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Renal Safety of TAF vs TDF and ABC in a Pooled Analysis of 26 Phase 2/3 Clinical Trials

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Introduction

- Tenofovir alafenamide (TAF) is a novel tenofovir (TFV) prodrug associated with 91% lower plasma TFV levels compared with tenofovir disoproxil fumarate (TDF)[1]
  - Higher plasma TFV levels have been associated with nephrotoxicity[2,3]
- For people living with HIV (PLH) who have experienced TDF-associated renal toxicity (eg, proximal renal tubulopathy [PRT]), treatment guidelines recommend switching from TDF to TAF[4,5] or a non-TFV drug[5]
- Compared with TDF, TAF showed improved renal safety across multiple randomized trials
  - Early improvements in renal biomarkers, including estimated glomerular filtration rate (eGFR), total and tubular proteinuria, and albuminuria, compared to TDF-containing regimens in several boosted and unboosted agents[6-10]
  - Abacavir (ABC) is a nucleoside reverse transcriptase inhibitor (NRTI) not associated with renal toxicity
- The relationship between improvements in renal biomarkers and improved clinical renal outcomes was not established in the individual trials
- Our objective was to conduct a large, integrated analysis of individuals from 26 TAF clinical trials
  - To increase the statistical power in order to evaluate if the improved renal biomarker signals in the individual clinical trials were indeed associated with improvements in clinical renal safety

Methods

Studies Included in Integrated Analysis

Study Population	Study No.	Study Design	N	Treatment
Treatment-naive adults (n=7)	292-0102	DB, R	170	E/C/F/TAF vs E/C/F/TDF
	141-1475	DB, R	98	BIC+F/TAF vs DTG+F/TAF
	380-1490	DB, R	645	B/F/TAF vs DTG+F/TAF
	299-0102	DB, R	153	DRV/COBI/FTC/TAF vs DRV+COBI+FTC/TDF
	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
	380-1489	DB, R	629	B/F/TAF vs ABC/DTG/3TC
Virologically suppressed adults (n=12)	380-1878	OL, R	577	B/F/TAF vs boosted PI-regimens
	380-1844	DB, R	563	B/F/TAF vs ABC/DTG/3TC
	366-1160	DB, R	875	E/V/F/TC/TDF vs FTC/RPV/TAF
	366-1216	DB, R	630	FTC/RPV/TAF vs FTC/RPV/TDF
	311-1089	DB, R	663	F/TAF+3rd agent vs F/TDF+3rd agent
	311-1717	DB, R	556	F/TAF+3rd agent vs ABC/3TC+3rd agent
	292-0109	OL, R	1436	E/C/F/TAF vs TDF-containing regimens
	292-1823	OL, R	274	E/C/F/TAF vs ABC/3TC+3rd agent
	366-1992	OL, R	148	E/C/F/TAF vs R/F/TAF
	366-1961	OL, R	470	B/F/TAF vs E/C/F/TAF, E/C/F/TDF or ATV+RTV+F/TDF
	236-0128	OL, R	212	E/C/F/TAF vs ATV/r + FTC/TDF
Treatment-naive & virologically suppressed adults (n=1)	292-1824	Single arm	37	E/C/F/TAF
Virologically suppressed adolescents (n=1)	292-1249	Single arm	77	E/C/F/TAF
Treatment-experienced adults (n=2)	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 & virologically children (n=1)	292-0106	Single arm	102	E/C/F/TAF
Virologically suppressed adolescents (n=1)	292-1515	Single arm	60	E/C/F/TAF
Treatment-naive & virologically suppressed children 6 adolescents (n=3)	311-1269	Single arm	28	F/TAF
	380-1474	Single arm	24	B/F/TAF

Primary outcomes (N=26 trials, 10,330 participants)
1) Proximal renal tubulopathy
2) Discontinuations due to renal AEs

Secondary outcomes (N=10 trials; n=3 naïve [2362 participants], n=7 suppressed [5300 participants])
1) Treatment-emergent renal AEs (renal and urinary disorders system organ class from MedDRA v18.1-19.1)
2) SCr (mg/dL)
3) eGFR by Cockcroft-Gault (mL/min)
4) Treatment-emergent total proteinuria (dipstick)
5) UACR
6) Tubular proteinuria (urine RBP:Cr and β2M:Cr)

3TC, lamivudine; AE, adverse event; ATV, atazanavir; B, BIC, bictegravir; β2M, beta-2-microglobulin; C, COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; DB, double-blind; E, elvitegravir; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; F, FTC, emtricitabine; OL, open label; PI, protease inhibitor; R, randomized; R, RPV, rilpivirus; RBP, retinol-binding protein; RTV, ritonavir; SCr, serum creatinine; STR, single tablet regimen; UACR, urine albumin:creatinine ratio.

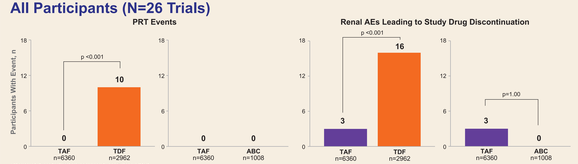
Results

Baseline Characteristics

		TAF n=6360	TDF n=2962	ABC n=1008	Total N=10,330
Patient-Years (py) of exposure		12,519	5947	1029	19,495
Age, years		41 (7, 80)	42 (18, 79)	45 (18, 82)	42 (7, 82)
Sex, n (%)	Male	4966 (78)	2436 (82)	862 (86)	8264 (80)
	Female	1394 (22)	526 (18)	146 (15)	2066 (20)
Race, n (%)	White	3796 (60)	1884 (64)	687 (68)	6367 (62)
	Black	1799 (28)	739 (25)	267 (27)	2805 (27)
	Asian	373 (6)	181 (6)	25 (3)	579 (6)
	Native Hawaiian or Pacific Islander	24 (<1)	8 (<1)	2 (<1)	34 (<1)
	American Indian or Alaska Native	30 (1)	19 (1)	6 (1)	55 (1)
	Other	322 (5)	126 (4)	18 (2)	466 (5)
	Not collected*	16 (<1)	5 (<1)	3 (<1)	24 (<1)
Ethnicity, n (%)	Hispanic or Latino	1188 (19)	537 (18)	159 (16)	1884 (18)
Treatment status, n (%)	Naive	2191 (34)	975 (33)	315 (31)	3481 (34)
	Experienced	4169 (66)	1987 (67)	693 (69)	6849 (66)
eGFR (CrCl), mL/min		108.8 (91.2, 129.6)	107.7 (90.9, 128.4)	108.0 (89.4, 129.7)	108.6 (91.0, 129.3)
eGFR, Schwartz, mL/min/1.73 m^2		153.3 (136.1, 170.9)			153.3 (136.1, 170.9)

Data are median (interquartile range) or n (%), except for age, which is median (range). *Race data collection not permitted by jurisdiction. eGFR, Schwartz, estimated glomerular filtration rate by the Schwartz formula (pediatric individuals only).

All Participants (N=26 Trials)



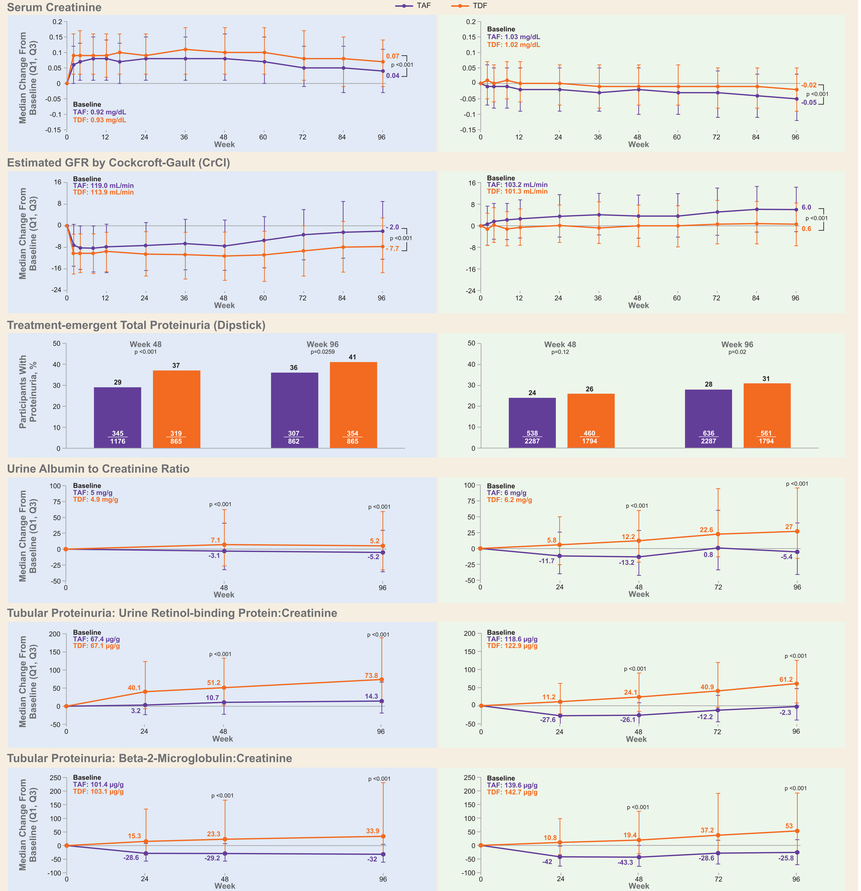
Differences between treatment groups compared using Fisher exact test.

- There were no cases of PRT or Fanconi syndrome that occurred after 12,519 py of exposure to TAF vs 10 cases after 5947 py of exposure to TDF (p <0.001)
- Fewer participants discontinued for renal AEs on TAF vs TDF (3 vs 16, p <0.001)
- Assuming participants receiving TAF had a similar risk for PRT as those receiving TDF (0.34%), the chance of observing no PRT cases in those on TAF would be <1 in 100,000 based on hypergeometric distribution

TAF vs TDF

Treatment-naïve Participants (N=3 Trials)

Virologically Suppressed Participants (N=7 Trials)



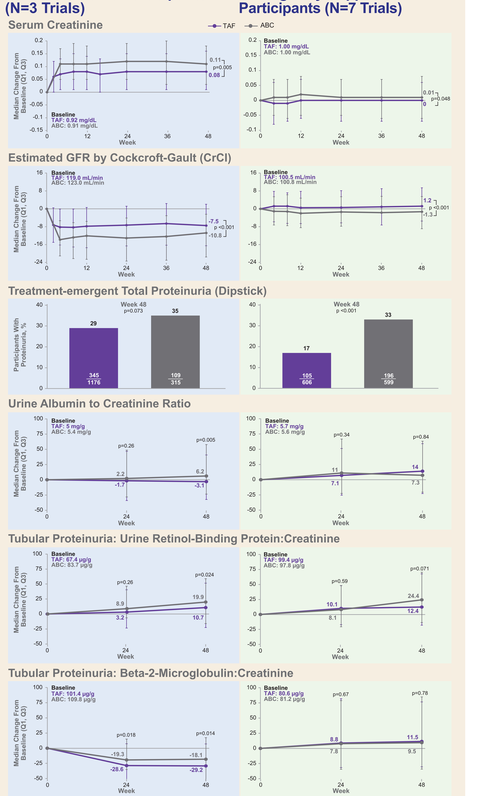
Differences between treatment groups in changes or % changes from baseline compared using Wilcoxon rank sum test or rank analysis of covariance (if baseline values needed to be adjusted), except treatment-emergent proteinuria (defined as ≥1 grade increase from baseline) which was compared using Fisher exact test.

- Renal and urinary adverse events:
  - **Treatment naïve:** Significantly less frequently for TAF than for TDF [62/1180 (5%) vs 72/867 (8%); p=0.007]
  - **Virologically suppressed:** No difference in rate between TAF and TDF groups [135/2291 (6%) vs 100/1801 (6%) p=0.68]
- Pooled renal biomarker analyses (SCr, eGFR, dipstick proteinuria, UACR, RBP:Cr, β2M:Cr) favored TAF vs TDF in studies of both treatment-naïve and virologically suppressed participants

TAF vs ABC

Treatment-naïve Participants (N=3 Trials)

Virologically Suppressed Participants (N=7 Trials)

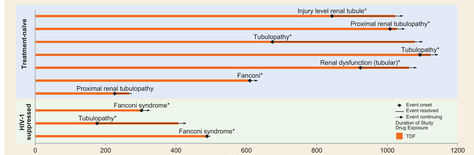


Differences between treatment groups in changes or % changes from baseline compared using Wilcoxon rank sum test or rank analysis of covariance (if baseline values needed to be adjusted), except treatment-emergent proteinuria (defined as ≥1 grade increase from baseline) which was compared using Fisher exact test.

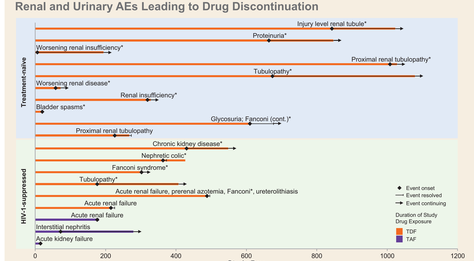
- Renal and urinary AEs: no differences in those initiating TAF or ABC or switching from ABC to TAF
  - Discontinuations: 3 of 6360 (TAF group) vs 0 of 1008 (ABC group), p=1.00; no PRT or Fanconi syndrome reported in either group
- TAF had a smaller decline in eGFR, total proteinuria, tubular proteinuria, and albuminuria than ABC in treatment-naive adults; virologically suppressed adults who switched to TAF had improvements in eGFR and total proteinuria, but no changes in tubular proteinuria or albuminuria
- These potentially novel findings favoring renal safety for TAF vs ABC were identified with the increased power of pooled data from multiple trials and are unadjusted for other antiretroviral drugs in the combinations studied
- DTG is a more potent inhibitor of OCT-2/MATE-1 (tubular secretion of creatinine) than BIC which may have driven the statistical differences in SCr and eGFR in the pooled analysis
- Clinical significance of the observed renal safety differences between TAF vs ABC requires further investigation

All Participants (N=26 Trials)

Development of PRT in Participants on TDF (n=10 of 2962)



Renal and Urinary AEs Leading to Drug Discontinuation



*Considered to be drug-related. PRT events listed as reported terms.

Conclusions

- This pooled analysis of 26 studies with >12,000 py of TAF exposure provided the statistical power to demonstrate a clear clinical renal safety advantage of TAF over TDF, consistent with biomarker differences in individual clinical trials
- PLH initiating or switching to TAF did not experience PRT and had significantly lower rates of renal discontinuations, compared with those on TDF
- As expected, the pooled biomarker analysis was consistent with the individual trials and favored renal safety of TAF vs TDF
- TAF's clinical renal safety profile (with statistically significant favorable renal biomarkers) is likely similar to ABC
- Long-term renal safety of TAF, TDF and ABC-containing regimens will continue to be monitored

References

1. Sax P, et al. Lancet 2015;385:2606-15. **2.** Hall AM, et al. Am J Kidney Dis.2011;57:773-80. **3.** Ray AS, et al. Antimicrob Agents Chemother. 2006;50:3297-3304. **4.** DHHS Guidelines. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. March 27, 2018. **5.** EACS Guidelines, www.eacsociety.org/files/guidelines_9.0-english.pdf. Accessed May 30, 2018. **6.** Arribas JR, et al. J Acquir Immune Defic Syndr 2017;75:215-8; **7.** Gallant JE, et al. J Acquir Immune Defic Syndr 2017;75:61-6. **8.** Mills A, et al. Lancet Infect Dis. 2016;16:43-52. **9.** Orkin C, et al. Lancet HIV 2017;4:e195-e204. **10.** DeJesus E, et al. Lancet HIV 2017;4:e205-e213.

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