Impact of Age and Medical Comorbidities on Renal Outcomes in the DISCOVER Trial

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Introduction

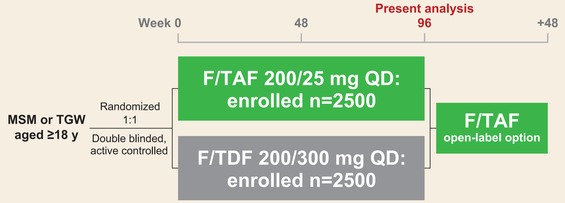
- Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are prodrugs of the antiretroviral nucleotide analog tenofovir (TFV)
  - TFV can cause proximal renal tubulopathy, including rare cases of acute kidney injury or Fanconi syndrome
  - TAF is associated with ~90% lower TFV exposures than TDF, resulting in less impact on renal function and fewer renal adverse events (AEs) when used for HIV treatment[1]
- DISCOVER (NCT02842086) is an ongoing, randomized, controlled trial comparing emtricitabine/TAF (F/TAF) with emtricitabine/TDF (F/TDF) for HIV pre-exposure prophylaxis (PrEP) in men who have sex with men (MSM) and transgender women (TGW)
- At the primary endpoint (when all participants reached 48 wk and half reached 96 wk) and Week 96, DISCOVER demonstrated that:
  - F/TAF was noninferior to F/TDF for HIV prevention[2,3]
  - F/TAF had a superior renal biomarker profile compared with F/TDF[2-4]

Objective

- To study Week-96 renal outcomes in DISCOVER participants receiving F/TAF or F/TDF who had demographic or medical characteristics predisposing to renal dysfunction, including older age, diminished baseline (BL) renal function, and medical comorbidities such as diabetes mellitus (DM) and hypertension (HTN)[5]

Methods

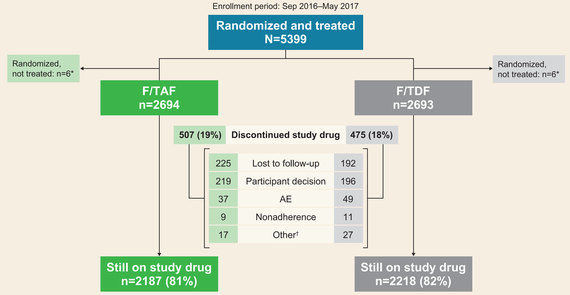
Study Design



- Eligibility: high sexual risk of HIV
  - 2+ episodes of condomless anal sex in past 12 wk, or rectal gonorrhea/chlamydia or syphilis in past 24 wk
  - HIV and hepatitis B virus negative, and estimated glomerular filtration rate by Cockcroft-Gault ($eGFR_{CG}$) ≥60 mL/min
  - Prior use of F/TDF for PrEP allowed
- Conducted in Europe and North America in cities/sites with high HIV incidence
- Safety assessments:
  - Renal AEs: investigator reported; categorized as study drug related if the investigator felt there was a reasonable possibility that the AE may have been caused by study drug
  - Renal function by $eGFR_{CG}$
  - Biomarkers of proximal tubular dysfunction, including urine β2-microglobulin (β2M):creatinine (Cr) and urine retinol-binding protein (RBP):Cr ratios

Results

Participant Disposition Through Week 96



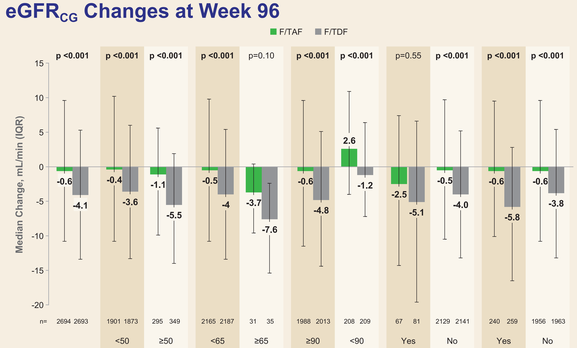
*Includes withdrew consent (n=8), HIV-1 infection (n=2), protocol violation (n=1), and investigator's discretion (n=1); †Includes investigator discretion (n=18), HIV infection (n=15), protocol violation (n=7), and death (n=4).

Baseline Characteristics

		F/TAF n=2694	F/TDF n=2693
Demographics	Median age, y (range)	34 (18–76)	34 (18–72)
	Age ≥50 y, n (%)	330 (12)	386 (14)
	Age ≥65 y, n (%)	33 (1)	36 (1)
	Race, n (%)		
	White	2264 (84)	2247 (84)
	Black*	240 (9)	234 (9)
	Asian	113 (4)	120 (4)
	Hispanic or Latinx, n (%)	635 (24)	683 (25)
	TGW, n (%)	45 (2)	29 (1)
Medical Characteristics	Median $eGFR_{CG}$, mL/min (IQR)	123 (105, 143)	121 (104, 142)
	$eGFR_{CG}$ <90 mL/min, n (%)	243 (9)	250 (9)
	History of DM, n (%)	79 (3)	89 (3)
	History of HTN, n (%)	282 (10)	298 (11)

*Includes mixed Black race. IQR, interquartile range.

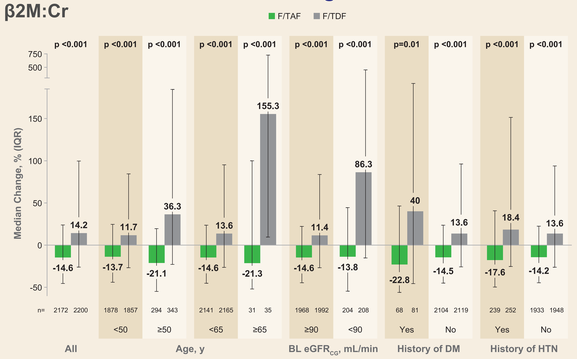
$eGFR_{CG}$ Changes at Week 96



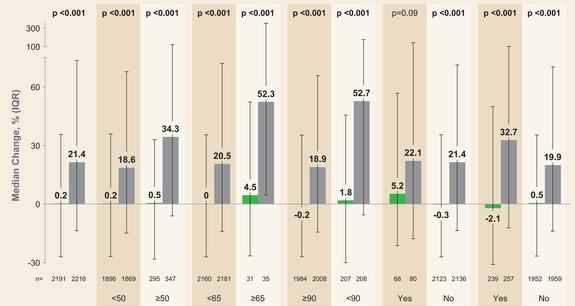
- F/TAF was associated with improvement or smaller decline in $eGFR_{CG}$ overall and in participants aged ≥50 y, or with BL $eGFR_{CG}$ <90 mL/min or history of HTN

Proximal Tubule Biomarker Changes at Week 96

β2M:Cr



RBP:Cr



- F/TAF was associated with improvements or smaller declines in biomarkers of proximal renal tubule function
- Renal biomarker differences were most pronounced in participants with age ≥50 or 65 y, baseline $eGFR_{CG}$ <90 mL/min, DM, or HTN

Drug-Related Renal Adverse Events Through Week 96

n (%)	F/TAF n=2694	F/TDF n=2693
Renal and urinary disorders	14 (0.5)	26 (1.0)
Proteinuria	8 (0.3)	9 (0.3)
Other urine abnormalities*	3 (0.1)	3 (0.1)
Acute kidney injury	1 (<0.1)	3 (0.1)
Renal impairment	0	4 (0.1)
Microalbuminuria	0	3 (0.1)
Urinary calculus	0	1 (<0.1)
Chronic kidney disease	0	1 (<0.1)
Dysuria	0	1 (<0.1)
Fanconi syndrome acquired	0	1 (<0.1)
Nephrotic syndrome	1 (<0.1)	0
Pollakiuria (polyuria)	1 (<0.1)	0
Renal colic	1 (<0.1)	0
Renal tubular necrosis	0	1 (<0.1)

*Includes glycosuria (n=1: F/TDF), hematuria (n=1: F/TAF), ketonuria (n=1: F/TAF), leukocyturia (n=1: F/TDF), urine abnormality (n=1: F/TAF), and abnormal urine odor (n=1: F/TDF).

Baseline Medical Characteristics of Participants With Drug-Related Renal AEs

	All (n=40)	F/TAF (n=14)	F/TDF (n=26)	p-Value
Median age, y (IQR)	41 (33, 51)	39 (33, 40)	44 (33, 52)	0.07
Median $eGFR_{CG}$, mL/min (IQR)	114.7 (91.0, 135.5)	130.1 (119.4, 144.1)	102.0 (86.4, 125.0)	0.017
Age ≥50 y, n (%)	11 (28)	1 (7)	10 (38)	0.037
$eGFR_{CG}$ <90 mL/min, n (%)	8 (20)	1 (7)	7 (27)	0.14
DM, n (%)	3 (8)	2 (14)	1 (4)	0.24
HTN, n (%)	9 (23)	3 (21)	6 (23)	0.91
Any: age, $eGFR_{CG}$, DM, or HTN, n (%)	18 (45)	5 (36)	13 (50)	0.39

- While many participants with drug-related AEs had ≥1 examined risk factor, 55% had none
- Participants taking F/TDF who developed drug-related AEs had lower baseline $eGFR_{CG}$ and were more likely to be aged ≥50 y

Conclusions

- Among DISCOVER participants with factors predisposing to renal dysfunction, F/TAF was associated with improvements or smaller declines in $eGFR_{CG}$ compared with F/TDF
  - Differences were statistically significant for all categories except age ≥65 y and DM, which was likely due to small numbers of participants
- F/TAF was associated with stable or improved proximal renal tubular function in all subgroups, whereas F/TDF was associated with worsening proximal tubular function
  - The magnitude of proximal tubular function differences was greatest in participants aged ≥50 y and those with baseline $eGFR_{CG}$ <90 mL/min
- While many participants who developed drug-related AEs had predisposing factors, the majority had none of the examined risk factors
- F/TAF had a more favorable impact on renal function overall and in participants with risk factors for kidney disease

References: 1. Gupta SK, et al. AIDS 2019;33:1455-65; 2. Mayer K, et al. Lancet 2020;396:239-54; 3. Ogbuagu O, et al. CROI 2020, *abstr* 92; 4. Mills A, et al. IDWeek 2019, oral 1962; 5. Nelson RG, et al. JAMA 2019;322:2104-14. **Acknowledgments:** We extend our thanks and appreciation to the DISCOVER study participants, their families, and the study investigators. This study was funded by Gilead Sciences, Inc.