Descovy® (FTC/TAF) Renal Safety of FTC/TAF-Containing Regimens in HIV-1 Treatment

This document is in response to your request for information from key clinical trials and real-world studies that assessed the renal safety of Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF])-based regimens, including Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]), Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), and Odefsey® (rilpivirine/emtricitabine/tenofovir alafenamide [RPV/FTC/TAF]) in people with HIV (PWH).

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Summary

Product Labeling[1]

FTC/TAF and FTC/TAF-based regimens are not recommended in individuals with severe renal impairment (estimated CrCl of 15 to <30 mL/min), or ESRD (estimated CrCl <15 mL/min) who are not receiving chronic HD.[1-4] BIC/FTC/TAF is also not recommended in individuals with no ARV treatment history and ESRD who are receiving chronic HD.[2]

Postmarketing cases of renal impairment, including acute renal failure, PRT, and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related AEs.[1-4]

Clinical Trials: Renal Safety of FTC/TAF-Containing Regimens in PWH

An integrated analysis of 26 TAF clinical trials (N=9322) yielded the following:[5]

- No cases of PRT/Fanconi syndrome were reported in participants who received TAF, compared with 10 reported cases in participants who received TDF.
- Significantly fewer DCs due to renal AEs occurred after exposure to TAF than after exposure to TDF. Renal AEs were significantly less frequent in treatment-naive participants on TAF than in those on TDF (*P*=0.042), and all renal biomarker results significantly favored TAF over TDF.

A summary of renal safety results from Gilead clinical trials is presented below.[6-13]

In FANTA (N=28), a phase 4 trial that evaluated the renal safety of TAF treatment in participants with a prior history of PRT/Fanconi syndrome on a TDF-containing regimen, no participants experienced recurrent PRT over the course of 5 years of TAF exposure.[14]

Real-World Data: Renal Safety of FTC/TAF-Containing Regimens in PWH

- In PWH who switched from TDF-based to TAF-based ARV regimens, significant improvements in eGFR were observed after switching, particularly in patients with pre-switch eGFRs <90 mL/min/1.73 m^2.[15]
- In a study among TE PWH and a history of CKD in BICSTaR, median eGFR levels were stable through 24 months of BIC/FTC/TAF treatment.[16]
- In ARV-naive PWH who initiated FTC/TAF-based regimens in the TAFNES cohort study, there was a significant decrease in eGFR (*P*<0.001) from baseline to Month 3 and a significant increase in the median SCr level (*P*<0.0001) from baseline to Month 24; among TE participants who switched from TDF to TAF and had a baseline eGFR (MDRD) <60 mL/min/1.73 m^2, there was a significant increase in eGFR of +5.7 mL/min/1.73 m^2 (*P*=0.003).[17]
- Case reports of renal events in individuals taking TAF have rarely been reported since the approval of TAF-containing products. Most of these cases are characterized by the presence of known risk factors for renal dysfunction (eg, history of prior TDF use, preexisting renal disease, diabetes or hypertension, HIV/HCV co-infection, coadministration with nephrotoxic drugs).[18-25]

Product Labeling[1]

Dosage and Administration

Not recommended in patients with severe renal impairment

FTC/TAF is not recommended in individuals with severe renal impairment (estimated CrCl of 15 to <30 mL/min), or ESRD (estimated CrCl <15 mL/min) who are not receiving chronic HD.[1-4] BIC/FTC/TAF is also not recommended in individuals with no antiretroviral treatment history and ESRD who are receiving chronic HD.[2]

Warnings and Precautions

New onset or worsening renal impairment

Postmarketing cases of renal impairment, including acute renal failure, acute tubular necrosis, PRT, and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related AEs. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Individuals taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including nonsteroidal anti-inflammatories are at increased risk of developing renal-related adverse reactions.[1-4]

Clinical Pharmacology

Pharmacodynamics: effects on SCr

BIC[2]

BIC has been shown to increase SCr due to inhibition of tubular secretion of Cr without affecting renal glomerular function. Mean change from baseline in SCr in healthy subjects who received BIC 75 mg (1.5 times the approved recommended dosage) once daily with food for 14 days was 0.1 mg/dL on Days 7 and 14 compared to placebo. BIC did not have a significant effect on the estimated CrCl or on the actual GFR (determined by the clearance of probe drug, iohexol).

COBI[3]

COBI, a component of E/C/F/TAF, produces elevations of SCr due to inhibition of tubular secretion of Cr without affecting GFR. The elevation of SCr is typically seen within 2 weeks of starting therapy and is reversible after DC. Patients who experience a confirmed increase in SCr of >0.4 mg/dL from baseline should be closely monitored for renal safety.

The actual GFR, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of COBI among subjects with an estimated CrCl of ≥50 mL/min, indicating COBI inhibits tubular secretion of Cr, reflected as a reduction in estimated CrCl without affecting the actual GFR.

Clinical Trials: Renal Safety of FTC/TAF-Containing Regimens in PWH

Background

The renal safety profile of TAF-containing regimens has been well established, with >41,000 PY experience in clinical trials and >3.7 million PY experience with post-approval use worldwide.[5,26] Results from clinical trials involving TAF-containing regimens have demonstrated a renal safety profile comparable to regimens without tenofovir, such as regimens with ABC or DTG/3TC in PWH.[6,8,27]

In clinical trials of TAF-containing regimens for HIV treatment, PrEP, and HBV treatment, there have been no cases of PRT.[5,26] Significantly fewer cases of renal AEs and fewer DCs due to renal AEs were observed in PWH taking TAF than in those taking TDF in clinical trials.[5,11] Additionally, more favorable renal tubular biomarkers, such as RBP:Cr and β2M:Cr (increased levels of which signify evidence of potential tubular injury in PWH), were recorded in clinical trials with TAF use than with TDF use in the HIV treatment (Table 3), PrEP, and HBV treatment populations.[5,11,28-30]

Pooled Analysis of 26 TAF Clinical Trials

Study design[5]

An integrated analysis of participants from 26 TAF clinical trials (N=9322) was conducted to evaluate whether the improved renal biomarker profiles in the individual clinical trials were associated with improvements in clinical renal safety. Study details, primary outcomes, and

secondary outcomes regarding the 26 clinical trials included in the analysis are listed in Table 1. Baseline demographics and characteristics of all participants are listed in Table 2.

Table 1. Pooled Analysis: Studies Included in the Integrated Analysis[5,6,31]

Study Population	Study Number	Study Design	N	Treatment
Treatment-Naive Adults (n=7 trials)	292-0102	DB, R	170	E/C/F/TAF vs E/C/F/TDF
	141-1475	DB, R	98	BIC + FTC/TAF vs DTG + FTC/TAF
	380-1490	DB, R	645	BIC/FTC/TAF vs DTG + FTC/TAF
	299-0102	DB, R	153	DRV/COBI/FTC/TAF vs DRV + COBI + FTC/TDF
	380-1489	DB, R	629	BIC/FTC/TAF vs ABC/DTG/3TC
	292-0104	DB, R	867	E/C/F/TAF vs E/C/F/TDF
	292-0111	DB, R	866	E/C/F/TAF vs E/C/F/TDF
Virologically Suppressed Adults (n=12 trials)	366-1160	DB, R	875	EFV/FTC/TDF vs RPV/FTC/TAF
	366-1216	DB, R	630	RPV/FTC/TAF vs RPV/FTC/TDF
	311-1089	DB, R	663	FTC/TAF + third agent vs FTC/TDF + same third agent
	292-0109	OL, R	1436	E/C/F/TAF vs TDF-containing regimens
	380-1878	OL, R	577	BIC/FTC/TAF vs boosted PI regimens
	380-1844	DB, R	563	BIC/FTC/TAF vs ABC/DTG/3TC
	311-1717	DB, R	556	FTC/TAF + third agent vs ABC/3TC + same third agent
	292-1823	OL, R	274	E/C/F/TAF vs ABC/3TC + third agent
	366-1992	OL, R	148	E/C/F/TAF vs RPV/FTC/TAF
	380-1961	OL, R	470	BIC/FTC/TAF vs E/C/F/TAF, E/C/F/TDF or ATV + RTV + FTC/TDF
	236-0128	OL, R	212	E/C/F/TAF vs ATV/r + FTC/TDF
	292-1824	Single arm	37	E/C/F/TAF
Treatment-Naive and Virologically Suppressed Adults (n=1 trial)	292-1249	Single arm	77	E/C/F/TAF
Treatment-Experienced Adults (n=2 trials)	292-0117	DB, R	37	TAF + failing regimen vs placebo + failing regimen
	292-0119	OL, R	133	E/C/F/TAF + DRV vs pre-existing regimen
Treatment-Naive and Virologically Suppressed Children (n=1 trial)	292-0106	Single arm	102	E/C/F/TAF
Virologically Suppressed Adolescents (n=1 trial)	292-1515	Single arm	60	E/C/F/TAF
Treatment-Naive and Virologically Suppressed Children and Adolescents (n=2 trials)	311-1269	Single arm	28	FTC/TAF
	380-1474	Single arm	24	BIC/FTC/TAF

Primary Outcomes (N=26 trials, 9322 participants)
1) PRT
2) DC due to renal AEs

Secondary Outcomes (N=7 trials; n=2 naive [1733 participants], n=5 suppressed [4092 participants])
1) Treatment-emergent renal AEs (renal and urinary disorders system organ class from Medical Dictionary for Regulatory Activities v18.1–19.1)
2) SCr (mg/dL)
3) $CrCl_{CG}$ (mL/min)
4) Treatment-emergent total proteinuria (dipstick)
5) UACR
6) Tubular proteinuria (urine RBP:Cr and β2M:Cr)

Abbreviations: ATV=atazanavir; ATV/r=ritonavir-boosted atazanavir; DB=double blind; EFV=efavirenz; OL=open label; PI=protease inhibitor; R=randomized; RTV=ritonavir.

Table 2. Pooled Analysis: Baseline Demographics and Characteristics[5]

Key Demographics and Characteristics		TAF (n=6360)	TDF (n=2962)	Total (N=9322)
PY of exposure		12,519	5947	-
Age, median (range), years		41 (7–80)	42 (18–79)	42 (7–80)
Male, n (%)		4966 (78)	2436 (82)	7402 (79)
Race, n (%)	White	3796 (60)	1884 (64)	5680 (61)
	Black	1799 (28)	739 (25)	2538 (27)
	Asian	373 (6)	181 (6)	554 (6)
Treatment status, n (%)	Naive	2191 (34)	975 (33)	3166 (34)
	Experienced	4169 (66)	1987 (67)	6156 (66)
CrCl, median (IQR), mL/min		108.8 (91.2–129.6)	107.7 (90.9–128.4)	108.6 (91.1–129.3)

Results

There were no cases of PRT or Fanconi syndrome after 12,519 PY of exposure to TAF, compared with 10 cases after 5947 PY of exposure to TDF (*P*<0.001). A significantly greater number of participants discontinued treatment due to renal AEs after exposure to TDF than after exposure to TAF (14 vs 3; *P*<0.001).

Renal AEs were significantly less frequent in the TAF group than in the TDF group in studies of treatment-naive participants (47/866 [5.4%] vs 74/867 [8.5%]; *P*=0.042). However, there was no difference in the rate of renal AEs between the TAF and TDF groups in studies of virologically suppressed participants (114/2291 [5%] vs 89/1801 [5%]; *P*=1).

All pooled renal biomarker analyses (SCr, CrCl, dipstick proteinuria, UACR, RBP:Cr, β2M:Cr) in both treatment-naive and virologically suppressed participants significantly favored TAF over TDF (Table 3).

Table 3. Renal Biomarker Analyses for TDF and TAF at Week 96[5]

Renal Parameter	Treatment-Naive Participants (n=2 Trials)			Virologically Suppressed Participants (n=5 Trials)		
	TAF	TDF	*P*-Value	TAF	TDF	*P*-Value
SCr, median change from baseline, mg/dL	+0.04	+0.07	<0.001	-0.05	-0.02	<0.001
$CrCl_{CG}$, median change from baseline, mL/min	-2	-7.5	<0.001	+6	+0.6	<0.001
Treatment-emergent proteinuria, %	36	41	0.034	28	31	0.04
UACR, median change from baseline, %	-5.2	+4.9	<0.001	-5.4	+27	<0.001
RBP:Cr, median change from baseline, %	+13.8	+74.2	<0.001	-2.3	+61.2	<0.001
β2M:Cr, median change from baseline, %	-32.1	+33.5	<0.001	-25.8	+53	<0.001

Note: Differences in the change or percentage change from baseline between the two treatment groups were compared using a linear regression analysis and rank analysis of covariance (baseline values were adjusted), respectively. Differences in incidence rates between treatment groups were compared using a logistic regression model.

Select Gilead Clinical Trial Data

Long-term data from clinical trials showed that the beneficial effects on markers of renal safety were maintained through Week 144 when TDF was compared with TAF in Studies 0104 and 0111.[11] When comparing regimens containing TAF vs ABC (Studies 1489 and

1717), changes in markers of renal safety were comparable between the study arms.[6,9] Additionally, in a pooled analysis of Studies 1489 and 1490 (BIC/FTC/TAF vs DTG + FTC/TAF), changes in eGFR were not statistically different between BIC/FTC/TAF and DTG-containing regimens in the comparator arms at Week 144 (DTG/ABC/3TC, *P*=0.13; DTG + FTC/TAF, *P*=0.28).[12]

FANTA Trial

Study design and demographics

FANTA was a phase 4, open-label, single-arm, multicenter trial in the UK that assessed the renal safety of a TAF-based regimen in participants who had previously developed PRT/Fanconi syndrome while receiving TDF (N=28).[14,32] Participants without diabetes, with HIV RNA <200 c/mL, eGFR >30 mL/min/1.73 m^2, and UPCR <100 mg/mmol who were naive to TAF were followed for 5 years on a TAF-based ARV regimen. Participants had a median age of 55 years, and 89% were White; the median time since HIV diagnosis was 21.3 years, and the median time since TDF discontinuation was 6.8 years.[14]

Results[14]

At Year 5, 26/28 participants (93%) remained on TAF. Two participants discontinued TAF (treatment simplification, n=1; switch in critical care unit for COVID-19 treatment, n=1). No participants experienced recurrent PRT during 134 PY of follow-up. No significant changes in eGFR, albuminuria, proteinuria, fractional excretion of phosphate, or ALP were observed.

Real-World Data: Renal Safety of FTC/TAF-Containing Regimens in PWH

Renal Outcomes With TDF to TAF Conversions[15]

Study design and demographics

A retrospective study assessed changes in eGFR in PWH (N=1037) who switched from TDF- to TAF-based regimens. The included patients had received each regimen for ≥6 months, had ≥2 eGFR measurements (≥6 months apart) for each regimen and a baseline eGFR measurement within 6 months prior to the switch, and were not taking other HIV medications other than the switch regimens of interest. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

The cumulative mean duration of prior exposure to TDF was approximately 4.8 years. Details of baseline demographics are summarized in Table 4.

Table 4. Baseline Demographics, Clinical Characteristics, and Drug Exposure (Rathbun et al)[15]

Key Demographics and Clinical Characteristics	Total Cohort (N=1037)	Baseline eGFR (mL/min/1.73 m^2) Subgroups		
		eGFR ≥90 (n=426)	eGFR <90	
			eGFR 60 to <90 (n=524)	eGFR <60 (n=87)
Age at regimen switch, mean, years	48.2	42.1	51.1	60.5

Key Demographics and Clinical Characteristics		Total Cohort (N=1037)	Baseline eGFR (mL/min/1.73 m^2) Subgroups		
			eGFR ≥90 (n=426)	eGFR <90	
				eGFR 60 to <90 (n=524)	eGFR <60 (n=87)
Male, n (%)		935 (90.2)	391 (91.8)	469 (89.5)	75 (86.2)
Comorbidities, n (%)	HTN	255 (24.6)	68 (16)	143 (27.3)	44 (50.6)
	T2DM	98 (9.5)	40 (9.4)	47 (9)	11 (12.6)
	CVD	119 (11.5)	26 (6.1)	63 (12)	30 (34.5)
Baseline eGFR, mean ± SD, mL/min/1.73 m^2[a]		85.7±18.2	103.2±9.8	76.7±8.4	53.6±6

[a]Baseline eGFR was measured during treatment with TDF, within 6 months before switching to TAF.

Results

In general, mean adjusted eGFR improved after patients switched to a TAF-based regimen, with greater improvements observed in patients with eGFR <90 mL/min/1.73 m^2 at baseline.

Table 5. Adjusted Changes in Mean eGFR[15a]

Regimen	Total Cohort (N=1037)	Baseline eGFR (mL/min/1.73 m^2) Subgroups			
		eGFR ≥90 (n=426)	eGFR <90 (n=611)	eGFR 60 to <90 (n=524)	eGFR <60 (n=87)
eGFR during TAF treatment, mean (95% CI), mL/min/1.73 m^2	88.4[b] (87.5–89.2)	102.45[b] (101–103.9)	79.2[b] (78.2–80.2)	82.6[b] (81.5–83.7)	60.5[b] (58.5–62.4)
eGFR during TDF treatment, mean (95% CI), mL/min/1.73 m^2	85.6[b] (84.8–86.3)	103.03[b] (101.7–104.4)	73.7[b] (72.8–74.5)	77.4[b] (76.4–78.4)	53[b] (51.7–54.3)
Change in eGFR, mean (95% CI), mL/min/1.73 m^2	2.8[b] (2.2–3.4)	-0.58 (-1.5 to 0.3)	5.5[b] (4.8–6.3)	5.2[b] (4.4–6)	7.5[b] (5.6–9.3)

[a]Mean eGFR changes were adjusted for individual and clinical characteristics, comorbidities, and concomitant medications and were stratified by baseline eGFR (≥90 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2).
[b]*P*<0.001.

Adjusted, annualized eGFR slope calculations found that in patients with eGFR <90 mL/min/1.73 m^2 during TDF treatment (baseline), eGFR increased significantly after switching to TAF. Among patients with baseline eGFR <90 mL/min/1.73 m^2, patients with baseline eGFR ≥90 mL/min/1.73 m^2, and the entire cohort, annualized eGFR slopes calculated from the mean baseline eGFR to the first eGFR measurement during TAF treatment were +6.51 (*P*<0.001), +0.54 (*P*=0.82), and +3.57 (*P*<0.01), respectively, over a mean time period of approximately 270 days. Annualized slopes to the last eGFR measurement during TAF treatment were +3.23 (*P*<0.001), -0.77 (*P*=0.52), and +1.51 (*P*=0.025), respectively, over a mean period of approximately 520 days.

BICSTaR Study[16]

Study design and demographics

BICSTaR is an ongoing, multinational, prospective cohort study investigating the effectiveness and safety of BIC/FTC/TAF in ARV-naive and TE PWH. The primary endpoint is virologic suppression (HIV-1 RNA <50 c/mL) at 12 months. A study was conducted to assess the renal safety profile and effectiveness of BIC/FTC/TAF in TE participants with a history of CKD. Participants who had baseline and Month 24 data or had discontinued

BIC/FTC/TAF and/or the study prior to the analysis cutoff date (February 2022) and had baseline eGFR data were included (N=843). Baseline demographics are presented in Table 6.

Table 6. BICSTaR: Baseline Demographics and Characteristics by Baseline eGFR[16]

Key Demographics and Characteristics		Baseline MDRD eGFR, mL/min/1.73 m^2				
		<50 (n=18)	50–59 (n=72)	60–89 (n=451)	≥90 (n=302)	Total (N=843)
Male sex, n (%)		16 (89)	61 (85)	396 (88)	229 (76)	702 (83)
Age ≥50 years,[a] n (%)		17 (95)	54 (75)	234 (52)	90 (30)	395 (47)
HIV-1 RNA <50 c/mL,[b] n (%)		16 (89)	64 (94)	423 (95)	253 (87)	756 (92)
MDRD eGFR, median (Q1, Q3), mL/min/1.73 m^2		44.4 (40.2, 47.8)	56 (53.9, 57.9)	76.9 (70.4, 82.4)	104.2 (96, 116.5)	82.2 (70.8, 97.6)
Comorbid condition,[a] n (%)	≥1 CVD[c]	14 (78)	35 (49)	113 (25)	40 (13)	202 (24)
	Diabetes mellitus	6 (33)	5 (7)	26 (6)	20 (7)	57 (7)
	HTN	10 (56)	30 (42)	89 (20)	32 (11)	161 (19)
	Renal and urinary disorder	2 (11)	1 (1)	15 (3)	4 (1)	22 (3)

[a]At time of BIC/FTC/TAF initiation.
[b]According to a M=E analysis.
[c]According to the IA7 definition.

Results

A total of 90/843 participants (11%) with baseline eGFR data had CKD (eGFR <60 mL/min/1.73 m^2); median eGFR values were stable through 24 months (Table 7).

Table 7. BICSTaR: MDRD eGFR Changes Through Month 24[16]

eGFR, Median, mL/min/1.73m^2	Baseline MDRD eGFR, mL/min/1.73 m^2			
	30–49 (n=12)	50–59 (n=45)	60–89 (n=293)	≥90 (n=187)
Baseline	46.8	55.7	76.6	104.2
Change from baseline to Month 6	44.5	59.8	73.2	96.2
Change from baseline to Month 12	43.1	59	74.1	94.7
Change from baseline to Month 24	43.3	57.7	72.8	93.2

At 24 months, all participants with baseline CKD were virologically suppressed (HIV-1 RNA <50 c/mL). One participant with baseline CKD <50 mL/min/1.73 m^2 had a drug-related AE of proteinuria that did not result in a discontinuation of BIC/FTC/TAF.

TAFNES Study[17]

Study design and demographics

TAFNES was a prospective, multicenter, non-interventional study conducted in Germany between 2016 and 2019 in ARV-naive (n=301) and TE (n=466) PWH who initiated or switched to an FTC/TAF-based treatment regimen (ie, E/C/F/TAF, RPV/FTC/TAF, or FTC/TAF + third agent). Outcomes included changes from baseline in SCr and eGFR MDRD and CG equations. Overall baseline demographics and disease characteristics are presented in Table 8.

Table 8. TAFNES: Baseline Demographics and Characteristics[17]

Key Demographics and Characteristics		Overall (N=767)
Male, n (%)		706 (92)
Age, median (IQR), years		46 (34–54)
Race, White/Black, n (%)		709 (93)/31 (4)
CD4 count, median (IQR), cells/mcL		556 (390–765)
Full CKD risk score, low/medium/high,[a] %	ARV-naive participants	78/14/8
	TE participants	36/27/38

[a]Baseline scores were available for 253 ARV-naïve participants and 365 TE participants; 2% and 7%, respectively, were excluded from calculations due to an eGFR <60 mL/min/1.73m^2.

Results

Among ARV-naive participants, the median (IQR) eGFR (MDRD) decreased from baseline to Month 3 by -11.3 (-21.2 to -1.6) mL/min/1.73 m^2 (n=177; *P*<0.001) and was maintained thereafter; the median (IQR) change in $eGFR_{CG}$ was -3.2 (-17.4 to 6.5) mL/min/1.73 m^2 (n=119). From baseline to Month 24, the median level of SCr increased by +0.1 mg/dL (n=178; *P*<0.0001). In TE participants overall, eGFR (MDRD) was stable, and there were no significant changes in SCr regardless of treatment regimen or age at Month 24. Among those who switched from TDF to TAF and had a baseline eGFR (MDRD) <60 mL/min/1.73 m^2, there was a significant increase in eGFR of +5.7 mL/min/1.73 m^2 (*P*=0.003), with similar results seen when calculated with $eGFR_{CG}$.

At Month 24, the median (IQR) change in the full 5-year CKD risk score among ARV-naive participants was 0% (0–0.6%); median 5-year risks for CKD were low, medium, and high in 0.2%, 2.1%, and 7.1%, respectively. The median (IQR) change among TE participants was 0% (0–0.8; n=178; *P*<0.001), and median 5-year risks for CKD were low in 0.4%, medium in 2.1%, and high in 8%. In participants who switched from TDF to TAF, the median change in 5-year CKD risk was estimated as 0% (0–0.6; n=127), compared with 0% (0–1.7; n=51) in all other participants.

Virologic suppression (HIV RNA <50 c/mL) at Month 24 was 96% (M=E). Overall, 133/767 participants (17%) discontinued; there was no significant difference in persistence between ARV-naive (80%) and TE participants (82%) at Month 24. Discontinuations due to ADRs were reported in 30/767 participants (4%). One ARV-naive participant discontinued study drug due to an ADR of nephropathy toxic.

Case Reports of TAF and Suspected Renal Injury or Fanconi Syndrome

Renal events in individuals taking TAF have been reported rarely since the approval of TAF-containing products.[26] Rare is generally defined as a frequency of 0.01% to 0.1%.[33] Events identified post marketing in the Gilead safety database informing 2021 product label updates included acute renal failure (58/88 [66%] cases), acute tubular necrosis (5/88 [6%] cases), proximal renal tubulopathy (16/88 [18%] cases), and Fanconi syndrome (12/88 [14%] cases), primarily in PWH. Most of these cases are characterized by the presence of known risk factors for renal dysfunction (eg, history of prior TDF use, pre-existing renal disease, diabetes or hypertension, HIV/HCV co-infection, coadministration with nephrotoxic drugs).[19-23,26] Table 9 describes published case reports of AKI or suspected Fanconi syndrome development in patients who were switched to or initiated on TAF either empirically or because of TDF-associated tubulopathy. Please note this table only includes case reports where the primary focus is AKI or Fanconi syndrome. This list is not exhaustive

of all cases found in the literature. Case reports not included can be found by conducting a literature search via PubMed or other databases.

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on the uncontrolled observational nature of a spontaneous case report. Additionally, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of spontaneous case reports include the retrospective nature of the information provided and publication bias.[34]

Table 9. Summary of Published Case Reports With TAF and Suspected Renal Injury or Fanconi Syndrome[18-25]

Demographics	Relevant Past Medical History	Presentation Details	Resolution	Additional Information
17-year-old, pregnant female with suspected Fanconi syndrome[18]	Congenital HIV-1 that was well-controlled with BIC/FTC/TAF	Presented at 21.6 weeks pregnant with leukocytosis, hydronephrosis, pyelonephritis, urosepsis, and persistent severe hypokalemia. Patient was subsequently treated for severe hypokalemia, and imaging confirmed bilateral hydronephrosis. Polyuria, electrolyte imbalance, and microcytic anemia with suspected AKI and Fanconi were reported. AKI was considered secondary to BIC/FTC/TAF; however, BIC/FTC/TAF was continued due to low risk of renal toxicity of TAF.	Electrolytes were replenished for 5 days, and the patient was discharged with a diagnosis of post-obstructive diuresis.	Clinically complex case of a pregnant adolescent. Patient underwent emergency cesarean section at 25.2 weeks and delivered a viable infant with a 1-minute Apgar score of 2 and a 5-minute Apgar score of 7.
54-year-old male with suspected Fanconi syndrome[19]	Laryngeal cancer, HIV diagnosed in 1994 (stable on TDF for 10 years), empirically switched to DRV/r + RAL + FTC/TAF to avoid chronic toxicities	After 2 months on TAF, presented with AKI; hypokalemia; non-anion gap acidosis; glycosuria. Concurrent medications: rosuvastatin, omeprazole, L-thyroxine	Resumed normal renal function after TAF DC and initiation of non-tenofovir regimen.	Patient had long history of TDF use (10 years) prior to switching to TAF for a 2-month period.
70-year-old male with HIV/HCV develops AKI[20]	Established HIV care Dec 2016, started DTG/ABC/3TC prior to E/C/F/TAF switch, HCV genotype 1 with a history of decompensated Class B cirrhosis, alcohol use disorder. Started on LDV/SOF	After 5 months on TAF (with ~1 month of overlapping LDV/SOF treatment), patient was asymptomatic but presented with features of proximal renal tubular acidosis (elevated fractional excretion of phosphate [40%], persistently low serum bicarbonate). Other renally cleared medications: aspirin, furosemide, lisinopril, spironolactone	Patient's kidney function worsened after initiation of LDV/SOF but resumed baseline renal function post LDV/SOF and TAF DC.	Patient had multiple risk factors, including advanced liver disease, for kidney injury and was on concomitant renally cleared medications.
58-year-old male with HIV/HCV develops AKI[21]	Poorly controlled HIV and cirrhotic HCV, active heroin and cocaine abuse, long-standing T2DM correlated with nephrotic-range proteinuria	After 8 weeks on DRV/c + FTC/TAF, presented with low serum albumin; elevated 24-hour urine protein; glycosuria; urine sediment analysis revealed granular and tubular epithelial cell casts; kidney biopsy revealed evidence of diabetic nephropathy, immune complex deposition, proximal tubule mitochondrial distortion; cryoglobulin consisting of monoclonal IgG kappa and polyclonal IgG, IgM, kappa and lambda	Renal function recovered to baseline after dialysis treatment and DC of TAF.	Patient had SCr increase with TDF exposure 2 years prior and had multiple risk factors for liver injury: uncontrolled HIV, HCV co-infection with cirrhosis, Black race, age.

Demographics	Relevant Past Medical History	Presentation Details	Resolution	Additional Information
64-year-old male with proximal tubule mitochondrial toxicity[22,24]	HIV diagnosed in 1987, empirically switched from TDF to TAF after unexplained eGFR decline to 51 mL/min, occasional nonsteroidal anti-inflammatory drug use	After switching to TAF, patient presented with continued eGFR decline, normal urinalysis, renal ultrasound, and UPCR. A renal biopsy after 12 months on TAF revealed proximal tubule mitochondrial toxicity with atypical, enlarged mitochondria	Renal function continued to decline for 2 months after TAF DC but began to improve the following month.	Patient's renal decline had begun prior to TAF initiation and continued after TAF DC.
53-year-old female with symptoms consistent with renal tubular acidosis[23]	Recently diagnosed with HIV and started on E/C/F/TAF, no other details provided	Presented to emergency department with large gallstone suggestive of cholecystitis; severe sepsis; nausea; vomiting; diarrhea; severe diffuse abdominal pain; fever; metabolic acidosis; creatinine 2.2 mg/dL	Septic shock and metabolic acidosis resolved several days later after management in the ICU.	Patient had only recently started TAF; missing patient history or additional details.
49-year-old female with HIV develops AKI after switching to DTG + FTC/TAF[25]	HIV diagnosed in 1997 (achieved undetectable viral load in 2001), comorbid HTN and dyslipidemia, started LPV/r + FTC/TDF in 2015 and switched to DTG + FTC/TAF in 2019	After switching to DTG + FTC/TAF, SCr increased from 1.05 to 1.47 mg/dL at 3 months and to 2.3 mg/dL at 6 months, at which time eGFR was 24 mL/min/1.73 m^2. Concomitant medications: amlodipine 5 mg/day (increased to 10 mg/day at 3 months) and atorvastatin 20 mg/day	Discontinued DTG + FTC/TAF and initiated LPV/r + 3TC. Two months later, SCr decreased to 1.82 mg/dL, and eGFR increased to 32 mL/min/1.73 m^2, which stabilized to 35–40 mL/min/1.73 m^2 over the next 6 months.	Pathological findings suggest the patient had acute tubular injury and IgA nephropathy. Cause could be multifactorial. Patient switched from amlodipine to losartan after renal function stabilized to reduce proteinuria and control blood pressure.

References

1. Enclosed. Gilead Sciences Inc, DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA.
2. Enclosed, Gilead Sciences Inc. BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
3. Enclosed. Gilead Sciences Inc, GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
4. Enclosed. Gilead Sciences Inc, ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
5. Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. *AIDS.* 2019;33(9):1455-1465.
6. Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. *Lancet HIV.* 2018;5(4):e162-171. http://dx.doi.org/10.1016/S2352-3018(18)30010-9
7. Workowski K, Orkin C, Sax P, et al. Four-year outcomes of B/F/TAF in treatment-naïve adults [Poster 2268]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI) Virtual; 6-10 March, 2021.
8. Orkin C, DeJesus E, Sax PE, et al. Three-Year Outcomes of the Fixed-Dose Combination Bictegravir, Emtricitabine, and Tenofovir Alafenamide vs Dolutegravir-Containing Regimens for Initial Treatment of HIV-1 Infection: Week 144 Results from Two Randomised, Double-Blind, Multicentre, Phase 3, Non-Inferiority Trials. *The Lancet HIV.* 2020;7:e389–400.
9. Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials [Supplementary Appendix]. *The Lancet HIV.* 2020;7(6):e389-e400. https://www.ncbi.nlm.nih.gov/pubmed/32504574
10. Winston A, Post FA, DeJesus E, et al. Randomized Double-blind Trial Comparing Switching to TAF/FTC- versus Continuing ABC/3TC-based Regimens in Virologically Suppressed Adults (Study 1717): 48 Week Results [Presentation]. Paper presented at: 16th European AIDS Conference; 25-27 October, 2017; Milan, Italy.
11. Arribas JR, Thompson M, Sax PE, et al. Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. *J Acquir Immune Defic Syndr.* 2017;75(2):211-218. http://www.ncbi.nlm.nih.gov/pubmed/28282300
12. Orkin C, Sax PE, Arribas J, et al. Long-term Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in ART-Naïve Adults [Poster PE3/14]. Paper presented at: 17th European AIDS Conference; 06-09 November, 2019; Basel, Switzerland.
13. Wohl DA, Pozniak A, Workowski K, et al. B/F/TAF Five-Year Outcomes in Treatment-Naïve Adults [Poster 494]. Paper presented at: Virtual Conference on Retroviruses and Opportunistic Infections (CROI) 2022; 12-16 February, 2022.
14. Campbell L, Barbini B, Cromarty B, et al. Safety of Tenofovir Alafenamide in individuals with a history of Proximal Renal Tubulopathy on TDF [Poster 828]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2024; Denver, CO.
15. Rathbun R, Skol L, Kandilian R, et al. Real-World HIV Renal Outcomes With TDF to TAF Switch. Paper presented at: AIDS 2022; 29 July-2 August, 2022; Montreal, Quebec, Canada.
16. Rieke A, De Wet J, Esposito V, et al. Real-World Effectiveness and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) in Treatment-Experienced (TE) People With HIV With a History of CKD [Poster TH-PO1072]. Paper presented at: ASN Kidney Week; November 2-5, 2023; Philadelphia, PA.
17. Stephan C, Spinner CD, Rieke A, et al. Effectiveness, safety, and patient-reported outcomes of emtricitabine/tenofovir alafenamide-based regimens for the treatment of HIV-1 infection: Final 24-

month results from the prospective German TAFNES cohort study. *HIV Med.* 2025;26(2):239-251.
18. Davis S, Mendez PR, Sampson R, Silverman R, Kaul V. Obstructive Nephropathy versus Tenofovir-induced Fanconi Syndrome in a 17 y/o Gravida with Congenital HIV: A case Report. [Abstract #83]. *Journal of Pediatric and Adolescent Gynecology.* 2025;38(2):270.
19. Bahr NC, Yarlagadda SG. Fanconi Syndrome and Tenofovir Alafenamide: A Case Report. *Annals of Internal Medicine.* 2019;170(11):814-815. https://www.ncbi.nlm.nih.gov/pubmed/30690644
20. Serota DP, Franch HA, Cartwright EJ. Acute Kidney Injury in a Patient on Tenofovir Alafenamide Fumarate After Initiation of Treatment for Hepatitis C Virus Infection. *Open Forum Infect Dis.* 2018;5(8):ofy189. https://www.ncbi.nlm.nih.gov/pubmed/30151414
21. Novick TK, Choi MJ, Rosenberg AZ, McMahon BA, Fine D, Atta MG. Tenofovir alafenamide nephrotoxicity in HIV-positive patient. *Medicine (Baltimore).* 2017;96(36).
22. Ibrahim BB, Lamarche J, Velez AP, et al. Tenofovir Alafenamide and proximal tubule mitochondrial toxicity. *American Journal of Kidney Diseases.* 2018;7(4).
23. Abbasi AA, Patti R, Ghatak A, Seneviratne C, Kupfer Y, Kamholz S. Tenofovir Alafenamide-Induced Renal Tubular Acidosis. *Am J Ther.* 2019;26(5):e627-e628. https://www.ncbi.nlm.nih.gov/pubmed/31498779
24. Lamarche J, Ibrahim BB, Radoianu N, et al. Tenofovir alafenamide and proximal tubule mitochondrial toxicity [Poster]. 2018.
25. Ueaphongsukkit T, Gatechompol S, Avihingsanon A, et al. Tenofovir alafenamide nephrotoxicity: a case report and literature review. *AIDS Res Ther.* 2021;18(1):53.
26. Gilead Sciences Inc. Data on File.
27. van Wyk J, Ajana F, Bisshop F, et al. Switching to DTG/3TC Fixed-Dose Combination (FDC) is Non-Inferior to Continuing a TAF-Based Regimen (TBR) in Maintaining Virologic Suppression Through 96 Weeks (TANGO Study) [Presentation]. Paper presented at: HIV Drug Therapy Glasgow 2020 Virtual; 05-08 October, 2020.
28. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet.* 2020;396(10246):239-254.
29. Chan HLY, Lim YS, Seto WKW, et al. 3-Year Efficacy and Safety of Tenofovir Alafenamide Compared With Tenofovir Disoproxil Fumarate in HBeAg-Negative and -Positive Patients With Chronic Hepatitis B [Poster 381]. Paper presented at: AASLD: The Liver Meeting® 2018; 09-13 November, 2018; San Francisco, CA.
30. Fiseha T, Gebreweld A. Urinary Markers of Tubular Injury in HIV-Infected Patients. *Biochem Res Int.* 2016;2016:1501785.
31. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV.* 2016;3(4):e158-165. https://www.ncbi.nlm.nih.gov/pubmed/27036991
32. Campbell L, Barbini B, Burling K, et al. Safety of Tenofovir Alafenamide in People With HIV Who Experienced Proximal Renal Tubulopathy on Tenofovir Disoproxil Fumarate. *J Acquir Immune Defic Syndr.* 2021;88(2):214-219.
33. European Medicines Agency. *New product information wording – Extracts from PRAC recommendations on signals. EMA/PRAC/1320/2016.* January 2016.
34. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264. https://www.ncbi.nlm.nih.gov/pubmed/24758689

Abbreviations

3TC=lamivudine
ABC=abacavir
ADR=adverse drug reaction
AE=adverse event
AKI=acute kidney injury
ALP=alkaline phosphatase
ARV=antiretroviral
β2M=β-2 microglobulin
BIC=bictegravir
CG=Cockcroft-Gault
CKD=chronic kidney disease
COBI=cobicistat
CVD=cardiovascular disease
DC=discontinuation
DRV=darunavir
DRV/c=darunavir/cobicistat
DRV/r=darunavir/ritonavir
DTG=dolutegravir
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF=elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ESRD=end-stage renal disease
FTC=emtricitabine
HD=hemodialysis
HTN=hypertension
ICU=intensive care unit
LDV/SOF=ledipasvir/sofosbuvir
M=E=missing=excluded
MDRD=Modification of Diet in Renal Disease
PWH=people with HIV
PrEP=pre-exposure prophylaxis
PRT=proximal renal tubulopathy
PY=patient years
RAL=raltegravir
RBP=retinol-binding protein
RPV=rilpivirine
T2DM=type 2 diabetes mellitus
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TE=treatment-experienced
UACR=urine albumin:creatinine ratio
UPCR=urine protein:creatinine ratio

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