidence of HCC in TAF and TDF Cohorts[7]



On univariable and multivariable analyses, treatment with TDF, older age, male sex, and presence of cirrhosis were among the factors that were significantly associated with a higher risk of HCC development (Table 8).

Table 8. PS-Matched Cohorts: Factors Analyzed via Univariable and Multivariable Analyses for HCC Development[7]

Select Factors (Reference)		Univariable Analysis		Multivariable Analysis	
		SHR (95% CI)	*P*-Value	SHR (95% CI)	*P*-Value
TAF (TDF)		0.74 (0.66–0.83)	<0.001	0.76 (0.67–0.85)	<0.001
Male sex (female)		2.69 (2.38–3.03)	<0.001	2.48 (2.17–2.83)	<0.001
Age (18–39 years)	40–49 years	4.84 (3.7–6.32)	<0.001	4.13 (3.15–5.42)	<0.001
	50–59 years	9.98 (7.71–12.91)	<0.001	8.06 (6.18–10.51)	<0.001
	60–69 years	14.34 (10.99–18.73)	<0.001	11.63 (8.78–15.39)	<0.001
	≥70 years	16.46 (12.1–22.38)	<0.001	15.32 (10.96–21.41)	<0.001

Select Factors (Reference)		Univariable Analysis		Multivariable Analysis	
		SHR (95% CI)	*P*-Value	SHR (95% CI)	*P*-Value
Cirrhosis (none)		4.27 (3.88–4.71)	<0.001	2.94 (2.65–3.27)	<0.001
BMI (<25 kg/m^2)	≥25 kg/m^2	1.31 (1.16–1.49)	<0.001	1.15 (1.01–1.31)	0.03
Smoking (never)	Previous	2.2 (1.88–2.57)	<0.001	1.29 (1.09–1.53)	0.003
	Current	2.42 (2.1–2.79)	<0.001	1.61 (1.37–1.9)	<0.001
AST ≥40 U/L (<40 U/L)		2.2 (1.77–2.3)	<0.001	1.67 (1.38–2.02)	<0.001
ALT ≥40 U/L (<40 U/L)		1.26 (1.11–1.42)	<0.001	0.68 (0.56–0.81)	<0.001
Comorbidities (none)	Dyslipidemia	0.97 (0.88–1.07)	0.59	0.81 (0.73–0.91)	<0.001
	Hypertension	1.99 (1.79–2.2)	<0.001	1.13 (1–1.27)	0.05
	DM	1.57 (1.42–1.75)	<0.001	1.06 (0.93–1.2)	0.39
	Stroke	1.73 (1.29–2.32)	<0.001	0.95 (0.7–1.29)	0.73
	CKD	1.32 (0.8–2.16)	0.27	0.8 (0.48–1.32)	0.37
Alcohol consumption (none)	Mild	0.89 (0.77–1.02)	0.09	0.78 (0.67–0.9)	<0.001
	Increased	1.39 (1.04–1.85)	0.02	0.87 (0.65–1.18)	0.37
	Excessive	2.02 (1.43–2.85)	<0.001	1.21 (0.85–1.73)	0.28
CCI (score, 0)	1	0.55 (0.42–0.72)	<0.001	0.6 (0.45–0.79)	<0.001
	2	0.62 (0.47–0.82)	<0.001	0.55 (0.42–0.73)	<0.001
	≥3	0.84 (0.65–1.09)	0.2	0.56 (0.42–0.74)	<0.001

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Abbreviations

β_2:Cr=β-2 microglobulin to Cr ratio
AASLD=American Association for the Study of Liver Diseases
AE=adverse event
BMD=bone mineral density
CCI=Charlson Comorbidity Index
CHB=chronic hepatitis B
CKD=chronic kidney disease
CTX=C-terminal telopeptide of type 1 collagen
DB=double-blind
DM=diabetes mellitus
DXA=dual x-ray absorptiometry
CG=Cockcroft-Gault equation
GT=genotype
GGT=γ-glutamyl transferase
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
M=E=missing=excluded
NUC=nucleos(t)ide analog
OL=open-label
P1NP=N-terminal propeptide of type 1 procollagen
PS=propensity score
PY=patient-years
RBP:Cr=retinol-binding protein to Cr ratio
SAE=serious adverse event
SHR=subdistribution hazard ratio
TAF=tenofovir alafenamide
TC=total cholesterol
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
TG=triglyceride
TN=treatment-naive
UA:Cr=urine albumin to Cr ratio
ULN=upper limit of normal
URTI=upper respiratory tract infection

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