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Vemlidy® (tenofovir alafenamide) Renal Safety

This document is in response to your request for information regarding the renal safety of Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of chronic hepatitis B (CHB). This response was developed according to evidence-based medicine and contains data from clinical studies and real-world studies with N≥100 participants.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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

Product Labeling[1]

Prior to or when initiating TAF, and during treatment with TAF on a clinically appropriate schedule, assess SCr, estimated CrCl, urine glucose, and urine protein in all patients. In patients with CKD, also assess serum phosphorus. Discontinue TAF in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Clinical Data on Renal Safety With TAF Use for CHB

In phase 3 Studies 108 and 110,[2,3] the median $eGFR_{CG}$ showed a minimal decline from baseline among those who received TAF through Year 8.[4] Among participants in the TDF2y→OL6y and TDF3y→OL5y TAF groups, there was improvement in $eGFR_{CG}$ after participants switched to TAF at Year 2 or 3.[5]

In a meta-analysis in participants with CKD who switched from TDF to TAF, a significant improvement in eGFR was observed in the pooled analysis (OR for improvement in eGFR, 24.13; 95% CI: 18.31–31.09; *P*<0.01).[6]

In phase 3 Study 4018, participants who switched from TDF to TAF, including those with risk factors for TDF use and those with renal impairment, demonstrated stable or improved renal parameters and CKD stage.[7,8]

In a study in Korea that assessed outcomes of participants with multiple-drug–resistant HBV who either switched from TDF to TAF or continued TDF (N=174), participants who switched to TAF had significant improvements in eGFR at Week 24 (*P*<0.001) and Week 48 (*P*=0.05) compared with participants who continued TDF.[9]

In a prospective cohort study, a slight decrease in mean eGFR from baseline to Week 12 was observed in TN participants with CHB and histologically confirmed liver fibrosis, with no significant changes observed up to Week 48.[10]

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Real-World Data on Renal Safety With TAF Use for CHB

Participants on various HBV regimens who began or were switched to TAF experienced stable renal function and/or improvement in renal tubular markers.[11-19] In one study, there was no significant difference in the incidence of RRT between PS-matched cohorts treated with TAF or TDF.[11]

Clinical Data on Renal Safety With TAF Use for CHB

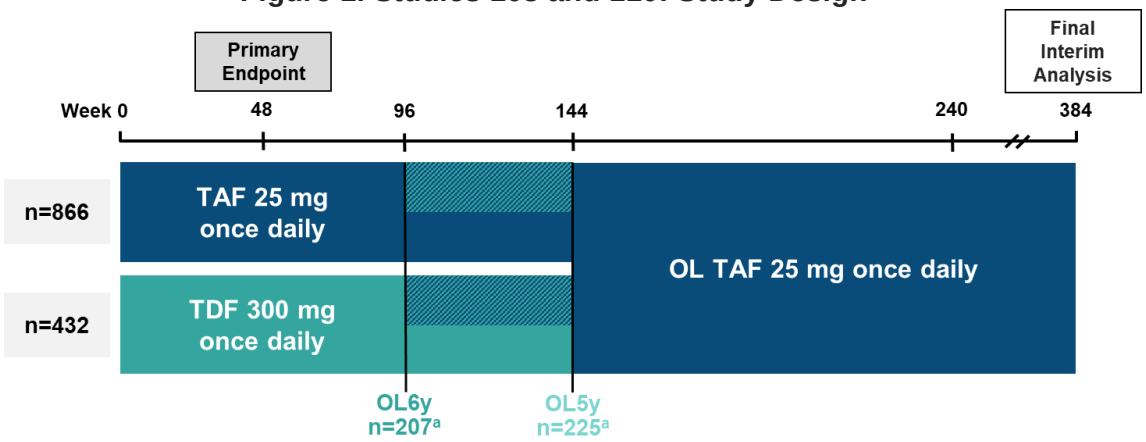
Studies 108 and 110

Study designs and demographics

Studies 108 and 110[2,3] were phase 3 clinical trials that compared outcomes in predominantly NUC-naive participants with CHB who were randomly assigned (2:1) to receive once-daily TAF 25 mg or TDF 300 mg. A total of 1298 HBeAg- and HBeAg+ adult participants with an HBV DNA level ≥20,000 IU/mL, both with and without compensated cirrhosis, and an $eGFR_{CG}$ ≥50 mL/min received double-blind treatment for 3 years in Studies 108 (HBeAg-; n=425) and 110 (HBeAg+; n=873). The study allowed participants in both treatment groups to switch to OL TAF at Year 2 or Year 3, and the OL TAF phase was extended to Year 8.[5]

In addition to the primary endpoint of proportion of participants with HBV DNA <29 IU/mL at Week 48 with a noninferiority margin of 10%, renal endpoints included changes in $eGFR_{CG}$ and dipstick proteinuria.[2,3] A total of 647 of the original 866 participants in the TAF group and 327 of the original 382 participants in the TDF to OL TAF groups completed the OL TAF phase of the study.[5]

Figure 1. Studies 108 and 110: Study Design[5,20]



[a]Participants who received TDF during the double-blind period and then switched to TAF.
Note: Randomization was stratified by HBV DNA level and TN/TE status.

Table 1. Studies 108 and 110: Baseline Demographics and Disease Characteristics[5]

Key Demographics and Characteristics	TAF8y[a] (n=866)	TDF2y→ OL6y TAF[b] (n=207)	TDF3y→OL5y TAF[c] (n=225)
Age, mean ± SD, years	40±11.8	42±12.2	41±12.4
Male, n (%)	544 (63)	126 (61)	149 (66)

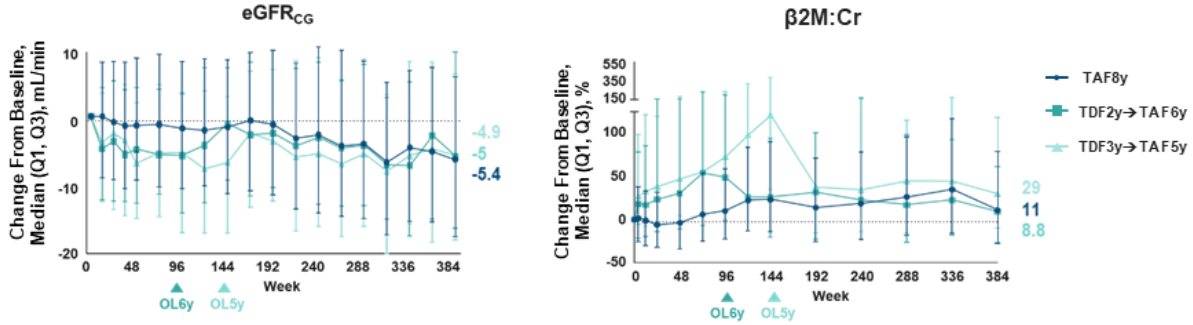
Key Demographics and Characteristics		TAF8y[a] (n=866)	TDF2y→ OL6y TAF[b] (n=207)	TDF3y→OL5y TAF[c] (n=225)
Asian, n (%)		687 (79)	167 (81)	166 (74)
BMI, mean ± SD, kg/m^2		24±4.13	24.3±3.85	24.5±4.05
ALT, median (Q1, Q3), U/L		80 (56, 123)	81 (53, 136)	79 (51, 121)
NUC experienced, n (%)		211 (24)	50 (24)	58 (26)
HBV genotype, A/B/C/D/other,[d] %		6/19/48/26/1	6/26/45/21/2	8/16/48/28/1
HBV DNA, mean ± SD, $\log_{10}$ IU/mL		7±1.59	7±1.66	7.1±1.6
HBeAg+, n (%)		569 (66)	133 (64)	157 (70)
History of cirrhosis, n (%)		65 (10)	22 (15)	16 (9)
FibroTest score ≥0.75, n/N (%)		76/846 (9)	16/200 (8)	26/221 (12)
$eGFR_{CG}$, median (Q1, Q3), mL/min		106 (91, 125)	105 (86, 125)	104 (93, 121)
Comorbid conditions, HTN/DM, n (%)		99 (11)/57 (7)	30 (15)/9 (4)	32 (14)/20 (9)
Osteopenia,[e] n (%)	Hip/spine	255 (30)/309 (36)	71 (35)/71 (35)	60 (27)/82 (37)
Osteoporosis,[e] n (%)	Hip/spine	12 (1)/57 (7)	2 (1)/21 (10)	0/8 (4)

[a]Participants who received double-blind TAF, followed by OL TAF.
[b]Participants who switched to OL TAF at Year 2 (Week 96).
[c]Participants who switched to OL TAF at Year 3 (Week 144).
[d]Included genotypes E, F, H, and unknown.
[e]Bone mineral density T-scores: osteopenia, -2.5 to <-1; osteoporosis, <2.5.

Renal safety through Year 8

In the TAF8y group, the median $eGFR_{CG}$ decreased by approximately 5 mL/min from baseline, which is consistent with the decline that occurs during the normal aging process (Figure 2). Among participants in the TDF to OL TAF groups, there was improvement in $eGFR_{CG}$ after the switch to TAF at 2 or 3 years. In the TAF8y group, the median percent increases in UBCR were small (11%) and remained relatively stable, whereas UBCR improved following the switch to TAF among participants who switched from TDF at 2 or 3 years (Figure 2).[5] Findings for retinol-binding protein to Cr ratios were similar to those observed for UBCR; median Year 8 values were as follows: TAF8y, 43.2%; TDF2y→TAF6y, 53%; TDF3y→TAF5y, 49.8%.[20] Tubular proteinuria increased during the double-blind TDF treatment and improved after switching from TDF to TAF.[4]

Figure 2. Studies 108 and 110: Renal Parameter Changes Through Year 8[5]



Most of the participants by Year 8 maintained the CKD stage that was present at baseline or had improved renal function (Table 2); no participants had Stage 3 CKD at Year 8.[5,20]

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Table 2. Studies 108 and 110: Shifts in CKD Stage From Baseline to Year 8 (Safety Analysis Set[a])[5,20]

Year 8 CKD Stage, n or n (%)	TAF8y			TDF2y→TAF6y			TDF3y→TAF5y		
	Baseline CKD Stage								
	1 (n=664)	2 (n=197)	3 (n=5)	1 (n=146)	2 (n=59)	3 (n=2)	1 (n=177)	2 (n=46)	3 (n=2)
1	376 (84)	38 (27)[b]	0[b]	72 (84)	5 (14)[b]	0[b]	101 (77)	5 (15)[b]	0[b]
2	70 (16)[c]	88 (62)	1 (25)[b]	14 (16)[c]	24 (65)	0[b]	31 (24)[c]	22 (67)	0[b]
3	0[c]	16 (11)[c]	3 (75)	0[c]	8 (22)[c]	0	0[c]	6 (18)[c]	2 (100)
Missing	218	55	1	60	22	2	45	13	0

[a]The safety analysis set included participants who received ≥1 dose of their treatment.
[b]Indicated an increase in CKD stage from baseline to Year 8.
[c]Indicated a decrease in CKD stage from baseline to Year 8.
Note: The denominator for the percentages in each cell was the number of participants without missing values at baseline and Year 8.

Meta-Analysis: Switch From TDF to TAF in Participants With CHB and CKD[6]

Study design

A single-arm meta-analysis was performed to evaluate improvements in renal function in participants with CKD who switched from TDF to TAF for the treatment of CHB. Ten RCTs (N=1179) met the following eligibility criteria: RCTs or cohort studies that measured renal function pre- and post-switch from TDF to TAF in those with CKD; had complete data; did not include participants with kidney and/or liver transplants; and did not have overlapping participant populations. There was no consistent reporting of other secondary renal-related outcomes (eg, progression to end-stage renal disease, markers of tubular injury, or bone health indicators); therefore, the analysis was limited to analyzing improvements in eGFR.

Renal safety

A significant improvement in eGFR was observed in the pooled analysis (OR for improvement in eGFR, 24.13; 95% CI: 18.31–31.09; *P*<0.01). Although high heterogeneity was observed (I^2=79%), the effect was consistent across the 10 identified studies.

Several sensitivity analyses were performed. In a leave-one-out analysis that removed results from the most heterogeneous study, results similar to those of the pooled analysis were observed (OR for eGFR improvement, 22.29; 95% CI: 17.75–27.61; *P*<0.01). In another sensitivity analysis, which removed the four most heterogeneous studies, the association was no longer statistically significant (OR for eGFR improvement, 18.7; 95% CI: 14.77–23.4; *P*=0.16). Finally, in a mixed-effects meta-regression, baseline eGFR values (*P*<0.001) and age (*P*<0.001) were each significantly associated with heterogeneous study results; however, neither male (*P*=0.8) nor female (*P*=0.77) sex had significant associations with heterogeneity.

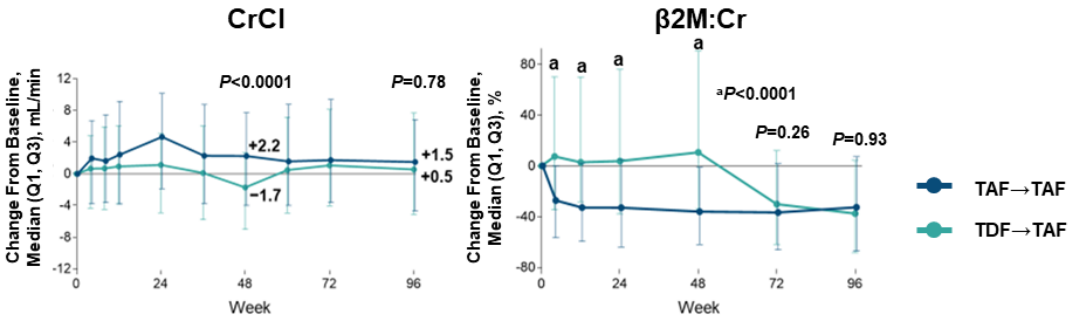
Study 4018: Switching From TDF to TAF

Study 4018 was a double-blind, randomized, phase 3 study that evaluated 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. At the end of the

48-week, double-blind study period, participants who were randomly assigned to receive TDF or who were switched to TAF at baseline were switched to OL TAF through Week 96.[21]

Participants who switched to TAF experienced improvements in CrCl and markers of proximal tubular function that were sustained through Week 96 (Figure 3).[7]

Figure 3. Study 4018: Renal Safety Through Week 96[7]



Subanalysis in participants with risk factors[8]

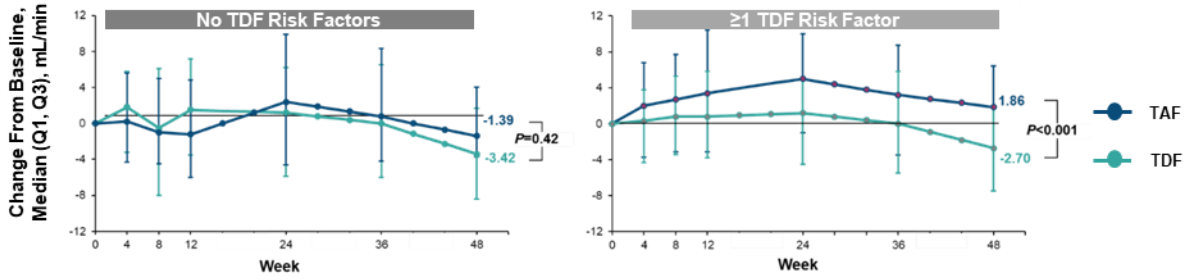
Study design and demographics

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. Risk factors included advanced age (>60 years), bone disease, renal impairment, albuminuria, hypophosphatemia, obesity, and comorbidities.

Renal safety

Switching from TDF to TAF was associated with significant improvement in renal function in participants with ≥1 risk factor, with a trend towards improvement in participants with no risk factors (Figure 4). Improvements in renal tubular markers were also observed.

Figure 4. Study 4018 Subanalysis: Change in $eGFR_{CG}$ According to the Presence of Risk Factors[8]



Switching From TDF to TAF in Multiple-Drug–Resistant HBV[9]

A randomized, active-controlled, OL, multicenter, noninferiority study was conducted in Korea to assess the safety and efficacy of switching from TDF to TAF, compared with continuing TDF, in participants with HBV resistant to multiple drugs. Participants who were taking TDF (N=174) were randomly assigned to either continue TDF (n=87) or switch to TAF (n=87) for 48 weeks.

At Week 24, the mean change in eGFR in the group that switched to TAF was 7.5 mL/min/1.73 m^2, compared with a mean change of 1.5 mL/min/1.73 m^2 in the group that continued TDF (*P*<0.001). At Week 48, the mean change in eGFR in the group that switched to TAF was 6.9 mL/min/1.73 m^2, compared with a mean change of 3.2 mL/min/1.73 m^2 in the group that continued TDF (*P*=0.05).

Prospective Cohort Study[10]

A prospective cohort study in TN participants with CHB and histologically confirmed liver fibrosis (N=100) from 10 hospitals in China evaluated the efficacy and safety of TAF treatment for 48 weeks. The safety analysis included changes in $eGFR_{CKD\text{-}EPI}$. Of the 100 participants, 59% were male, and the mean ± SD age was 42.2±10.3 years. At baseline, 23% had cirrhosis, the median (Q1, Q3) ALT level was 45.2 (29.7, 79.1) U/L, and the mean ± SD eGFR was 118±14 mL/min/1.73 m^2.

Rates of ALT normalization (<40 U/L) from baseline to Week 24 and Week 48 were 61% and 75%, respectively. There was a significant decrease in eGFR between baseline and Week 12 (*P*<0.001) that was maintained up to Week 48 (Table 3).

Table 3. Changes in eGFR Through 48 Weeks of TAF Treatment (Zhou et al)[10]

Renal Parameter	Baseline	Week 12	Week 24	Week 48
eGFR, mean ± SD, mL/min/1.73 m^2	118±14	105±9.8[a]	105.3±10.1[b]	104.9±10

[a]*P*<0.001, compared with baseline. [b]*P*=0.91, compared with Week 12.

Real-World Data on Renal Safety With TAF Use for CHB

Korean Matched Cohort Study[11]

Study design and demographics

A real-world, population-based, PS-matched (1:1) cohort study used claims data from the Korean National Health Insurance Service to compare the incidence of RRT and CKD between patients who began treatment with TAF or TDF between 2017 and 2022. RRT was defined as claims for HD or peritoneal dialysis on >2 occasions or registration with a relevant rare and intractable disease program code. A total of 46,663 patients (TAF, n=16,885; TDF, n=29,778) were eligible for study inclusion, and the PS-matched population included 15,609 patients in each treatment cohort. Overall, the median (IQR) age was 48 (40–56) years, and 61.3% of the study population was male. The median (IQR) duration of follow-up was 2.61 (1.52–3.75) years.

Renal safety

There was no significant difference in the incidence of RRT between treatment cohorts in the overall and PS-matched populations (Table 4), and treatment with TAF was not associated with an increased risk of RRT relative to treatment with TDF in a multivariable analysis (HR, 0.74; 95% CI: 0.47–1.16; *P*=0.19). The following characteristics were associated with an increased risk of RRT in a multivariable analysis: male sex (*P*<0.001); older age (age subgroups: 40–49, 50–59, 60–69, and ≥70 years vs 18–39 years; each,

P<0.001), HTN (*P*=0.052), stroke (*P*=0.02), cirrhosis (*P*=0.015), and current smoker (*P*<0.001).

Table 4. Korean Matched Cohort Study: Overall Incidence and Cumulative Risk of RRT[11]

Cohort	Treatment Group	Incidence of RRT, Per 1000 PY	HR (95% CI)	*P*-Value
Overall cohort	TAF	0.56	0.74 (0.47–1.16)	0.187
	TDF	0.96	Reference	
PS-matched cohort	TAF	0.58	0.67 (0.4–1.1)	0.113
	TDF	0.91	Reference	

There was no significant difference in the incidence of CKD between treatment cohorts in the PS-matched population (Table 5).

Table 5. Korean Matched Cohort Study: Overall Incidence and Cumulative Risk of CKD[11]

Cohort	Treatment Group	Incidence of CKD, per 1000 PY	HR (95% CI)	*P*-Value
Overall cohort	TAF	2.86	1.26 (1.01–1.57)	0.033
	TDF	2.94	Reference	
PS-matched cohort	TAF	2.99	1.2 (0.93–1.56)	0.144
	TDF	2.52	Reference	

Japanese Study: Renal Safety[12]

Study design and demographics

A prospective, multicenter, real-world study was conducted in Japan to evaluate the efficacy and safety of TAF in 580 TN and TE participants who were treated with TAF for 144 weeks. The mean age was 58 years, 60.7% were male, 81.6% were TE, 18.4% were TN, 14.4% had cirrhosis, 3.8% had HCC, 9% had renal impairment, 42.1% were HBeAg-, and 19.2% were HBeAg+. ALT levels were reported as follows: 63.1% of participants had levels ≤ULN, 29.5% had levels >ULN, and 7.5% had levels that were either unknown or not reported at baseline. The distribution of CKD stages at baseline was 59.3% for Stage 1, 25.5% for Stage 2, 5.9% for Stage 3a or 3b, and 0.2% for Stage 4. The median (Q1, Q3) $eGFR_{CKD\text{-}EPI}$ at baseline was 96 (83, 107) mL/min/1.73 m^2.

Renal safety

In the safety analysis set (n=577), 9 participants (1.6%) had renal ADRs, none of which were classified as serious ADRs, and no participants required TAF discontinuation due to a serious ADR. Hypophosphatemia was reported in 7 participants (1.2%): 4 recovered, 2 did not recover, and 1 had an unknown or unreported outcome. Decreases in serum phosphorus levels were reported in 2 participants. One participant with low baseline serum phosphorus had TAF temporarily discontinued and later recovered, whereas the other participant was reported as recovering.

There was a significant median change in $eGFR_{CKD\text{-}EPI}$ (-2 mL/min/1.73 m^2, *P*<0.0001) from baseline at Week 144. Changes in $eGFR_{CKD\text{-}EPI}$ according to CKD stage at baseline were also analyzed. Throughout TAF treatment, most participants either had no change in their CKD stage or experienced an improvement. At Week 144, of the 232 participants with Stage 1 CKD at baseline, 83.6% showed no difference in renal function, 16% progressed to Stage 2, and 0.4% declined to Stage 3a/3b. Among the Stage 2 CKD group (n=101) at

baseline, 81.2% stayed in Stage 2, 10.9% improved to Stage 1, and 7.9% declined to Stage 3a/3b at Week 144. In participants with Stage 3a/3b (n=22) at baseline, 68.2% showed no difference in renal function, 22.7% improved to Stage 2, and 9% declined to Stage 4. Participants with paired data (n=366) showed a mean ± SD change in ALT level of -18.6±103 U/L and in AST level of -16.1±121 U/L from baseline to Week 144 (*P*<0.0001 and *P*=0.0019, respectively).

Long-Term Efficacy and Safety Study[13]

Study design and demographics

A long-term, multicenter, real-world cohort study was conducted among TN and TE participants who received up to 4 years of TAF as treatment for CHB (N=578).

Table 6. Baseline Demographics and Disease Characteristics (Ogawa et al)[13]

Key Demographics and Characteristics		TN (n=115)	TE (n=463)
Age, mean ± SD, years		56.5±13.1	57.9±12.6
Male, n (%)		61 (53)	287 (62)
Cirrhosis, n (%)		16 (13.9)	69 (14.9)
History of HCC, n (%)		14 (12.2)	57 (12.3)
HBeAg+, n (%)		29 (34.5)	73 (15.8)
AST/ALT, median (Q1, Q3), U/L		34 (22, 64)/38 (20, 60)	25 (20, 30)/21 (16, 31)
eGFR, median (Q1, Q3), mL/min/1.73 m^2		79 (68, 95)	71 (60, 82)
Prior NUC, n (%)	ETV	–	199 (43)
	TDF	–	135 (29.2)
	NUC combination	–	129 (27.9)
Duration of prior NUC treatment, mean, years		–	5.8

Renal safety

Among TE participants who switched from a TDF-containing regimen to TAF, there was a significant improvement in eGFR from baseline to Month 6 (+3.1 mL/min/1.73 m^2; *P*-value not reported). TN participants showed a significant decline in eGFR from baseline to Month 6 (83 to 79.2 mL/min/1.73 m^2; *P*<0.01). After Month 6, there were no notable changes observed in eGFR through Year 4. Hypophosphatemia (<2.5 mg/dL) was reported in 9.3% of TN participants after TAF treatment. ALT normalization rates increased from 34.8% at baseline to 83.3% at Year 4 in TN participants and from 76.8% at baseline to 84.6% at Year 4 in TE participants.

Switch to TAF From Other NUCs[14]

Study design and demographics

A retrospective, multicenter, observational cohort study was conducted between March 2017 and June 2019 and included adult patients who had received an NUC for ≥2 years and switched to TAF 25 mg once daily for CHB treatment. The primary endpoint was the proportion of patients at Year 5 with HBV DNA <10 IU/mL among patients with and without CKD. Secondary endpoints included ALT levels, eGFR, and serum phosphate levels.

Table 7. Baseline Demographics and Disease Characteristics (Ogawa et al)[14]

Key Demographics and Characteristics		Total (N=414)	Normal eGFR (n=314)	CKD (n=100)
Age, median (range), years		59 (47–68)	55 (46–65)	67 (61–71)
Male, n (%)		254 (61.4)	206 (65.6)	48 (48)
Cirrhosis, n (%)		54 (13)	34 (10.8)	20 (20)
HBeAg+, n (%)		63 (15.2)	44 (14)	19 (19)
AST/ALT, median (IQR), U/L		25 (21–29)/ 22 (16–31)	24 (20–29)/ 23 (16–32)	25 (22–29)/ 19 (15–26)
eGFR, median (IQR), mL/min/1.73 m^2		72 (60–83)	77 (69–86)	53 (47–56)
Prior NUC, n (%)	ETV	177 (42.8)	136 (43.3)	41 (41)
	TDF	122 (29.5)	95 (30.3)	27 (27)
	NUC combination[a]	115 (27.8)	83 (26.4)	32 (32)

[a]LAM/ADV, LAM/TDF, ETV/ADV, or ETV/TDF.

Renal safety

Among patients with CKD who switched from TDF or a NUC combination to TAF, the mean ± SD change in eGFR was +3.3±2.6 mL/min/1.73 m^2 from baseline to Month 6 and +0.6±3.3 mL/min/1.73 m^2 at Year 5 (difference between groups, *P*<0.001). Among patients with CKD who switched from ETV to TAF, the mean change from baseline to Year 5 was -1.8 mL/min/1.73 m^2. Among patients with normal eGFR at baseline, the change from baseline to Year 5 in eGFR was -3±4.8 mL/min/1.73m^2 in patients who switched from TDF or a NUC combination and -3.9±4.5 mL/min/1.73m^2 in patients who switched from ETV; however, the decline in eGFR was slower in patients who switched from TDF or NUC combination than in patients who switched from ETV (*P*<0.05).

There were no significant changes in serum phosphate levels from baseline to Year 5 among patients with or without CKD. From baseline to Year 5, ALT normalization by AASLD criteria significantly improved from 63.4% to 71% (*P*=0.041) in the normal eGFR group and from 66% to 79% in the CKD group (*P*=0.04).

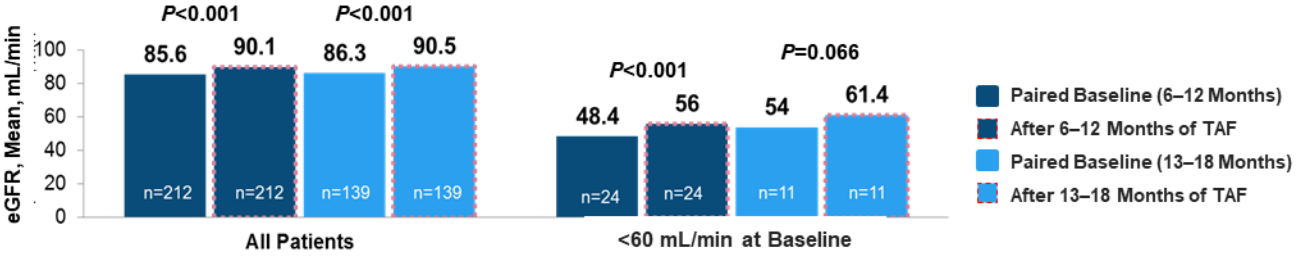
TRIO HBV Registry[15]

The TRIO HBV Registry is composed of patients from 10 centers (6 academic and 4 community centers) in the US. The current study was conducted to assess the real-world clinical experience of TAF in 250 patients who either were TN or had switched from a previous regimen to TAF. Patients received TAF for ≥6 months and were followed for up to 18 months; the median duration of TAF treatment was 13 months.

Patients were predominantly male (59%) and Asian (88%). In TE patients, prior to switching to TAF, HBV therapy included TDF (84%), ETV (6.4%), FTC/TDF (1.6%), ADV (0.4%), LAM (0.4%), and telbivudine (0.4%). TN patients composed 6.8% of the study population.

Overall, as well as in patients with baseline $eGFR_{CKD\text{-}EPI}$ <60 mL/min, $eGFR_{CKD\text{-}EPI}$ increased from baseline in patients who received 6 to 12 months of TAF or 13 to 18 months of TAF (Figure 5).

Figure 5. TRIO HBV Registry: Paired Measures for Absolute Change in eGFR$_{CKD-EPI}$[15]



HERACLIS-TAF Study[16]

Study design and demographics

A prospective, multicenter cohort study in Greece was conducted to assess the efficacy and safety of TAF in participants with CHB. Adult participants (aged >16 years) with or without cirrhosis who were NUC-naive or experienced before initiating TAF between February 2018 and October 2019 were included. The primary endpoint was eGFR changes of >3 mL/min after 12 months of TAF, and secondary endpoints included eGFR changes of >3 mL/min after 24 months of TAF and ALT and serum phosphate changes at 12 and 24 months. All participants were followed for 24 months according to standard clinical practice.

Table 8. HERACLIS-TAF: Baseline Demographics and Disease Characteristics[16]

Key Demographics and Characteristics		TAF (N=176)
Age, mean ± SD, years		64±12
Male, n (%)		124 (70.5)
Undetectable HBV DNA, n (%)		150 (85.2)
HBeAg+, n (%)		2 (1.1)
CHB ± cirrhosis, n (%)		165 (93.8)
Normal ALT (<40 U/L), n (%)		151 (85.7)
DM, n (%)		42 (23.9)
CKD, n (%)		53 (30.1)
HD, n (%)		10 (5.7)
eGFR, mL/min	Overall, mean ± SD	66±27
	<30/30–49.9/50–60, n (%)	15 (8.5)/33 (18.7)/33 (18.7)
Serum phosphate <2.5, n (%)		38 (21.6)
NUC therapy prior to TAF, n/N (%)	TDF	141/160 (88.1)
	ETV	15/160 (9.4)

Renal safety

Of the 171 participants with baseline and ≥12-month follow-up data, 49.7% (n=85) had an eGFR increase >3 mL/min, and 32.7% (n=56) had an increase >10 mL/min. A multiple logistic regression analysis indicated that a >3 mL/min eGFR increase at 12 months was independently associated with a lower baseline eGFR (OR: 0.982; 95% CI: 0.967–0.997; *P*=0.019), a higher BMI (OR, 1.134; 95% CI: 1.1021–1.259; *P*=0.019), and no HD (OR, 25.336; 95% CI: 2.542–252.49; *P*=0.006).

Of the 161 participants with 24-month data, 53.4% (n=86) had an eGFR increase >3 mL/min, and 36% (n=58) had an increase >10 mL/min. Fifty percent of those with an eGFR increase >3 mL/min at 24 months had a baseline eGFR between 30 and 60 mL/min, compared with 23% of those without an increase >3 mL/min (*P*<0.001). Participants with an eGFR increase >3 mL/min at 24 months had a higher mean (± SD) BMI (26.9±3.6) than

those with no or smaller increases in eGFR (25.5±3.3; *P*=0.01). One participant (1.2%) receiving HD had an eGFR increase >3 mL/min, compared with 9 participants (12%) with no or smaller increases in eGFR (*P*=0.012).

Among the 38 participants who initiated TAF with serum phosphorus levels <2.5 mg/dL, the mean phosphorus level increased significantly from baseline (2.1±0.3 mg/dL) to 12 months (2.7±0.6 mg/dL) and 24 months (2.9±0.4 mg/dL; *P*<0.001 for both). No significant change from baseline to 12 or 24 months was observed among those who initiated TAF with serum phosphorus levels ≥2.5 mg/dL.

Italian Study: Switching to TAF per Guideline Criteria

Study design and demographics

A prospective, observational, two-center study in Italy was conducted in 146 consecutively enrolled participants with CHB to evaluate the virologic and biochemical effects of switching from TDF to TAF[17] according to EASL 2017 guideline recommendations.[22] To be eligible for the switch, participants had to meet ≥1 of the following criteria: age >60 years, bone disease (osteoporosis, prior fragility fracture, or chronic use of steroids), or renal disease (HD, GFR <60 mL/min, albuminuria [>30 mg] or moderate dipstick urine analysis, or low phosphate [<2.5 mg/dL]). In addition to currently being on TDF therapy, participants also had to have previous exposure to LAM or ETV. Virologic, metabolic, and renal parameters were assessed at baseline (time of switch); at 2, 6, and 12 months; and then every 6 months thereafter.[17]

Baseline characteristics were the following: median (range) age, 69 (38–88) years; male, 71%; White, 99%; cirrhosis, 42%; ADV-experienced, 65%; and median (range) duration of TDF therapy prior to switch, 118 (5–155) months. At baseline, 60% of participants were on a reduced TDF dose, 2% had active HCC, 34% had osteoporosis, and 98% had normal ALT levels. The predominant criterion for the switch to TAF was age >60 years (80%), followed by renal disease (56%) and bone disease (34%); 9% of participants met all three criteria.[17]

Renal safety[17]

During 6 months of TAF treatment, $eGFR_{CG}$ and $eGFR_{MDRD}$ were stable. Among markers of renal tubular function, there were rapid improvements in UBCR and UPCR through 6 months of TAF treatment (Table 9). Of 77 participants who had abnormal UBCR at baseline, 24 showed normalization of these levels at 6 months, with the median level decreasing from 1550 mg/g at baseline to 448 mg/g at 6 months. Overall, TAF was well tolerated, and none of the participants discontinued treatment.

Table 9. Renal Parameters Through 6 Months of TAF Treatment (Loglio et al)[17]

Renal Parameters	Baseline	Month 2	Month 6
$eGFR_{CG}$, median (range), mL/min	68 (22–227)	–	67 (27–146)
$eGFR_{MDRD}$, median (range), mL/min	66 (22–122)	–	66 (21–119)
SCr,[a] median (range), mg/dL	1.05 (0.5–2.85)	1.03 (0.5–2.76)	1.06 (0.5–3.04)
Blood phosphate <2.5 mg/dL,[b] n (%)	22 (15)	6 (6)	10 (7)
UACR, median (range), mg/g	7 (1–768)	5 (2–752)	6 (1–381)
UBCR, median (range), mg/g	658 (14–81,298)	433 (17–31,034)	315 (19–32,936)
UPCR, median (range), mg/g	82 (16–466)	68 (14–805)	52 (12–554)

Abbreviation: UACR=urine albumin to Cr ratio.
[a]One participant on HD was excluded.
[b]Data were available from 144 samples at baseline, 122 at Month 2, and 134 at Month 6.

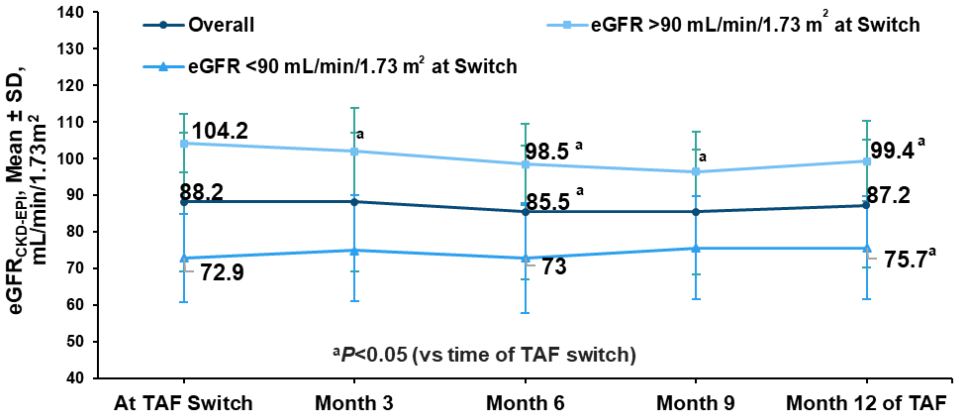
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Switching From Another NUC: Efficacy and Renal Safety[18]

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 was conducted. The primary endpoint was viral 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 switching to TAF included TDF (75%), ETV (5%), LAM (3%), and ADV combined with others (17%).

Overall mean $eGFR_{CKD\text{-}EPI}$ did not change significantly 12 months after patients switched to TAF. There was significant improvement, however, among patients with baseline $eGFR_{CKD\text{-}EPI}$ <90 mL/min/1.73 m^2 (Figure 6).

Figure 6. Mean $eGFR_{CKD\text{-}EPI}$ Level (Yeh et al)[18]



Canadian Hepatitis B Network[19]

Study design and demographics

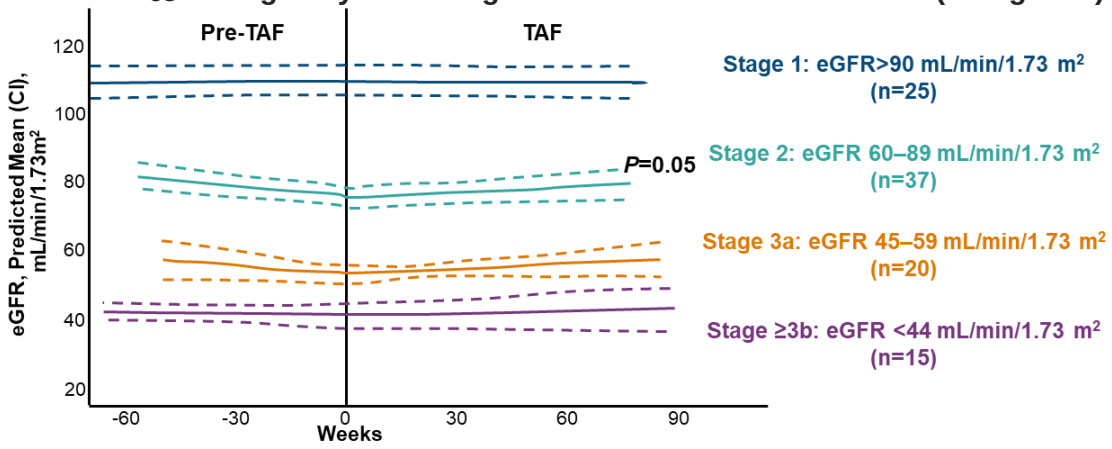
A multicenter study was conducted among TN and TE patients to evaluate the real-world efficacy and renal safety of TAF (N=103). Baseline characteristics included the following: mean age, 52 years; male sex, 69%; Asian race, 81%; cirrhosis, 12%; detectable HBV DNA, 30%; and HBeAg+ status, 33%. Previous therapies in TE patients included TDF (79%), LAM (2%), and ETV (1%). TN participants comprised 14% of the study population.

Renal safety

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

Patients with baseline Stage 2 CKD experienced a significant decrease in $eGFR_{CG}$ pre-TAF (-0.51 mL/min per month [-0.89 to -0.14]; *P*=0.01) and a significant increase after TAF initiation (+0.2 mL/min per month [0.01 to 0.41]; *P*=0.05). Patients with baseline Stage 3a and Stage 3b or higher CKD showed trends of declining $eGFR_{CG}$ pre-TAF and increasing $eGFR_{CG}$ after switching to TAF (Figure 7).

Figure 7. $eGFR_{CG}$ Changes by CKD Stage Pre- and Post-Switch to TAF (Farag et al)[19]



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Abbreviations

β2M:Cr=β-2 microglobulin to Cr ratio
AASLD=American Association for the Study of Liver Diseases
ADR=adverse drug reaction
ADV=adefovir dipivoxil
CG=Cockcroft-Gault equation
CHB=chronic hepatitis B
CKD=chronic kidney disease
CKD-EPI=CKD Epidemiology Collaboration equation
DM=diabetes mellitus
EASL=European Association for the Study of the Liver
ETV=entecavir
FTC=emtricitabine
HBeAg=hepatitis B envelope antigen
HCC=hepatocellular carcinoma
HD=hemodialysis
HTN=hypertension
LAM=lamivudine
MDRD=Modification of Diet in Renal Disease
NUC=nucleos(t)ide analog
OL=open-label
OR=odds ratio
PS=propensity score
Q=quartile
RCT=randomized clinical trial
RRT=renal replacement therapy
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
TN=treatment-naive
UBCR=urinary β2 microglobulin to Cr ratio
ULN=upper limit of normal
UPCR=urine protein to Cr ratio

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