GILEAD | Medical Information

Vemlidy® (tenofovir alafenamide) Switching From Tenofovir Disoproxil Fumarate

This document is in response to your request for information regarding the efficacy and safety of switching from tenofovir disoproxil fumarate (TDF) to Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of chronic hepatitis B (CHB).

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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 Switching From TDF to TAF

A phase 3 trial (Study 4018) in virologically suppressed CHB participants showed similar virologic suppression, significant improvement in renal and bone parameters, and significantly higher ALT normalization rates in participants who switched to TAF compared with those who continued treatment with TDF. TAF was well tolerated, with AEs similar to those of TDF.[1-3]

- Similar results were observed in two substudies that evaluated prior TDF duration (<4 years or ≥4 years) and participants with TDF-associated risk factors.[4,5]

In a phase 2 trial (Study 4035), participants with renal or hepatic impairment who switched to TAF maintained virologic suppression, with high or improved normal rates of ALT and stable or improved renal and bone safety.[6,7]

A study that evaluated the safety and efficacy of switching to TAF for 48 weeks after ≥96 weeks of TDF vs continuing TDF in participants with multiple drug resistance found that switching to TAF yielded results that were not inferior to staying on TDF. Those who switched to TAF had improved renal and bone parameters at Week 48.[8]

Real-World Studies on Switching From TDF to TAF

In real-world studies, efficacy and general safety results after switching from TDF to TAF were comparable to phase 3 clinical study results. In studies with patients who had detectable HBV DNA, improved virologic suppression, ALT level normalization, and/or the incidence of normal ALT levels were reported.[9-21]

- After patients switched to TAF, improved renal tubular markers (β2M:Cr and RBP:Cr) were observed across studies[11,12,15,22]; however, other renal markers or indicators of renal function were variable.[9,10,13,15,16] In one long-term study, patients with CKD who switched to TAF from TDF or a NUC combination had an initial improvement in eGFR at Month 6, though the overall change from the time of the switch to Year 5 was minimal.[21]

- Additionally, after a switch to TAF, BMD measurements were stable or improved,[11,12,18] and one study showed improved APRI scores.[14]

Clinical Data on Switching From TDF to TAF

Study 4018: Switch From TDF to TAF

Study design and demographics[2]

Study 4018 was a double-blind, randomized, phase 3 study to evaluate the safety and efficacy of switching from TDF to TAF (n=243) compared with continuing TDF (n=245) in virologically suppressed participants with CHB who had been treated with TDF for ≥48 weeks prior to screening and had $eGFR_{CG}$ ≥50 mL/min at screening. The primary endpoint was the number of participants with HBV DNA ≥20 IU/mL (non-inferiority to TDF) at Week 48.[1] Final results from the Week 96 analysis are presented.

Figure 1. Study 4018: Study Design[2]

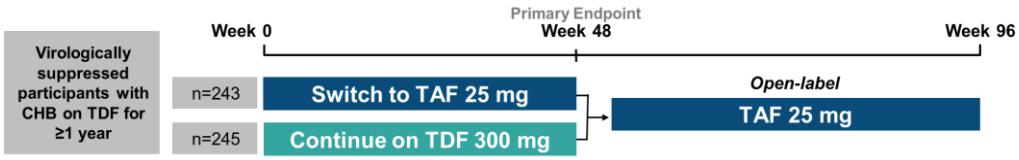


Table 1. Study 4018: Baseline Demographics and Disease Characteristics[1]

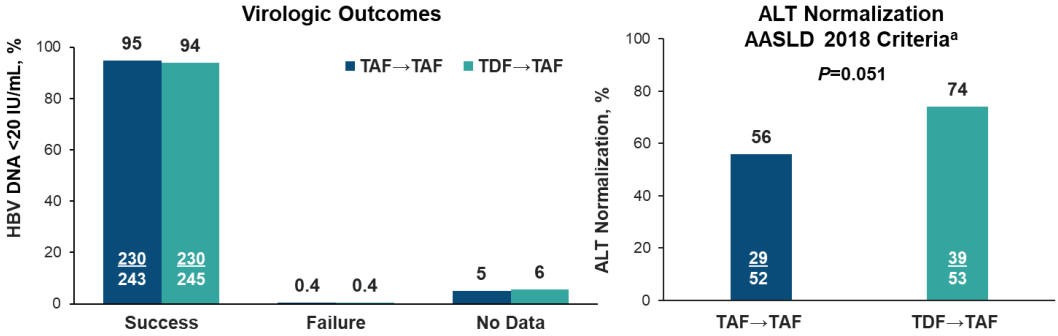
Key Demographics and Characteristics		TAF(n=243)	TDF (n=245)
Age, mean (SD), years		51 (10.5)	51 (10.8)
≥50 years, n (%)		136 (56)	136 (56)
Male, n (%)		179 (74)	166 (68)
Asian, n (%)		195 (80)	205 (84)
HBeAg-, n (%)		165 (68)	166 (68)
History of cirrhosis, n (%)		32 (13)	45 (18)
ALT, median (IQR), U/L		23 (18–32)	24 (18–31)
$eGFR_{CG}$, median (IQR), mL/min		91 (77–110)	90 (76–108)
Normal BMD status (T-score ≥-1)	Hip, n/N (%)	143/241 (59)	124/244 (51)
	Spine, n (%)	125 (51)	120 (49)

Efficacy

In terms of virologic suppression, the primary endpoint was met in that switching to TAF was non-inferior to remaining on TDF at Week 48 (4% margin; 95% CI approach by FDA modified snapshot algorithm). In participants with abnormal ALT levels at baseline, those who switched to TAF demonstrated a higher rate of ALT level normalization than those who continued with TDF.[1]

At the end of the 48-week, double-blind study period, participants who were randomly assigned to TDF were switched to open-label TAF (Figure 1).[1] The results of treatment with TAF were non-inferior to those of continued TDF with a switch to TAF at Week 48: the treatment difference between groups was 0% (95% CI: -1.9 to 1.9). ALT level normalization was higher among participants who switched to TAF at Week 48 than among those who received TAF for 96 weeks (Figure 2).[2]

Figure 2. Study 4018: Efficacy at Week 96[2]



[a]The ULN for AASLD criteria: 35 and 25 U/L in men and women, respectively.

No resistance was detected in either the TAF or TDF group through Week 96.[2]

Safety

Overall, switching to TAF from TDF was well tolerated, with TEAEs similar to those observed with TDF through Week 48.[1] The safety profile remained essentially unchanged, with similar TEAEs between treatment groups during the open-label study period (ie, Week 48 through Week 96; Table 2).[2]

Table 2. Study 4018: Safety From Week 48 Through Week 96[2]

Safety Outcomes, n (%) or n/N (%)		TAF→TAF (n=235)	TDF→TAF (n=237)
AE		81 (34)	84 (35)
Grade 3–4 AE		8 (3)	7 (3)
Grade 3–4 AE related to study drug		0	0
SAE		8 (3)	5 (2)
SAE related to study drug		0	0
Discontinued due to AE		1 (<1)	0
HCC		2 (<1)	1 (<1)
Grade 3–4 laboratory abnormalities		12/235 (5)	28/235 (12)
Laboratory abnormalities in ≥2% of participants	LDL cholesterol	5 (2)[a]	13 (6)[a]
	Urine glucose	5 (2)[a]	4/165 (2)[a]
	Increased TC	0	5 (2)[a]
	Urine erythrocytes	0	4 (2)[a]

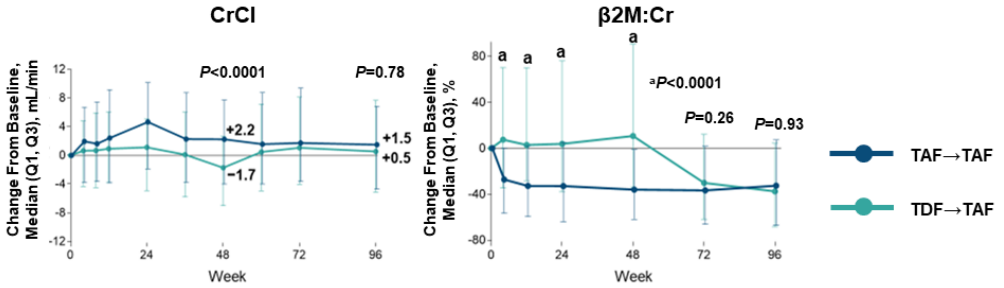
[a]All abnormalities were Grade 3.

TC, LDL, and HDL increased modestly in both groups from baseline to Week 96. However, the TC:HDL ratio was unchanged in both groups at Week 96 vs baseline. Median body weight increased by 1.4 kg and 1 kg in the TAF to TAF and TDF to TAF groups, respectively, from baseline to Week 96.[2]

Renal safety[2]

Participants who switched to TAF experienced improvements in CrCl and markers of proximal tubular function, which were sustained through Week 96 (Figure 3).

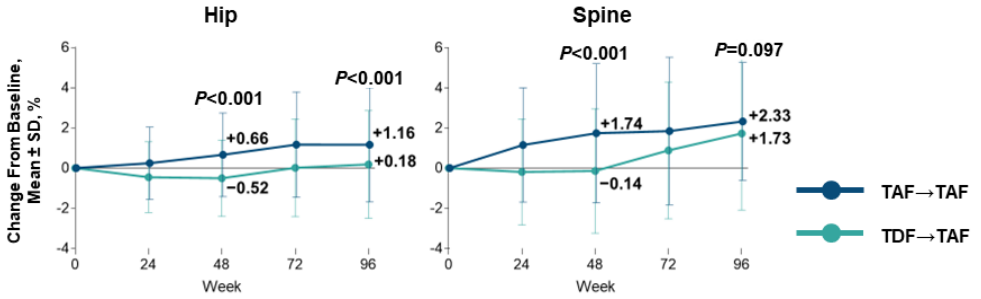
Figure 3. Study 4018: Renal Safety Through Week 96[2]



Bone safety[2]

Participants who switched to TAF experienced improvements in hip and spine BMD, which increased through Week 96 (Figure 4).

Figure 4. Study 4018: Changes in Hip and Spine BMD Through Week 96[2,3]



Study 4018 Subanalysis: Switch From TDF to TAF in Participants With Risk Factors[4]

The safety and efficacy of switching to TAF vs continuing TDF were assessed at Week 48 in 73% of participants (358/488) from Study 4018 who had risk factors for TDF-associated bone or renal toxicity.

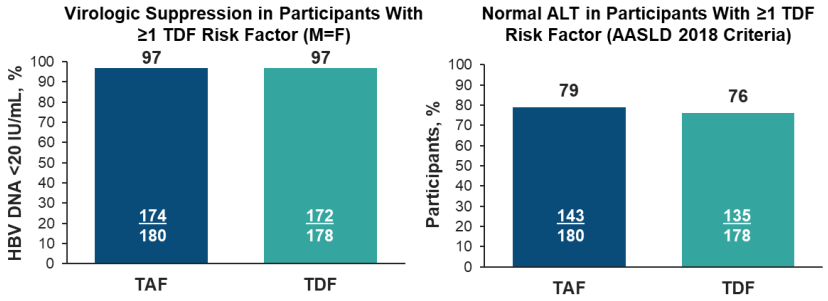
Table 3. Study 4018 Subanalysis: Baseline Demographics and Disease Characteristics of Participants With TDF Risk Factors[4]

Key Demographics and Characteristics		No TDF Risk Factors		≥1 TDF Risk Factor	
		TAF (n=63)	TDF (n=67)	TAF (n=180)	TDF (n=178)
Age, mean (range), years		44 (21–58)	44 (25–58)	53 (26–84)	54 (24–83)
Female, n (%)		11 (17)	12 (18)	53 (29)	67 (38)
Asian, n (%)		52 (83)	60 (90)	143 (79)	145 (82)
HBeAg+, n (%)		26 (41)	26 (39)	52 (29)	53 (30)
HBV DNA <20 IU/mL, n (%)		61 (97)	66 (99)	177 (98)	176 (99)
ALT, median (Q1, Q3), U/L		27 (19, 35)	25 (19, 30)	23 (18, 31)	23 (17, 31)
$eGFR_{CG}$, median (Q1, Q3), mL/min		107 (98, 118)	105 (95, 116)	85 (73, 99)	84 (71, 98)
Baseline TDF risk factors, n (%)	RI	N/A	N/A	117 (65)	121 (68)
	Comorbidities	N/A	N/A	79 (44)	71 (40)
	Advanced age (>60 years)	N/A	N/A	43 (24)	52 (29)
	Bone disease	N/A	N/A	34 (19)	29 (16)
	Albuminuria	N/A	N/A	28 (16)	25 (6)
	Obesity	N/A	N/A	19 (11)	15 (8)
	Hypophosphatemia	N/A	N/A	14 (8)	16 (4)

Efficacy

In participants with CHB who had risk factors associated with TDF use, virologic suppression was maintained with numerically higher rates of normal ALT levels at Week 48 in those switching from TDF to TAF (Figure 5). HBeAg seroconversion occurred in 4% and 0% of participants in the TAF and TDF groups, respectively, by Week 48. There were no HBsAg seroconversions in either group.

Figure 5. Study 4018: Efficacy Through Week 48 (Buti et al)[4]



Safety

Table 4 shows the summary of safety events through Week 48.

Table 4. Study 4018: Safety Summary Through Week 48 (Buti et al)[4]

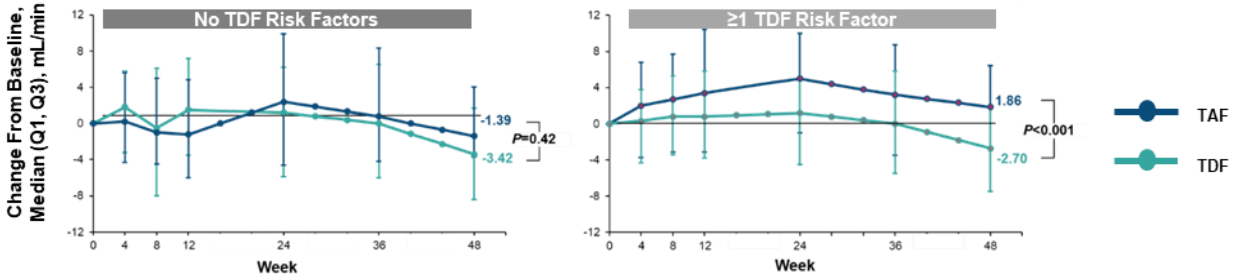
Safety Outcomes, n (%)	No TDF Risk Factors		≥1 TDF Risk Factor	
	TAF (n=63)	TDF (n=67)	TAF (n=180)	TDF (n=178)
Any AE	33 (52)	37 (55)	93 (52)	81 (46)
Grade 3–4 AE[a]	2 (3)	0	6 (3)	4 (2)
SAE[a]	3 (5)	2 (3)	8 (4)	1 (1)
DC due to AE[b]	1 (2)	0	1 (1)	0
Death	0	0	0	0

[a]No Grade 3 or 4 AEs or SAEs were related to study drug or reported in >1 participant.
[b]Discontinued due to AEs of breast cancer (risk factor group) and alopecia (no risk factor group; n=1 each).

Renal safety

Switching from TDF to TAF demonstrated significant improvement in renal function in participants with ≥1 risk factor, with a trend toward improvement in participants with no risk factors (Figure 6). Improvements in renal tubular markers were also observed.

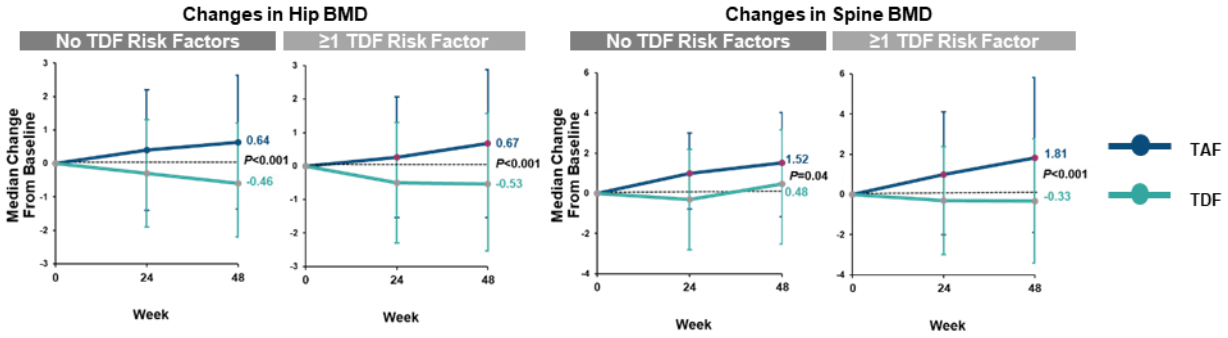
Figure 6. Study 4018: Change in $eGFR_{CG}$ (Buti et al)[4]



Bone safety

Switching from TDF to TAF demonstrated significant improvements in hip and spine BMD (Figure 7), as well as improvements in serum bone biomarkers.

Figure 7. Study 4018: Changes in BMD (Buti et al)[4]



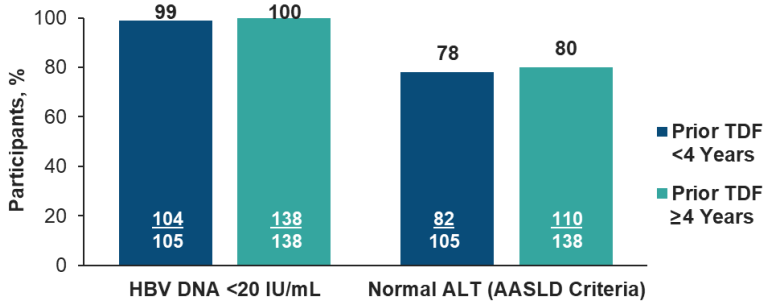
Study 4018 Subanalysis: Impact of Prior TDF Duration in Participants Switched to TAF[5]

To evaluate the impact of prior TDF duration on the efficacy and safety of TAF in virally suppressed participants who switched from TDF treatment, participants from Study 4018 who were randomly assigned to receive TAF were stratified according to duration of prior TDF therapy: <4 years or ≥4 years.

Results

Participants treated with TDF over different prior treatment durations showed similar virologic suppression and normal ALT rate after they switched to TAF for 48 weeks (Figure 8). In participants with prior TDF treatment for ≥4 years, HBeAg loss and seroconversion occurred in 13% (6/48) and 2% (2/48) of participants, respectively. There was no HBeAg loss/seroconversion in those with prior TDF treatment for <4 years. There was no HBsAg loss in either treatment group.

Figure 8. Study 4018 Subanalysis: Efficacy Through Week 48 (Chan et al)[5]



Renal and bone safety

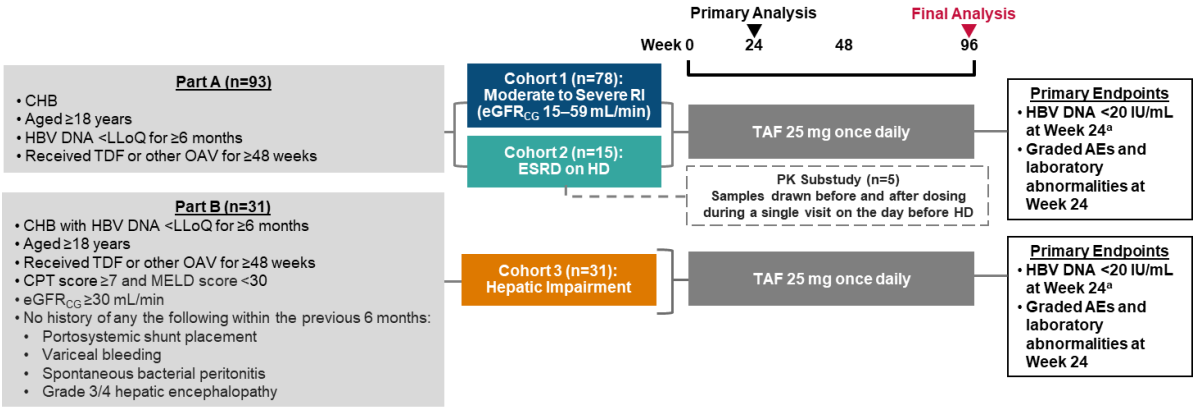
Improvements in bone and renal safety parameters after participants switched from TDF to TAF for 48 weeks were not affected by prior TDF duration.

Study 4035 Overview: Switching From TDF and/or Other OAVs to TAF in Participants With Renal or Hepatic Impairment

Study design and demographics[6]

Study 4035 was a phase 2, open-label, multicohort switch study that evaluated the efficacy and safety of switching from TDF and/or other OAVs to TAF 25 mg daily in virologically suppressed participants with CHB in the following groups (Figure 9): Part A/Cohort 1, moderate to severe RI ($eGFR_{CG}$ 15 to <60 mL/min; n=78); Part A/Cohort 2, ESRD maintained on HD ($eGFR_{CG}$ <15 mL/min; n=15); or Part B/Cohort 3, moderate to severe hepatic impairment (CPT score ≥7; n=31; moderate hepatic impairment, CPT 7–9; severe, CPT 10–12).

Figure 9. Study 4035: Study Design[6,7]



Abbreviations: LLoQ=lower limit of quantitation; MELD=model for end-stage liver disease.
[a]Evaluated in subgroups according to age (<65 years and ≥65 years) and by male or female sex.

Table 5. Study 4035: Baseline Demographics and Disease Characteristics[6,7]

Key Demographics and Characteristics	Moderate to Severe RI (n=78)	ESRD (n=15)	Hepatic Impairment (n=31)
Age, mean ± SD, years	66±10.1	54±12.8	55±10.8
Male, n (%)	57 (73)	12 (80)	21 (68)
Race, Asian/White/Black/other, %	76/19/4/1	87/0/0/13	81/13/3/3
HBeAg-, n (%)	65 (83)	12 (80)	28 (90)
HBV DNA <20 IU/mL, n (%)	77 (99)	14 (93)	31 (100)
ALT, median (IQR), U/L	19 (13–25)	12 (9–16)	27 (18–33)
ALT ≤ULN (AASLD criteria[a]), n (%)	73 (94)	15 (100)	21 (68)
History of cirrhosis, n (%)	27 (35)	5 (33)	30 (97)
FibroTest ≥0.75,[b] n (%)	11 (14)	0	19 (61)
CPT score, mean (range)	N/A	N/A	6 (5–10)
$eGFR_{CG}$, median (IQR), mL/min	45.7 (36.3–54.9)	7.3 (5.5–9.7)	98.5 (72.5–129.8)
T-score <-2.5, spine/hip, n (%)	19 (24)/7 (9)	3 (20)/7 (47)	6 (19)/1 (3)
Select comorbid conditions, HTN/hyperlipidemia/DM/CVD, %	58/33/27/18	73/20/13/40	23/13/23/13

Key Demographics and Characteristics	Moderate to Severe RI (n=78)	ESRD (n=15)	Hepatic Impairment (n=31)
Most common (>5% in any group) prior OAVs, TDF/ADV/LAM/ETV/IFN or pegIFN/LdT,[c] %	73/55/54/41/9/6	7/7/27/73/0/7	68/32/45/45/0/6

Abbreviations: CVD=cardiovascular disease; IFN=interferon; pegIFN=pegylated interferon.
[a]ULN ALT levels were ≤25 U/L for females and ≤35 U/L for males.
[b]FibroTest scores were not available for 1 participant in Cohort 1.
[c]Participants could have received >1 agent previously. Other agents included clevudine or a combination of OAVs.

Study 4035: RI subgroup

Efficacy[6,7]

Virologic suppression (HBV DNA <20 IU/mL) rates in Cohort 1 and Cohort 2 were 97.4% and 100%, respectively, at Week 24 (primary endpoint) and decreased to 83.3% and 86.7%, respectively, at Week 96. Virologic failure occurred in 1 participant (per FDA Snapshot Analysis) in Cohort 1 at Week 48 and was likely due to nonadherence; this participant was later resuppressed at Week 72 and had HBV DNA <20 IU/mL at Week 96. Virologic suppression rates at Week 24 were similar between subgroups according to age and sex (<65 years/≥65 years and male/female). In addition, in Cohort 1 and Cohort 2, normal ALT levels (AASLD criteria) were observed in 74.4% and 86.7% of participants, respectively, at Week 96. All 5 participants (all in Cohort 1) with ALT levels >ULN at baseline had normalized levels by Week 96 (2 at Week 24, 3 at Week 48, and 1 at Week 96).

Of the 16 participants who were HBeAg+ at baseline, 1 participant in Cohort 2 experienced HBeAg loss with seroconversion at Week 96, and 1 participant experienced HBsAg loss without seroconversion at Week 48. In a post hoc analysis, the mean decrease in quantitative HBsAg from baseline to each timepoint was small. Of the 11 participants with cirrhosis (FibroTest Metavir F4) at baseline, 9 had Week 96 data, and of those, 4 had a lower category of fibrosis compared with baseline.

Safety

Overall, treatment was well tolerated, and the observed AEs, SAEs, and laboratory abnormalities were consistent with those of participants with established renal disease (Table 6). No study drug-related Grade 3 to 4 AEs or SAEs were reported. The only study drug-related AE that occurred in ≥2 participants was proteinuria (3%; n=2, both in Cohort 1). Two participants had AEs that led to treatment interruption: 1 in Cohort 1 due to pneumonia and another in Cohort 2 due to coagulopathy, thrombocytopenia, thrombotic thrombocytopenic purpura, jaundice, and hemoptysis.[6]

Table 6. Study 4035 RI Subgroup: Overall Safety Through Week 96[6,7]

Safety Outcomes, n (%)	Cohort 1: Moderate to Severe RI (n=78)	Cohort 2: ESRD (n=15)
Any AE	58 (74)	15 (100)
Study drug-related AE	4 (5)	2 (13)
Grade 3–4 AE	14 (18)	4 (27)
SAE	12 (15)	8 (53)
DC due to AE	3 (4)[a]	0
Death	2 (3)[b]	1 (7)[c]
Grade 3–4 laboratory abnormalities	13 (17)	11 (73)

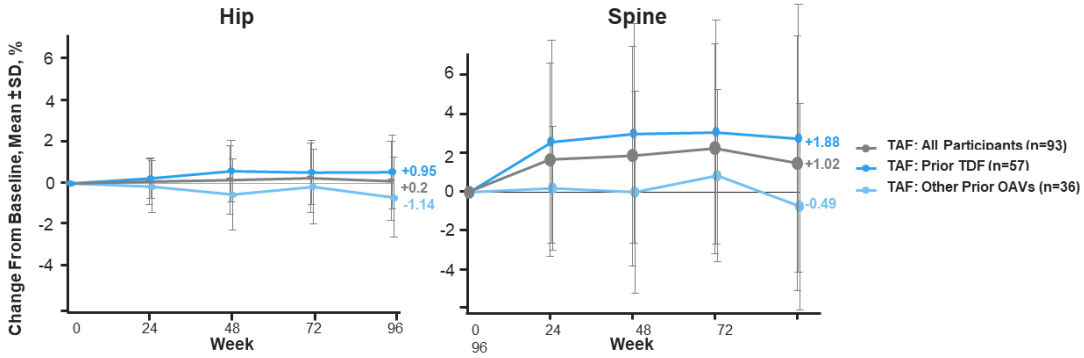
Safety Outcomes, n (%)		Cohort 1: Moderate to Severe RI (n=78)	Cohort 2: ESRD (n=15)
Grade 3–4 laboratory abnormalities in ≥2 participants	SCr increased	5 (6)	1 (7)
	Urine glucose	3 (4)	0
	Fasting serum glucose	2 (3)	0
	LDL increased	2 (3)[d]	0
	Hgb decreased	1 (1)	4 (27)
	Amylase increased	1 (1)	3 (20)

[a]Malignant lung neoplasm, respiratory failure, and rectal cancer; none were related to treatment.
[b]Chest infection and respiratory failure (on Day 261) and non-traumatic intracerebral hemorrhage (on Day 442).
[c]Severe thrombocytopenia (on Day 303). [d]LDL levels were available for 76 participants.

In Cohort 1, $eGFR_{CG}$ was stable through Week 96 overall (median change from baseline, +1 mL/min) and in subgroups according to prior use of TDF (n=56; +2.5 mL/min) or other OAVs (n=22; -2.6 mL/min).[6] In addition, after treatment was switched to TAF, proximal tubular markers decreased from baseline to Week 96 (median % change from baseline: RBP:Cr [n=64], -38.5%; β2M:Cr [n=63], -57%).[7]

Overall, switching to TAF from TDF or other OAVs resulted in stable hip (mean ± SD, +0.2±3.25%) and spine (mean ± SD, +1.02±4.44%) BMD measurements through Week 96 (Figure 10), and % increases in BMD were observed among those previously treated with TDF relative to those treated with other OAVs.[6,7]

Figure 10. Study 4035: Changes in BMD Overall and by Prior Use of TDF or Other OAVs Through Week 96[6]



Small to modest increases in lipid parameters overall were observed at Week 96 after participants switched to TAF (median changes: TC, +10 mg/dL; LDL, 0; HDL, +3 mg/dL; TG, +18 mg/dL), primarily in those who previously used TDF (due to removal of the lipid-lowering effect of TDF); no appreciable changes were seen in TC:HDL ratio. The median (IQR) change from baseline to Week 96 in body weight was +1 (-0.6 to +2.3) kg.[6,7]

TAF PK in participants with ESRD on HD were comparable to historical data from people with HIV.[6]

Study 4035: hepatic impairment subgroup

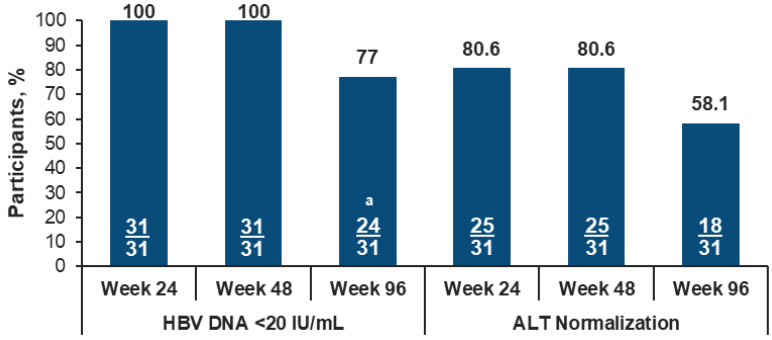
Efficacy[6]

At Week 24 (primary endpoint) and Week 48, using M=F data, 100% of participants were virologically suppressed; this rate decreased to 77% at Week 96 (Figure 11). Of the 7 participants who did not achieve virological suppression at Week 96, 6 participants did not have virological data; only 1 participant had virologic failure at Week 96 (HBV DNA: 23 IU/mL). Because the participant's HBV DNA did not meet the assay limit for sequencing

(≥69 IU/mL), no resistance testing was performed. Virologic suppression rates at Week 24 were identical between subgroups according to age and sex (<65 years/≥65 years and male/female).

Normal ALT levels (AASLD criteria) were observed in 58.1% of participants at Week 96 (Figure 11). Of the 10 participants with ALT levels >ULN at baseline, several had normalized levels by Week 96: 6 (60%) at Week 24; 6 (60%) at Week 48, and 5 (50%) at Week 96.

Figure 11. Study 4035 Hepatic Impairment Subgroup: Virologic Suppression and ALT Normalization Through Week 96[6]



[a]At Week 96, 1 participant (3%) had HBV DNA 23 IU/mL, and 6 (19%) had no virological data.

None of the 3 participants who were HBeAg+ at baseline had HBeAg loss during the study, and 2 participants (7%) experienced HBsAg loss without seroconversion. Of the 15 participants who had FibroTest data available at baseline and at Week 96, 11 (73%) had no change in cirrhosis category, and 4 (27%) had improvements in cirrhosis category.

At Week 96, of the 19 participants who were CPT Class A at baseline, 14 remained in Class A, and 1 worsened to Class B (missing data, n=4). Of the 9 participants who were CPT Class B at baseline, 2 improved to Class A, and 5 remained in Class B (missing data, n=2). All 3 of the participants who were CPT Class C at baseline had improvements at Week 96: 1 to Class A and 2 to Class B.

Safety

AEs that occurred in ≥10% of participants included upper respiratory tract infection, cough, pyrexia, diarrhea, decreased BMD, ascites, constipation, oropharyngeal pain, and arthralgia. One participant required an interruption of treatment for 4 days due to gastrointestinal hemorrhage, subdural hematoma, and subarachnoid hemorrhage.[6]

Table 7. Study 4035 Hepatic Impairment Subgroup: Safety Through Week 96[6,7]

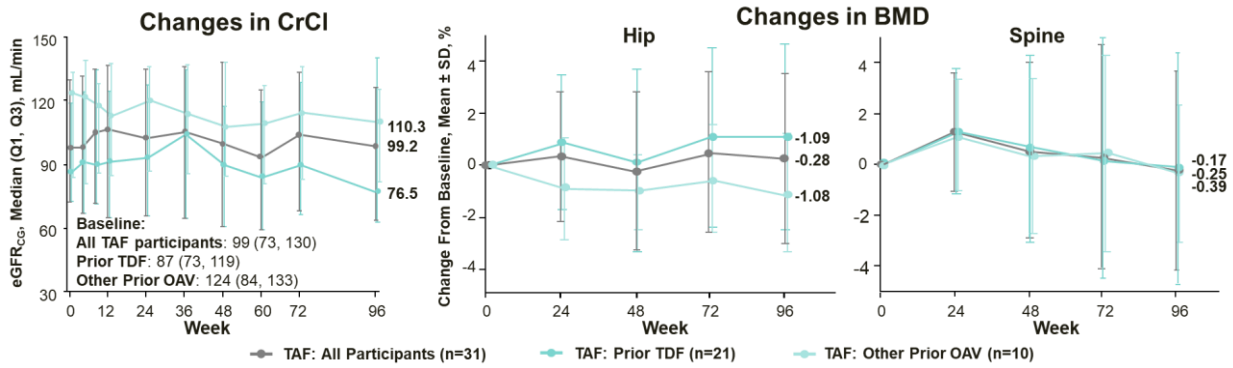
Safety Outcomes, n or n (%)	Hepatic Impairment (n=31)
Any AE	24 (77.4)
Study drug-related AE	4 (12.9)
Grade 3–4 AE[a]	8 (25.8)
SAE[a]	10 (32)
DC of study drug due to AE	1 (3)[b]
Death	2 (6.5)[c]
Grade 3/4 laboratory abnormalities	17 (54.8)

Safety Outcomes, n or n (%)		Hepatic Impairment (n=31)
Grade 3–4 laboratory abnormalities reported in ≥2 participants	Lymphocytes decreased	7 (23)
	Platelets decreased	4 (13)
	Bilirubin increased	4 (13)
	Hgb decreased	3 (10)
	Urine glucose	3 (10)
	Fasting serum glucose	2 (6)

[a]No Grade 3–4 AEs or SAEs were related to study treatment.
[b]Cr increase (Grade 2; non-serious; considered related to study treatment by the study investigators) in a 73-year-old male with CKD Stage 2 at baseline, which increased to Stage 3 and led to study drug discontinuation at Week 60.
[c]Neither death was related to treatment: respiratory failure (n=1, Day 612); aspiration pneumonia (n=1, Day 651).

Following the switch to TAF, CrCl and BMD (hip and spine) were stable through Week 96 (Figure 12). Most participants had stable or improved CKD stages at Week 96; however, 2 participants had a worsened CKD stage (baseline to Week 96, Stage 1 to Stage 2 [n=1]; Stage 2 to Stage 4 [n=1]). In addition, after treatment was switched to TAF, proximal tubular markers (RBP:Cr and β2M:Cr) initially decreased from baseline by approximately 20% but remained stable thereafter.[6,7]

Figure 12. Study 4035 Hepatic Impairment Subgroup: Renal and Bone Parameters at Week 96 Overall and by Prior Use of TDF or Other OAVs[6,23]



Overall, small median increases from baseline to Week 96 in TC (+8 mg/dL), LDL (+7 mg/dL), HDL (+2 mg/dL), and TG (+5 mg/dL) levels were seen in participants after they switched to TAF, but these increases were not considered clinically important. The median (IQR) change from baseline to Week 96 in body weight was +2.4 (-1.8 to +6) kg.[6,7]

Switch From TDF to TAF in Multiple Drug-Resistant HBV[8]

Study design and demographics

A randomized, open-label, multicenter, non-inferiority study was conducted in Korea between October 2017 and June 2018 to assess the safety and efficacy of switching from TDF to TAF after receiving ≥96 weeks of TDF monotherapy, compared with continuing TDF, in participants with HBV resistance to multiple drugs. Participants who were taking TDF (N=174) were randomly assigned 1:1 to either continue TDF (n=87) or switch to TAF (n=87) for 48 weeks. The primary endpoint was the proportion of participants with HBV DNA <60 IU/mL at Week 48. Secondary endpoints included the proportion of participants with HBV DNA <15 IU/mL and the proportion of participants with normal ALT levels by local laboratory and AASLD 2018 criteria.

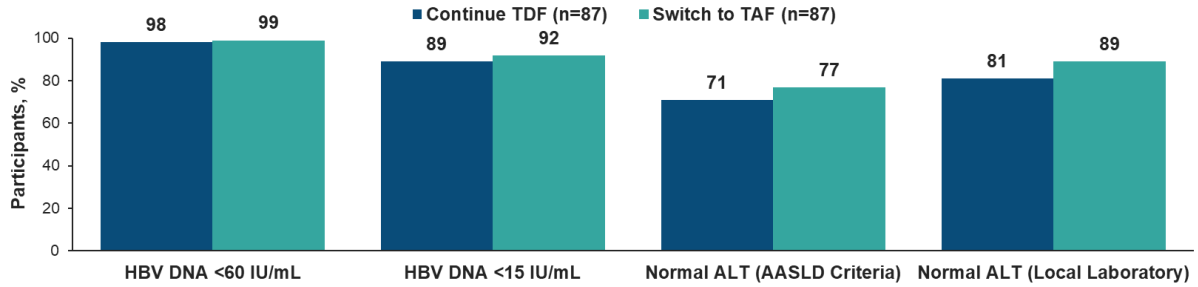
Table 8. Baseline Demographics and Disease Characteristics (Byun et al)[8]

Key Demographics and Characteristics	Continued TDF (n=87)	Switched to TAF (n=87)
Age, mean ± SD, years	53.3±9.5	56.4±9.4
Male, n (%)	73 (84)	67 (77)
Normal ALT (AASLD 2018 criteria), n (%)	67 (77)	61 (70)
HBeAg+, n (%)	56 (65)	52 (60)
HBV DNA ≥60 IU/mL, n (%)	7 (8)	3 (3)
HBV DNA ≥15 IU/mL, n (%)	18 (21)	8 (9)
LAM/ETV/ADV resistance, n (%)	79 (91)/43 (49)/32 (37)	81 (93)/37 (43)/28 (32)

Efficacy

In participants with multiple drug resistance, switching to TAF maintained virologic suppression with numerically improved rates of normal ALT at Week 48 (Figure 13).

Figure 13. Efficacy Results at Week 48 (Byun et al)[8]



Note: The between-groups difference in the proportion of patients with HBV DNA <60 IU/mL was 1.1% (95% CI: -2.7 to 5; *P*>0.99).

Renal and bone safety

At Week 48, the mean (IQR) change in eGFR from baseline in the TDF group was 1.9 (-1.2 to 9.9) mL/min/1.73 m^2, compared with a change of 7.3 (-1.1 to 15.1) mL/min/1.73 m^2 in the TAF group (*P*=0.047). The mean ± SD change from baseline in spine BMD in the TDF group was 0.2±4.2 g/cm^2, compared with a change of 1.8±4.9 g/cm^2 in the TAF group (*P*=0.02). There was no significant difference between groups in the mean change from baseline in hip BMD.

Real-World Studies on Switching From TDF to TAF

Long-Term Retrospective Multicenter Study: Switching to TAF From Other NUCs[21]

Study design and demographics

A retrospective, multicenter, real-world study evaluated the long-term effectiveness and renal safety of patients with and without CKD (eGFR <60 mL/min/1.73 m^2) who switched from another NUC for CHB treatment to TAF 25 mg and who underwent follow-up for >5 years. Through Year 5, the primary endpoints were virologic effectiveness (HBV DNA <10 IU/mL and reduction in HBsAg), ALT normalization (AASLD criteria: <35 U/L for males and <25 U/L for females; JSH criteria: <30 U/L for both sexes), and renal function. Data were stratified according to the absence (n=314) or presence (n=100) of CKD; those with

CKD were significantly older and were more likely to be female and have cirrhosis than those without CKD (Table 9).

Table 9. Long-Term Study: Baseline Demographics and Disease Characteristics[21]

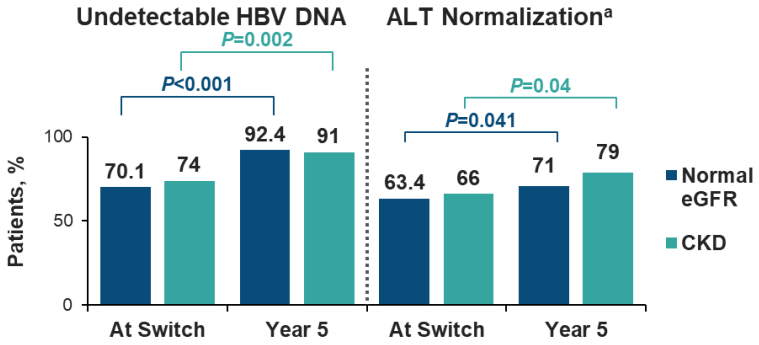
Key Demographics and Characteristics		Normal eGFR (≥60 mL/min/1.73 m^2; n=314)	CKD (eGFR <60 mL/min/1.73 m^2; n=100)	*P*-Value
Age,[a] years		55 (46–65)	67 (61–71)	<0.001
Male, n (%)		206 (65.6)	48 (48)	0.002
Cirrhosis, n (%)		34 (10.8)	20 (20)	0.018
HBeAg+, n (%)		44 (14)	19 (19)	0.23
HBV DNA, n (%)	Undetectable	220 (70.1)	74 (74)	0.33
	<20 IU/mL	57 (18.2)	11 (11)	
	20–2000 IU/mL	31 (9.9)	12 (12)	
	>2000 IU/mL	6 (1.9)	3 (3)	
Albumin,[a] g/dL		4.4 (4.2–4.6)	4.3 (4.1–4.5)	0.035
ALT,[a] U/L		23 (16–32)	19 (15–26)	0.073
Platelets,[a] 10^3/mL		191 (150–235)	178 (137–207)	0.004
eGFR,[a] mL/min/1.73 m^2		77 (69–86)	53 (47–56)	<0.001
Prior NUC, n (%)	ETV	136 (43.3)	41 (41)	0.55
	TDF	95 (30.3)	27 (27)	
	Combination	83 (26.4)	32 (32)	

[a]The source did not specify how data were presented (ie, median [IQR] or mean [range]).

Effectiveness

Over 5 years, TAF was associated with sustained virological and biochemical response regardless of renal function (Figure 14). No patients had HBV DNA breakthrough, and the annualized reduction of HBsAg was 0.077 log IU/mL, with a mean reduction from the time of treatment switch to Year 5 of 0.39 log IU/mL. Among those with normal eGFR, using AASLD and JSH criteria, 71% and 80.3% of patients, respectively, had normalized ALT levels at Year 5; among those with CKD, 79% and 90% had normalized ALT levels.

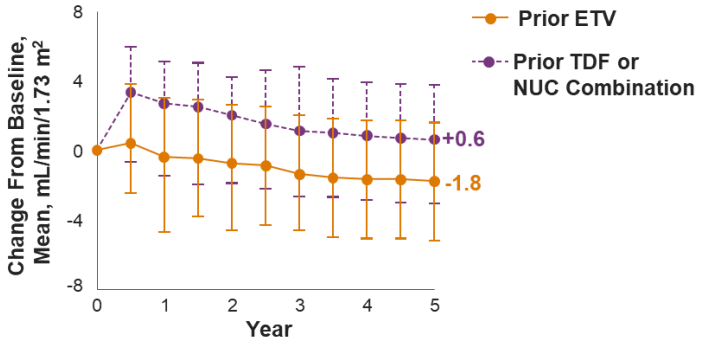
Figure 14. Long-Term Study: Undetectable HBV DNA and ALT Normalization at Switch and Year 5[21]



Renal safety

Patients with CKD who were previously treated with TDF or another NUC combination had a mean increase from baseline to Month 6 in eGFR of 3.3 mL/min/1.73 m^2, but the overall change from baseline through Year 5 was minimal (Figure 15). Patients previously treated with ETV had a small decrease in eGFR from baseline to Year 5.

Figure 15. Long-Term Study: Change in eGFR Through Year 5 After Switching to TAF Among Patients With CKD[21]



Retrospective Study: Switching to TAF From Other NUCs[24]

Study design and demographics

A retrospective, multicenter, observational cohort study was conducted between March 2017 and December 2018 and included adult patients from Japan who had received ≥2 years of a NUC and switched to 25 mg oral TAF once daily for CHB treatment. The primary endpoint was the proportion of patients with HBV DNA <10 IU/mL at Week 144 after the switch. Secondary endpoints included ALT levels, eGFR, serum phosphorus levels, and fasting lipid parameters.

Table 10. Baseline Demographics and Characteristics (Ogawa et al)[24]

Key Demographics and Characteristics		TAF (N=391)
Age, median (IQR), years		59 (47–68)
Male, n (%)		236 (60.4)
Cirrhosis, n (%)		31 (7.9)
AST/ALT, median (IQR), U/L		24 (20–29)/21 (15–31)
Serum phosphorus, median (IQR), mg/dL		3.2 (2.9–3.6)
eGRF, mL/min	Overall, median (IQR)	73 (61–83)
	30–60/15 to <30, n (%)	84 (21.5)/3 (0.8)
Prior NUC, ETV/TDF/NUC combination,[a] n		174/116/101
Duration of prior NUC treatment, median (IQR), years		5.3 (4–7.7)

[a]ETV + TDF, 33.7%; LAM + ADV, 33.7%; LAM + TDF, 29.7%; or ETV + ADV, 3.4%.

Effectiveness

At Week 144, 99.1% of patients (n=115/116; 95% CI: 94.8–100) who switched from TDF to TAF achieved HBV DNA <10 IU/mL, and none had an HBV breakthrough during the follow-up period. Among patients who switched from TDF to TAF and were HBeAg+ at the time of switch, HBeAg loss was reported in 27.3% (6/22) of patients at Week 144.

Among the patients with baseline CKD (eGFR <60 mL/min/1.73 m^2; n=87; 84/87 had CKD Stage 3), 100% of patients (n=24; 95% CI: 83.7–100) who switched from TDF to TAF achieved HBV DNA <10 IU/mL at Week 144, and ALT normalized per AASLD criteria at Week 144 at a rate of 91.7% (22/24; 95% CI: 73–98.8). Among those who switched from TDF to TAF, the rate of normal ALT levels increased from 72.4% at baseline to 85.3% at Week 144 (*P*=0.016). Among patients with elevated ALT levels at baseline, 62.5% of patients who switched from TDF to TAF achieved ALT normalization at Week 144.

At Week 144, the rate of hypophosphatemia (<2.5 mg/dL) in patients with prior TDF or ADV use was 10%.

Prospective Study: Switching to TAF From Other NUCs

Study design and demographics[18]

A prospective, multinational, real-world study was conducted to assess virologic, biochemical, renal, and bone outcomes in participants with CHB who switched to TAF after treatment for ≥1 year with other NUCs (N=270). This cohort was composed of participants from Japan, Korea, Taiwan, and the US, and all participants were monitored for 24 months after they switched to TAF.

The primary outcome was the percentage of participants with complete virologic suppression (HBV DNA level <20 IU/mL) at Month 24 after switch to TAF. Key secondary outcomes included changes in BMD (T-scores), virologic suppression + biochemical response (defined as ALT level <35 U/L for men and <25 U/L for women), and renal function (eGFR) changes through Month 24 after participants switched to TAF.

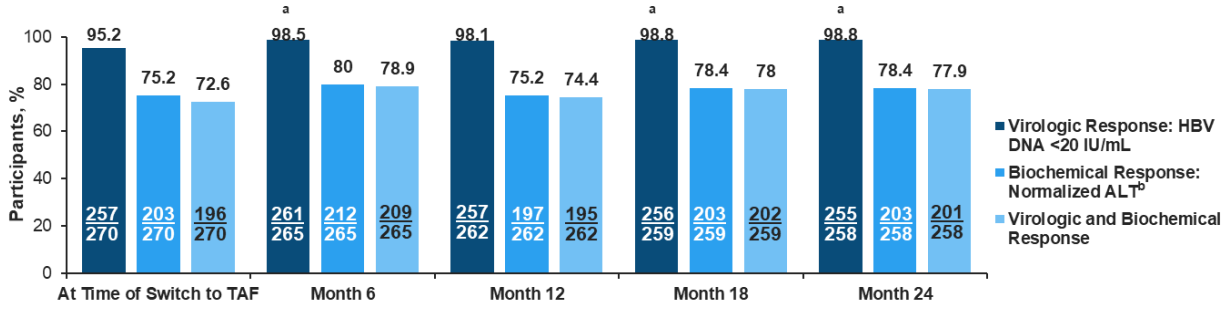
Table 11. Baseline Demographics and Disease Characteristics (Ogawa et al)[18]

Key Demographics and Characteristics	TAF (N=270)
Age, mean ± SD, years	58.1±10.6
Male, n (%)	157 (58.2)
Race, Asian/non-Asian, n (%)	269 (99.6)/1 (0.4)
Cirrhosis, n (%)	33 (12.2)
HBV DNA <20 IU/mL, n (%)	257 (95.2)
HBeAg+ (n=269), n (%)	43 (16)
FIB-4 index, >3.25/1.45–3.25/<1.45, n (%)	28 (10.4)/114 (42.2)/128 (47.4)
AST/ALT, median (IQR), U/L	24 (20–31)/21 (16–29)
$eGFR_{CKD-EPI}$, mean ± SD, mL/min	88.4±16.8
Prior NUC, ETV/TDF or ADV/other, n (%)	199 (73.7)/62 (23)/9 (3.3)
Duration of prior NUC treatment, mean ± SD, years	7.5±4
Select comorbid conditions, HTN/DM, n (%)	63 (23.3)/47 (17.4)

Effectiveness

Twelve participants did not complete the Month 24 follow-up. From study baseline through Month 24, there was a significant increase in the proportion of participants with HBV DNA <20 IU/mL (primary endpoint), as well as non-significant increases in biochemical response and virologic + biochemical responses (Figure 16). Similar results were observed for participants who switched from ETV.[18,25]

Figure 16. Virologic Suppression and Biochemical Responses Through Month 24 (Ogawa et al)[18,24]



[a]*P*<0.05 vs value at start of TAF. [b]ALT <35 U/L (males) or <25 U/L (females).

In multivariable analyses that adjusted for baseline age, cirrhosis and HBeAg status, and HBV DNA and ALT levels, older age and a high baseline HBV DNA level were associated with decreases in HBV DNA levels (*P*=0.015 and <0.0001, respectively) after switching to TAF treatment; older age and high ALT levels at baseline were associated with decreases in ALT with TAF (*P*=0.031 and <0.0001).[18]

Safety

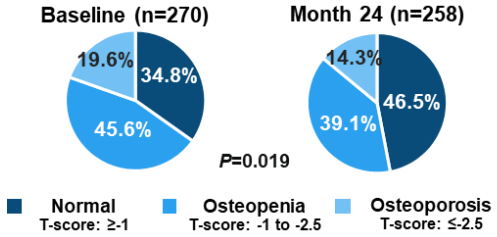
Nineteen AEs (7%) and 15 SAEs (5.6%) were observed; of the SAEs, none were TAF-related, and HCC and other malignancies were the only SAEs reported in >1 participant. Five AEs (1.9%) led to TAF discontinuation and 1 death, due to newly diagnosed gallbladder cancer, occurred. Eight (3%) Grade 3/4 laboratory abnormalities were observed, including 3 cases of Grade 3 hypertriglyceridemia.[18,24]

Among participants who switched from ETV, mean ± SD weight increased from baseline to Month 24: 60.2±16.9 to 63.6±13 kg, respectively (*P*=0.0002). No significant changes were observed for TC (*P*=0.31) and TG (*P*=0.37) levels.[18]

From baseline to Month 24, no significant changes in mean ± SD eGFR (Month 24, 89.5±16.3 mL/min/1.73 m^2; *P*=0.13) or the distribution of CKD stages (*P*=0.13) occurred. Most participants (61.9%) with Stage 3 CKD at baseline improved to Stage 1 or 2 at Month 24; 34% of those with Stage 2 CKD improved to Stage 1 CKD. In multivariable analyses, independent factors associated with worsened CKD stage were older age (aOR: 1.07; 95% CI: 1.01–1.12; *P*=0.019) and baseline eGFR (aOR: 1.04; 95% CI: 1–1.08; *P*=0.041).[18]

The mean ± SD T-score significantly improved from baseline (-1.43±1.36) to Month 24 (-1.17±1.38; *P*<0.0001). Additionally, the proportion of participants with normal BMD increased, while the proportion with osteoporosis/osteopenia decreased (Figure 17). In multivariable logistic regression analyses, male sex was the only independent factor significantly associated with a lower risk of worsening spine BMD (aOR: 0.29; 95% CI: 0.1–0.82; *P*=0.02). Independent factors associated with improving spine BMD were male sex (aOR: 2.26; 95% CI: 1.12–4.65; *P*=0.022) and baseline spine T-score (aOR: 0.56; 95% CI: 0.41–0.75; *P*<0.0001). No participants developed fragility fractures during the study.[18]

Figure 17. BMD Parameters at Baseline and Month 24 (Ogawa et al)[18]



TRIO HBV Registry[9]

Study design and demographics

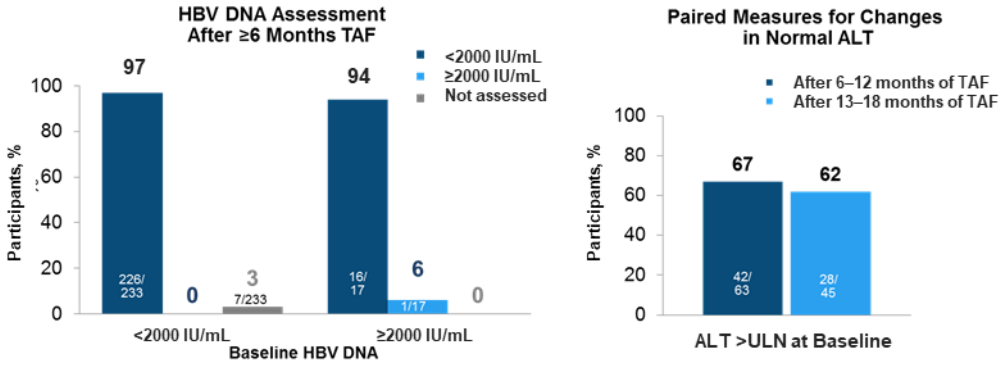
The TRIO HBV Registry is composed of participants at 10 academic and community centers in the US. The current study was conducted to assess the real-world clinical experience of TAF in 250 participants who were either TN or who switched from a previous regimen to TAF. Participants received TAF for ≥6 months and were followed up to 18 months; the median duration of TAF treatment was 13 months.

Participants were predominantly male (59%) and Asian (88%). In TE participants, before they switched to TAF, HBV therapy included TDF (84%), ETV (6.4%), FTC/TDF (1.6%), ADV (0.4%), LAM (0.4%), and LdT (0.4%); 6.8% of participants were TN.

Effectiveness

In participants treated with TAF for >6 months, 97% of those with baseline HBV DNA <2000 IU/mL (100% of those assessed) and 94% of those with baseline HBV DNA ≥2000 IU/mL achieved virologic suppression (Figure 18). ALT normalization also occurred in a majority of participants with baseline elevated ALT after switching to TAF among those who received 6 to 12 months of TAF and 13 to 18 months of TAF (Figure 18).

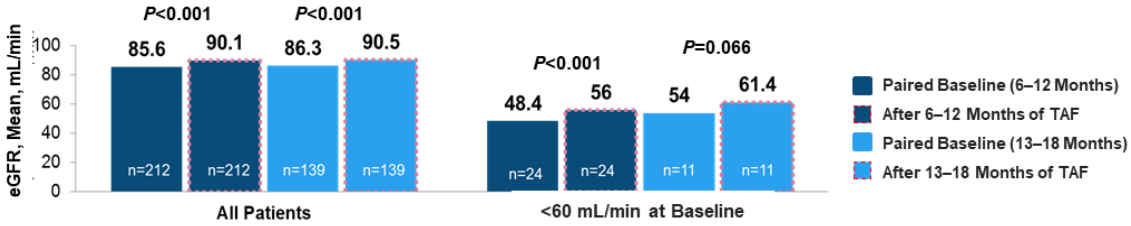
Figure 18. TRIO: Effectiveness Assessments[9]



Renal safety

Overall, as well as in participants with baseline $eGFR_{CKD\text{-}EPI}$ <60 mL/min, $eGFR_{CKD\text{-}EPI}$ increased from baseline in participants who received 6 to 12 months of TAF or 13 to 18 months of TAF (Figure 19).

Figure 19. TRIO: Paired Measures for Absolute Change in $eGFR_{CKD-EPI}$[9]



Canadian Hepatitis B Network[10]

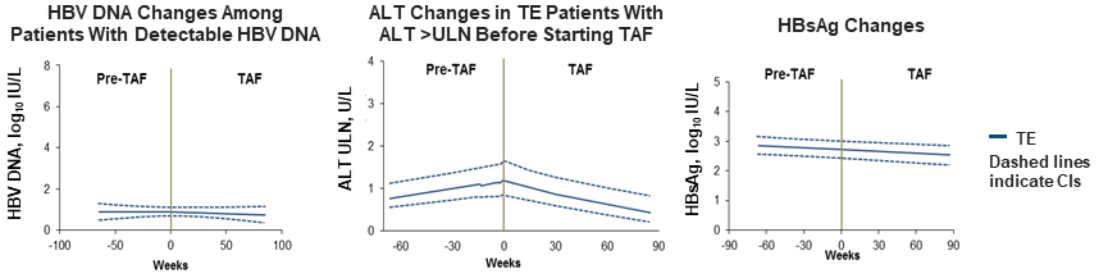
Study design and demographics

A multicenter study was conducted in 103 TN and TE participants to evaluate the real-world effectiveness and renal safety of TAF. Baseline characteristics included mean age of 52 years, 69% male, 81% Asian, 12% with cirrhosis, 30% with detectable HBV DNA, and 33% HBeAg+. Previous therapies in TE participants included TDF in 79%, LAM in 2%, and ETV in 1%. TN participants comprised 14% of the study population.

Effectiveness

After switching to TAF, among TE participants, there was a significantly increased rate of viral decline, ALT normalization, and HBsAg decline, as shown in Figure 20.

Figure 20. Effectiveness Assessments (Farag et al)[10]



Change per month in TE patients:
- Pre-TAF: +0.1 (-0.04 to 0.05); *P*=0.8
- After switch to TAF: -0.07 (-0.09 to -0.06); *P*<0.001

Change per month:
- Pre-TAF: +1.04 (1.01–1.07); *P*=0.01
- After switch to TAF: -1.02 (-1.03 to -1.01); *P*<0.01

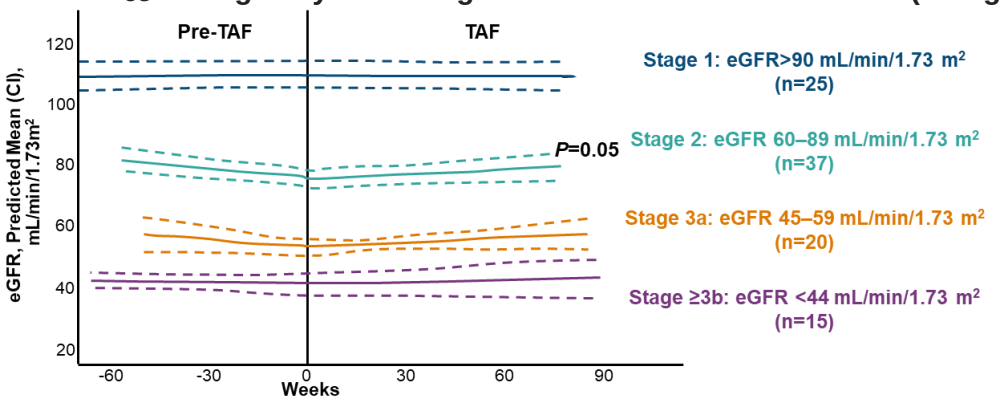
Change in TE patients:
- Pre-TAF: +0.11 (0.02–0.02); *P*=0.02
- After switch to TAF: -0.01 (-0.01 to -0.002); *P*=0.009

Renal safety

Overall, switching to TAF led to a significant improvement in renal function ($eGFR_{CG}$ decline pre-TAF: -0.19 [-0.35 to -0.02] mL/min/1.73 m^2 per month, *P*=0.02; $eGFR_{CG}$ increase after TAF: +0.11 [0.01–0.22] mL/min/1.73 m^2 per month, *P*=0.04).

In terms of change in renal function in patients with varying stages of CKD at baseline, participants with Stage 2 CKD experienced a significant decrease in $eGFR_{CG}$ pre-TAF (-0.51 [-0.89 to -0.14] mL/min/1.73 m^2 per month; *P*=0.01) and a significant increase after TAF (+0.2 [0.01–0.41] mL/min/1.73 m^2 per month; *P*=0.05). Participants with Stages 3a and above showed a declining $eGFR_{CG}$ trend pre-TAF and an increasing trend after they switched to TAF (Figure 21).

Figure 21. $eGFR_{CG}$ Changes by CKD Stage Pre- and Post-Switch to TAF (Farag et al)[10]



Switching From an ADV- or TDF-Based Regimen: Renal Safety[22]

Study design and demographics

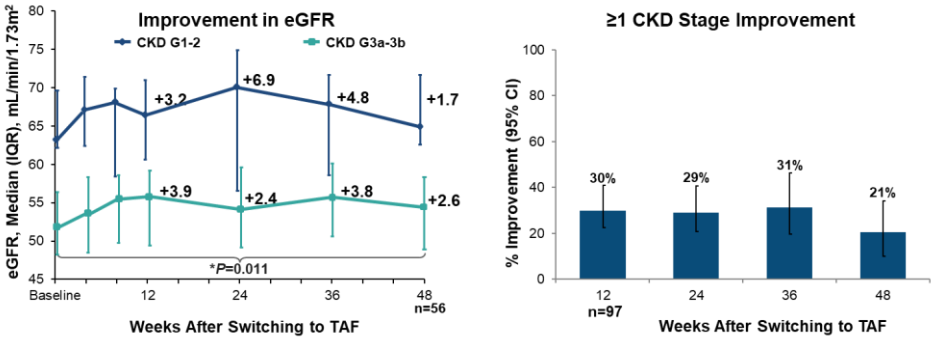
A prospective and retrospective cohort study was conducted to evaluate renal safety in 186 CHB patients who switched from an ADV-based regimen (ADV + LAM: n=69; ADV + ETV: n=4), a TDF-based regimen (TDF + LAM: n=54; TDF + ETV: n=36), or TDF monotherapy (n=23) to TAF for 48 weeks. All patients on combination therapy at baseline continued with LAM or ETV after they switched to TAF.

Baseline characteristics included median age of 60 years, 74% male, median BMI of 22.2 kg/m^2, 15% with cirrhosis, median ALT of 21 IU/mL, 26% HBeAg+, and median eGFR of 59.8 mL/min/1.73 m^2. The distribution of CKD stages at baseline per the KDIGO guideline was as follows: G1, 3.8%; G2, 43%; G3a, 46.2%; G3b, 6.5%; and G4, 0.5%. All patients had undetectable HBV DNA at baseline.

Results

Significant improvement in renal function and CKD stage in patients with baseline CKD Stage 3a, 3b, or 4 per the KDIGO guideline was seen after patients switched to TAF (Figure 22). No significant changes in serum phosphate were observed over time. Improvements were also seen in β2M:Cr (median decrease of 71% from baseline at Week 48; *P*=0.016) and percentage of tubular reabsorption of phosphate (median increase of 7.2% from baseline at Week 48; *P*=0.006) in patients with abnormal values at baseline.

Figure 22. Changes in eGFR and CKD Stage After Switching to TAF (Hosaka et al)[22]



Switching From TDF: Renal Function and BMD[11]

Study design and demographics

A prospective, single-arm, open-label study was conducted to evaluate the effect on renal function and BMD in 75 participants who switched from TDF to TAF and were followed for 24 weeks. Antiviral effectiveness (HBV DNA <20 IU/mL) was also evaluated. At baseline, the median age was 58 years, 65% were male, 97% were Asian, mean BMI was 24.2 kg/m^2, and median duration of TDF therapy prior to switch was 57 months. All participants had undetectable HBV DNA (<20 IU/mL) at baseline (time of switch).

Effectiveness

The overall effectiveness rate was 97%, with all but 2 participants maintaining undetectable HBV DNA through 24 weeks. Both participants were deemed non-compliant via pill count. Consequently, the compliance rate was 97%.

Renal safety

Significant improvements in markers of renal tubular function (β2M:Cr and RBP:Cr) were observed, as shown in Table 12. There was no significant change in $eGFR_{CG}$ from baseline to Week 24. However, in 2 of 8 participants with $eGFR_{CG}$ <60 mL/min at baseline, $eGFR_{CG}$ improved by 10 mL/min, and in 1 of those participants, the CKD stage improved from 3a to 2. One of the 23 participants with CKD Stage 2 at baseline ($eGFR_{CG}$ 30–59 mL/min/1.73 m^2) experienced a decrease to CKD Stage 3 by study end. $FePO_4$ increased significantly from baseline to Week 24, and the phosphate threshold for renal tubular reabsorption decreased significantly (Table 12).

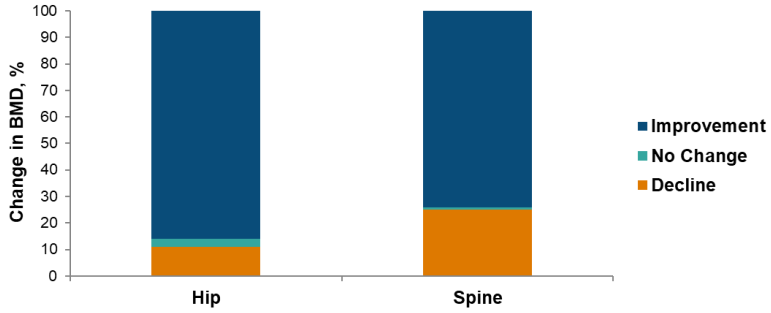
Table 12. Renal Safety (Fong et al)[11]

Renal Outcomes	Week 0	Week 12	Week 24	*P*-Value: Week 24 vs Week 0
$eGFR_{CG}$, mean ± SD, mL/min	95.9±29.1	96.6±29.9	93.7±26.9	Not significant
Serum phosphorus, mean ± SD, mg/dL	3.2±0.4	3.3±0.4	3.1±0.4	<0.05
$FePO_4$, median (range)	11.9 (4.5–41.7)	14 (3.5–38.6)	14 (3.1–30.4)	<0.05
Phosphate threshold for renal tubular reabsorption, mean ± SD, mg/dL	2.8±0.5	2.9±0.4	2.6±0.4	<0.01
UACR, median (range), mg/g	0.04 (0.01–1.9)	0.04 (0.01–0.6)	0.04 (0.02–2.5)	Not significant
Urine β2M:Cr, median (range), mcg/g	1.5 (0.1–770.6)	1 (0.1–138.5)	1.1 (0–52.6)	<0.01
Urine RBP:Cr, median (range), mcg/g	1.8 (0.7–656.6)	1.4 (0.4–101.7)	1.4 (0.5–20)	<0.01

Bone safety

Both hip and spine BMD increased significantly from baseline to Week 12 (+12.9% and +2.4%, respectively) and remained stable at Week 24. There was also significantly more improvement than loss in hip and spine BMD (Figure 23).

Figure 23. Proportion of BMD Changes by Week 24 (Fong et al)[11]



Long-term (72 weeks) follow-up[12]

Results at 72 weeks of follow-up from 61 participants were included in the long-term cohort.

Effectiveness

After 24 weeks of TAF treatment, 2 participants had detectable HBV DNA levels, and both participants had virologic relapses due to non-compliance. Overall, no significant changes in ALT levels were noted throughout the study. Of the 16 participants with abnormal ALT levels at baseline, 4 participants had normal ALT levels at Week 72. Of the participants with normal ALT levels at baseline, none experienced abnormal ALT levels at Week 72.

Renal safety

At Week 72, $eGFR_{CG}$ was significantly decreased to 90.9 mL/min from 96.3 mL/min at baseline (P<0.01) and from 94.4 mL/min at Week 24 (P<0.05). Of 16 participants with Stage 2 CKD at baseline, 2 progressed to Stage 3, and 1 participant improved to Stage 1 at Week 72. Of 6 participants with Stage 3 CKD at baseline, 1 participant improved to Stage 2 at Week 72. No significant changes in urine β2M and urine RBP were observed from Week 24 to Week 72; improvements observed at Week 24 for both parameters were sustained at Week 72 (P<0.01 vs baseline). No changes in UACR were observed during the 72 weeks of follow-up. Changes in parameters of renal phosphate handling (eg, serum phosphorus levels, phosphate threshold for renal tubular absorption, and $FePO_4$) that were observed at Week 24 had reverted at Week 72 and were no longer significantly different from baseline values.

Bone safety

Improvements in hip BMD that were observed at Week 24 were sustained at Week 72, whereas lumbar spine BMD improvement decreased from Week 24, although the change was no longer significantly different from baseline at Week 72.

Switching From Another NUC: Effectiveness and Renal Safety[13]

Study design and demographics

This was a retrospective study of 121 patients in the US and Taiwan who were switched to TAF after being treated with another NUC for ≥12 months. The primary endpoint was complete virologic suppression, defined as HBV DNA undetectable 12 months after

switching to TAF. ALT normalization and changes in renal function were secondary endpoints. Previous regimens prior to TAF switch included TDF (75%), ADV combined with other OAVs (17%), ETV (5%), and LAM (3%).

Table 13. Baseline Demographics and Disease Characteristics (Yeh et al)[13]

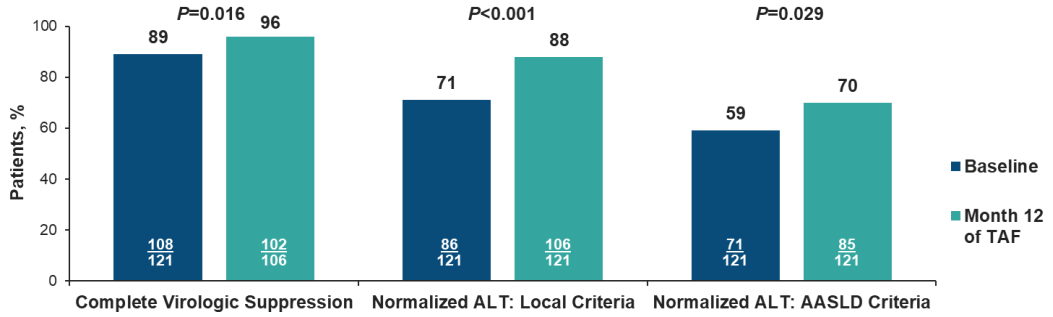
Key Demographics and Characteristics	Switched to TAF (N=121)
Male, n (%)	87 (72)
Age,[a] years	55±12
Asian, n (%)	117 (97)
Comorbid conditions, HTN/DM, n (%)	19 (16)/13 (11)
eGFR,[a] mL/min/1.73 m^2	88±19
Cirrhosis, n (%)	17 (14)
HBeAg+, n/N (%)	25/118 (21)
Duration of prior NUC,[a] months	65±48

[a]Measures (eg, mean, median, etc.) were not specified in source.

Effectiveness

Patients with CHB had significant improvement in complete virologic suppression and ALT normalization 12 months after switching to TAF (Figure 24). Of the 25 patients who were HBeAg+ baseline, 2 (8%) achieved HBeAg loss at Months 3 and 12, respectively.

Figure 24. Complete Virologic Suppression and ALT Normalization (Yeh et al)[13a]

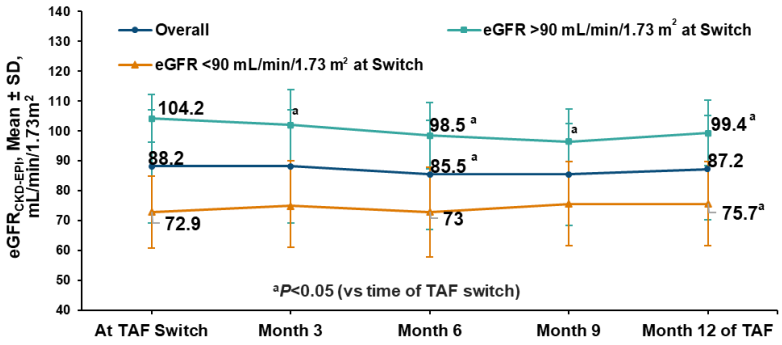


Note: Local criteria for normalized ALT was <40 U/L.

Renal safety

Overall mean $eGFR_{CKD-EPI}$ did not change significantly 12 months after patients switched to TAF. There was significant improvement, however, in patients with baseline $eGFR_{CKD-EPI}$ <90 mL/min/1.73 m^2 (Figure 25).

Figure 25. $eGFR_{CKD-EPI}$ Levels Over Time (Yeh et al)[13]



Switching From TDF: Effect on ALT and AST Levels and APRI Score[14]

Study design and demographics

A single-center, retrospective study evaluated the effect on ALT and AST levels and APRI score after switching from TDF to TAF for 2 years. Included patients had been switched to TAF between December 2016 and March 2019. A total of 60 patients with CHB were followed for a mean (range) of 21 (12.7–34.3) months. The mean age was 55 years, 50% were male, 28.3% were HBeAg+, and 13.3% had clinical evidence of cirrhosis. Mean baseline ALT and AST levels were 25.4 IU/L and 25.6 IU/L, respectively, and the mean baseline APRI score was 0.36.

Results

Improvements from baseline in ALT and AST levels were observed as early as Week 24 after switching, and the proportion of patients with improvement was over 80% for both ALT and AST levels by Week 48. At Week 96, compared with baseline, a greater proportion of patients had ALT levels <19/30 IU/L, AST levels <25/35 IU/L, or APRI scores <0.5. Univariate analyses found that improvement in APRI score at Week 96 was significantly associated with improvement in AST level at Weeks 24 and 96 (P=0.0001 for both factors) and improvement in ALT levels at Week 24 (P=0.043) and Week 96 (P=0.004).

Switching From TDF: Effectiveness and Renal Safety[15]

Study design and demographics

A single-center study in Japan evaluated the safety and effectiveness of TAF vs TDF in TN participants for 48 weeks and in participants who switched from TDF to TAF for 24 weeks. There were 36 participants who participated in the switch portion of the study. The mean age was 55.4 years, 75% were male, 25% were HBeAg+, and the median $eGFR_{CG}$ was 71.1 mL/min/1.73 m^2. The median TDF and TAF treatment duration was 799 and 227 days, respectively. All participants were virologically suppressed prior to switch.

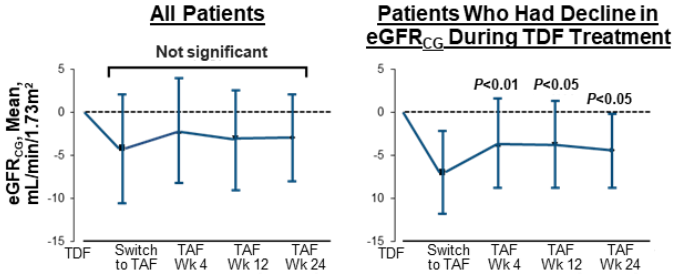
Effectiveness

HBV DNA suppression was maintained after participants switched from TDF to TAF. There was also no increase in HBsAg after participants switched from TDF to TAF.

Renal safety

In participants whose renal function decreased while on TDF, $eGFR_{CG}$ significantly improved after participants switched to TAF, as shown in Figure 26. Urinary β2M:Cr also decreased significantly after participants switched to TAF through 24 weeks (P<0.05).

Figure 26. Changes in $eGFR_{CG}$ From Start of TDF to Week 24 After Switch to TAF (Kaneko et al)[15]



TARGET-HBV Study[20]

Study design and demographics

TARGET-HBV is an ongoing, longitudinal, observational cohort study (NCT03692897) of patients with HBV managed according to local practice standards at 25 academic and community sites in the US. The study design includes a retrospective phase, which reflects a 3-year retrospective collection evaluation of patients on TAF and allows for a future prospective data collection phase. Presented in this analysis are data from the 500 patients enrolled into the retrospective phase of the study to evaluate clinical outcomes after they switched to TAF from a prior antiviral agent or with TAF as initial therapy. Of the 412 patients (82%) who were TE, most (72%) previously received treatment with TDF. At the end of the follow-up period, 98% of patients were still receiving TAF, with a median (Q1, Q3) duration of TAF treatment of 73.7 (40.9, 95.6) weeks. Prior to TAF initiation, relative to those treated with ≤1 year of previous therapies, a higher proportion of those who had received >1 year of previous therapies had undetectable HBV DNA and ALT levels ≤40 U/L; the proportion of those with a CrCl >60 mL/min was similar between groups.

Table 14. TARGET-HBV: Baseline Demographics and Disease Characteristics[20]

Key Demographics and Characteristics	TAF (N=500)
Age, median (range), years	54.5 (25–87)
Male, n (%)	328 (65.6)
Asian, n/N (%)	322/489 (65.8)
Cirrhosis, n (%)	75 (15)
Decompensated cirrhosis, n/N (%)	30/75 (40)
HBV DNA, not detected/detected to <2 /2–3/>3 log_{10} IU/mL, n (%)	266 (58.1)[a]/77 (16.8)[a]/23 (5)/92 (20.1)
HBeAg-, n (%)	379 (75.8)
HCV co-infection,[b] n (%)	45 (9)
$CrCl_{CG}$ (n=457), median (range), mL/min	89.4 (8–266.9)
≤60 mL/min, n/N (%)	67/457 (14.7)
ALT, median (range), U/L	28.5 (7–4248)
≤40 U/L, n/N (%)	306/474 (64.6)
Most common (≥20%) reasons for switching to TAF (n=412), TAF safety profile/unknown/provider decision, n (%)	142 (34.5)/134 (32.5)/96 (23.3)

Key Demographics and Characteristics		TAF (N=500)
Duration of prior therapy (n=412),[c] median (Q1, Q3), weeks	Known start date and >1 year of prior treatment (n=240)	151.6 (85.4, 313.9)
	<1 year of prior treatment (n=53)	20.9 (6, 38.7)

[a]Denominator was 458 patients.
[b]Per medical history, AEs, positive serology, or use of HCV direct-acting antivirals.
[c]Unknown start date and >3 years of prior treatment, n=119.

Effectiveness in switch patients

Outcomes were presented according to the length of time on treatment prior to switching to TAF. Switching to TAF from another antiviral regimen was associated with further improvement in HBV DNA (Table 15) and serum ALT level (Table 16).

Table 15. TARGET-HBV: HBV DNA Outcomes According to Duration of Treatment Prior to Switching to TAF[a] and Baseline Values[20]

HBV DNA	Baseline (n)	After 12–18 Months, n (%)			
		Not Detected	Detected to <2 log_{10} IU/mL	2–3 log_{10} IU/mL	>3 log_{10} IU/mL
>1 year of prior HBV treatment	Not detected (n=110)	**96 (87.3)**	13 (11.8)[b]	1 (1)[b]	0
	Detected to <2 log_{10} IU/mL (n=19)	12 (63.2)	**6 (31.6)**	1 (5.3)	0
	2–3 log_{10} IU/mL (n=5)	4 (80)	1 (20)	**0**	0
	>3 log_{10} IU/mL (n=1)	0	1 (100)	0	**0**
≤1 year of prior HBV treatment	Not detected (n=16)	**15 (93.8)**	1 (6.3)	0	0
	Detected to <2 log_{10} IU/mL (n=5)	3 (60)	**2 (40)**	0	0
	2–3 log_{10} IU/mL (n=1)	1 (100)	0	**0**	0
	>3 log_{10} IU/mL (n=6)	4 (66.7)	1 (16.7)	1 (16.7)	**0**

[a]Included paired patients who had ≥1 pre-TAF measurement and another at Month 12–18 after TAF initiation. Data were excluded for the 16 patients who underwent liver transplantation.
[b]Four of the 14 patients with de novo detectable HBV DNA post-TAF switch had quantifiable levels; 1 of these 4 patients had persistently quantifiable HBV DNA levels during follow-up.
Note: Bolded cells indicate values that were the same at TAF baseline and Month 12 to 18 after TAF initiation. Percentages are calculated using row totals.

Table 16. TARGET-HBV: ALT Outcomes According to Duration of Treatment Prior to Switching to TAF[a] and Baseline Values[20]

ALT	Baseline (n)	After 12–18 Months, n (%)			
		≤40 U/L	>40 to 60 U/L	>60 to 80 U/L	>80 U/L
>1 year of prior HBV treatment	≤40 U/L (n=135)	**126 (93.3)**	7 (5.2)	0	2 (1.5)
	>40 to 60 U/L (n=14)	6 (42.9)	**6 (42.9)**	2 (14.3)	0
	>60 to 80 U/L (n=5)	1 (20)	3 (60)	**0**	1 (20)
	>80 U/L (n=5)	1 (20)	1 (20)	0	**3 (60)**
≤1 year of prior HBV treatment	≤40 U/L (n=19)	**17 (89.4)**	2 (10.5)	0	0
	>40 to 60 U/L (n=8)	7 (87.5)	**0**	0	1 (12.5)
	>60 to 80 U/L (n=3)	3 (100)	0	**0**	0
	>80 U/L (n=4)	4 (100)	0	0	**0**

Note: Bolded cells indicate values that were the same at TAF baseline and Month 12 to 18 after TAF initiation. Percentages are calculated using row totals.

Of the 24 patients who were HBeAg+ before initiating TAF, 7 (29.2%) seroconverted to HBeAg- and 5 (20.8%) seroconverted to HBeAb+ after 12 to 18 months of TAF. Of the 82 patients with HBsAg data, 6 (7.3%) seroconverted to HBsAg-.

Safety

TAF was well tolerated. Ten patients discontinued TAF: 4 due to AEs (eg, fatigue, rash, and gastrointestinal intolerance in 1 patient each; 1 patient with preexisting kidney disease switched to TDF), 4 due to insurance/cost concerns, and 2 for unknown reasons. At baseline, of the 441 patients who had not undergone transplantation and had CrCl data, most (80.2%) had CrCl ≥60 mL/min; of the 59 patients with CrCl <60 mL/min pre-TAF, 29 patients had CrCl data post-TAF switch and their CrCl did not change. Most patients with a CrCl ≥60 mL/min maintained their renal function after 12 to 18 months of TAF, regardless of the length of their prior antiviral treatment.

Taiwanese Observational Study[19]

Study design and demographics

A prospective, multicenter, observational study in Taiwan evaluated changes in body weight (primary endpoint) for up to 48 weeks after switching to TAF treatment in 177 participants with CHB who had previously been treated with TDF (n=99) or ETV (n=78). Secondary endpoints included changes from baseline in lipid profiles (assessed 24 and 48 weeks after switching) and ASCVD score (assessed at 48 weeks).

Table 17. Baseline Demographics and Disease Characteristics (Cheng et al)[19]

Key Demographics and Characteristics	Overall (N=177)	TDF Switch (n=99)	ETV Switch (n=78)
Age, mean ± SD, years	56.3±11.6	54.7±11.2[a]	58.4±11.9
Male, n	114	63	51
BMI, mean ± SD, kg/m^2	24.4±4	24.7±4	24.1±4
HBV DNA, mean ± SD, IU/mL	734.3±4411.2	41.9±83.5	1505±6372.5
Detectable HBV DNA, n	102	60	42
HBeAg+, n	79	46	33
FIB-4 score, mean ± SD	1.5±0.7	1.4±0.7	1.5±0.7
Cirrhosis, n	33	19	14
Length of prior treatment, mean ± SD, days	–	1588.7±873.3[a]	1966.4±1313.3
AST/ALT, mean ± SD, U/L	25.7±9/28.2±15	27.1±9.8[a]/29.8±15.2	23.9±7.6/26.1±14.5
eGFR, mean ± SD, mL/min/1.73 m^2	84.4±13.2	84.3±11.8	84.4±15
Select comorbid conditions, HTN/DM, n	36/20	20/10	16/10
Receiving lipid-lowering agents, n	21	6[a]	15

[a]*P*<0.05 for between-group differences.

Effectiveness and safety

During 48 weeks of TAF treatment, significant increases from baseline through Week 48 in body weight were seen in the TDF switch group (*P*≤0.032), whereas body weight did not change significantly from baseline in the ETV switch group (Table 18). Among those who switched from TDF to TAF, female participants' body weight increased significantly from baseline through Week 36, and weight was relatively stable among male participants; of those who switched from ETV, weight decreased significantly from baseline to Week 48 among male participants, but not among female participants. During the study period, 12 patients (12.4%) who switched from TDF and 1 (1.6%) who switched from ETV had an increase in body weight >5% (*P*=0.016).

At baseline, the TDF switch group had significantly lower levels of TG (*P*=0.009), TC (*P*<0.001), LDL (*P*=0.001), and HDL (*P*=0.005) than the ETV switch group. In addition, there

were significant increases in all lipid parameters in the TDF switch group, whereas lipid profiles did not change significantly from baseline to Week 48 in the ETV switch group (Table 18). Similar numbers of patients required initiation of lipid-lowering agents during TAF treatment: TDF switch, n=2; ETV switch, n=4 (*P*=0.198).

ASCVD risk scores in both treatment groups showed no significant changes between baseline and Week 48 (TDF switch, *P*=0.064; ETV switch, *P*=0.309; Table 18).

Table 18. Body Weight, ASCVD, and Lipid Parameter Results (Cheng et al)[19]

Outcomes, Mean ± SD		Baseline	Week 24	Week 48
Body weight, kg	TDF Switch (n=93)	67.1±12.6	67.6±12.6[a]	67.9±12.8[a]
	ETV Switch (n=63)	64.1±12.4	64±12.4	63.6±11.9
Change in body weight from baseline, kg	TDF Switch (n=93)	–	0.57±2.33[a]	0.83±3.79[a]
	ETV Switch (n=63)	–	-0.17±2.28	-0.49±2.21
ASCVD score	TDF Switch (n=93)	7.2±9.8	Not available	7.8±9.7
	ETV Switch (n=63)	10.1±12.8	Not available	10.6±14.3
TC, mg/dL	TDF Switch (n=93)	165.3±33.3	188.8±37.2[a]	191.2±41[a]
	ETV Switch (n=63)	194.3±35.3	193.2±34.4	194.5±34.5
TG, mg/dL	TDF Switch (n=93)	88.7±50.4	98.2±59.5[a]	103.2±68.6[a]
	ETV Switch (n=63)	107.9±58.4	105.9±60.6	98±40
LDL, mg/dL	TDF Switch (n=93)	107.1±28	123.7±33.7[a]	124.8±35.3[a]
	ETV Switch (n=63)	123.7±28.9	122.8±29	127.1±27.4
HDL, mg/dL	TDF Switch (n=93)	48±12.3	53.5±13.7[a]	53.5±13.7[a]
	ETV Switch (n=63)	52.5±13.9	52.9±14.7	52.5±15.1

[a]*P*<0.05 for change from baseline.

From baseline to Week 48, fasting glucose, insulin, and HOMA-IR values were significantly greater among those in the TDF switch group than among those in the ETV switch group (each, *P*<0.05). HbA1c values were significantly greater in the TDF switch group than in the ETV switch group at Week 24 (*P*=0.034), but not at Week 48 (*P*<0.055). No significant changes from baseline through Week 48 or between groups throughout the study period were observed for HOMA-IR values. One patient in the TDF switch group and none in the ETV switch group began treatment for diabetes.

No effectiveness or additional safety results were included in this analysis.

Switching From an NUC to TAF Monotherapy: Effectiveness and Safety[16]

Study design and demographics

A retrospective, single-center, observational study included 104 patients with CHB who were treated with a NUC between March 2017 and June 2019. Included patients had been switched from a prior NUC (ETV, n=67; TDF, n=25; LAM/ADV, n=8; LAM/TDF, n=2; ETV/ADV, n=2) to TAF monotherapy. The primary endpoint was change in serum HBV DNA from baseline to Week 24. At baseline (time of switch), the median (range) age was 64 (23–85) years, 41% of patients were male, the median ALT level was 31 IU/L, the median eGFR was 64.3 mL/min, the median serum phosphorus level was 3.3 mg/dL, and all patients had had undetectable HBV DNA.

Effectiveness and safety

In the overall population, no significant changes were observed from baseline to Week 24 in serum ALT levels, serum phosphorus levels, or eGFR. All patients had undetectable HBV DNA at Week 24. In the cohort of patients who were switched from TDF to TAF, no significant changes in serum ALT levels or eGFR were observed; statistically significant improvements in serum phosphorus levels were observed 12 weeks after switching (mean serum phosphorus level with TDF versus TAF: 3.2 vs 3.5 mg/dL; *P*=0.014). AEs in the overall population consisted of elevated ALT level (n=1) and pruritus (n=2).

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Abbreviations

AASLD=American Association for the Study of Liver Disease
ADV=adefovir dipivoxil
AE=adverse event
aOR=adjusted odds ratio
APRI=AST to platelet ratio index
ASCVD=atherosclerotic cardiovascular disease
β2M=β-2 microglobulin
β2M:Cr=β2M to Cr ratio
BMD=bone mineral density
CG=Cockcroft-Gault
CHB=chronic hepatitis B
CKD=chronic kidney disease
CKD-EPI=CKD Epidemiology Collaboration
CPT=Child-Pugh-Turcotte
DC=discontinuation
DM=diabetes mellitus
ESRD=end-stage renal disease
ETV=entecavir
$FePO_4$=fractional excretion of phosphate
FIB-4=Fibrosis 4 index
FTC=emtricitabine
HBeAb=hepatitis B envelope antibody
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
HD=hemodialysis
HOMA-IR=Homeostatic Model Assessment for Insulin Resistance
HTN=hypertension
JSH=Japanese Society of Hepatology
KDIGO=Kidney Disease Improving Global Outcomes
LAM=lamivudine
LdT=telbivudine
M=F=missing=failure
NUC=nucleos(t)ide analogue
OAV=oral antiviral
PK=pharmacokinetic(s)
Q=quartile
RBP=retinol-binding protein
RBP:Cr=RBP to Cr ratio
RI=renal impairment
SAE=serious adverse event
TAF=tenofovir alafenamide
TC=total cholesterol
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
TEAE=treatment-emergent adverse event
TG=triglycerides
TN=treatment-naive
UACR=urine albumin to Cr ratio
ULN=upper limit of normal

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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