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Renal Safety of Tenofovir Alafenamide in Patients at High Risk of Kidney Disease

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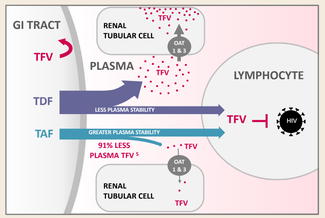
Background

- Risk factors for chronic kidney disease (CKD) in HIV people include older age, Black race, female sex, low CD4 cell count, diabetes, hypertension, dyslipidemia, renal impairment, and use of nephrotoxic agents[1-3]
- Tenofovir disoproxil fumarate (TDF) is a widely used antiretroviral for HIV infection that has been associated with an increased risk of CKD based on findings from cohort studies including the D:A:D[1,3-4]
- Due to a 91% lower plasma tenofovir level, tenofovir alafenamide (TAF) relative to TDF has demonstrated a significantly better renal safety profile and no discontinuations due to renal adverse events through 2 years in 2 randomized, double-blind studies (GS-US-292-0104 and GS-US-292-0111) comparing TAF to TDF, both co-formulated with elvitegravir, cobicistat, and emtricitabine as single-tablet regimens, E/C/F/TAF and E/C/F/TDF, respectively[5-6]
- Renal outcomes by CKD risk category in antiretroviral-naïve adults treated with E/C/F/TAF or E/C/F/TDF are described

Mechanism of Action
Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide



OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Methods

- Studies 104 and 111 are 2 Phase 3, international, double-blind, 144-week studies in which antiretroviral-naïve adults are randomized (1:1) to a single-tablet regimen of elvitegravir, cobicistat, and emtricitabine with TAF or TDF once daily
- Primary endpoints:
  - Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot analysis (12% non-inferiority margin)
  - Safety endpoints included changes in $eGFR_{CG}$, quantitative proteinuria, and adverse events
- A post-hoc analysis of renal outcomes by baseline CKD risk category was performed
  - Renal outcomes by CKD risk category included incident CKD, discontinuations due to renal adverse events, and changes in $eGFR_{CG}$.
    - CKD was defined as having post-baseline $eGFR_{CG}$ <60 mL/min and/or urine albumin to creatinine ratio (UACR) >30 mg/g for >3 months[7]
    - To account for the serum creatinine effect of cobicistat (i.e. ~10 mL/min decline in $eGFR_{CG}$ observed by Week 4), the incident CKD analysis set included only subjects with a baseline $eGFR_{CG}$ ≥70 mL/min, and UACR <30 mg/g
  - Additional endpoints included changes in quantitative proteinuria (urine protein [UPCR], urine albumin [UACR], urine retinol binding protein [RBPCR], and urine beta-2-microglobulin to creatinine ratios [B2MCR] and efficacy) by CKD risk category at Week 96

- **Analysis #1 by Number of CKD Risk Factors**
  - Risk factors for CKD: female sex, age ≥50 years, Black race, any NSAID use, CD4 <200 cells/μL, dyslipidemia, hypertension, and diabetes
  - **Analysis #1 CKD Risk Categories**
    - High risk (≥2 risk factors)
    - Low risk (≤1 risk factor)
- **Analysis #2 by D:A:D Risk Score**
  - A sensitivity analysis using the validated D:A:D CKD risk scoring method was performed and the findings compared to the results based on the number of CKD risk factors (above)[8,9]
  - **Analysis #2 D:A:D Risk Categories**
    - High (risk score: ≥5)
    - Medium (risk score: 0-4)
    - Low (risk score: <0)

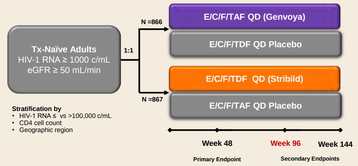
D:A:D Risk Score for CKD [8,9]

Subject Characteristics	CKD risk coefficient
Intravenous drug user	
No / Yes	0 / +2
HCV co-infection	
Negative / Positive	0 / +1
Age (years)	
≤35	0
>35 to ≤50	+4
>50 to ≤60	+7
>60	+10
Baseline eGFR (mL/min)[a]	
>60 to ≤70	+6
>70 to ≤90	0
>90	-6
Male / Female	0 / +1
Nadir CD4 count (cells/mm³)	
≤200 / >200	0 / -1
Hypertension [b]	
No / Yes	0 / +1
Prior CVD [b,c]	
No / Yes	0 / +1
Diabetes [b]	
No / Yes	0 / +2

a. Adjusted for body surface area.
b. As reported on medical history.
c. Myocardial infarction, invasive cardiovascular procedure, and/or stroke.

Study Design

Two Phase 3, international, randomized, double-blind, active-controlled studies



Stratification by
- HIV-1 RNA ≤ vs >100,000 c/mL
- CD4 cell count
- Geographic region

ClinicalTrials.gov Identifier: NCT01780506 and NCT01797445.

Conclusions

- Antiretroviral-naïve adults with both high and low risk for CKD treated with TAF had more favorable renal outcomes compared to those treated with TDF
  - Incident CKD through 2 years was 0.1% TAF vs 1.6% TDF
  - Incident CKD on TDF was observed in all CKD risk groups
    - There may be a graded increase in incident CKD on TDF (1%, 2%, and 5%, respectively) with increasing CKD risk
  - Treatment discontinuations due to renal AEs and changes in $eGFR_{CG}$ and quantitative proteinuria all favored TAF across CKD risk groups
    - Tubular proteinuria increased on TDF with increasing CKD risk, consistent with the emergence of a proximal renal tubulopathy (i.e. Fanconi Syndrome)
  - Adults on TAF and TDF maintained high rates of virologic suppression at Week 96
- These results further support the favorable renal safety profile and durable efficacy of TAF in populations with high and low risk for CKD

Results

Analysis #1 by Number of CKD Risk Factors

Baseline Risk Factors for CKD by Number of Risk Factors

	E/C/F/TAF n=866	E/C/F/TDF n=867
High risk for CKD (≥2 risk factors)	28% (246)	32% (274)
Low risk for CKD (≤1 risk factor)	72% (620)	68% (593)
Risk factors for CKD		
Black race	26%	25%
Female sex	15%	15%
Any NSAID use	16%	17%
Hypertension	14%	17%
CD4 cell count <200 cells/μL	13%	14%
Hyperlipidemia	11%	12%
Age ≥50 years	10%	13%
Diabetes	3%	5%

Renal Outcomes By Baseline CKD Risk

	High Risk for CKD [1]		Low Risk for CKD [2]	
	E/C/F/TAF n=246	E/C/F/TDF n=274	E/C/F/TAF n=620	E/C/F/TDF n=593
Median baseline $eGFR_{CG}$	115 mL/min	110 mL/min	117 mL/min	115 mL/min
Median change in $eGFR_{CG}$ at Week 4	-7 mL/min	-9 mL/min	-7 mL/min	-10 mL/min
Median change in $eGFR_{CG}$ at Week 96 [3,4]	**-1 mL/min**	**-5 mL/min**	**-2 mL/min**	**-8 mL/min**
Incident CKD [5]	0.4% (1)	1.8% (5)	0	1.5% (9)
Discontinuations due to renal AEs	0	1.8% (5) [6]	0	0.2% (1) [7]

1. High risk for CKD: ≥2 renal risk factors. 2. Low risk for CKD: ≤1 renal risk factor. 3. **P =0.002**. (High risk: TAF vs TDF). 4. **P <0.001** (Low risk: TAF vs TDF). 5. CKD defined as post-baseline $eGFR_{CG}$ <60 mL/min and/or UACR >30 mg/g for >3 months (with BL $eGFR_{CG}$ ≥70 mL/min and UACR <30 mg/g). TAF: isolated UACR elevation ([N=1], 38 year-old Black female with elevated UACR (36-73 mg/g) and $eGFR_{CG}$ >120 mL/min during study). TDF: isolated decreased $eGFR_{CG}$ (N =5), isolated UACR elevation (N =8), both decreased eGFR and UACR elevation (N =1). 6. Renal AEs: Elevated creatinine (N =1 [an incident CKD case]), Fanconi Syndrome (N =1), nephropathy (N =1), and renal failure (N =2). 7. Renal AE: Decreased GFR (N =1 [an incident CKD case]).

Analysis #2 by D:A:D Risk Score

Baseline Risk Factors for CKD by D:A:D Risk Scores

	E/C/F/TAF n=860 [a]	E/C/F/TDF n=861 [a]
High risk for CKD (risk score: ≥5)	7% (56)	10% (84)
Medium risk for CKD (risk score: 0-4)	12% (107)	15% (129)
Low risk for CKD (risk score: <0)	81% (697)	75% (648)
Risk factors for CKD		
IV drug users / HCV co-infection	1% / 0%	1% / <1%
Age (years)		
≤35 / >35 to ≤50	59% / 34%	52% / 37%
>50 to ≤60 / >60	6% / 2%	9% / 2%
Baseline $eGFR_{CG}$ (mL/min) [b]		
>60 to ≤70	1%	2%
>70 to ≤90	16%	20%
>90	82%	78%
Female sex	15%	15%
CD4 ≤200 cells/mm³	13%	14%
Hypertension / CVD / Diabetes	14% / 1% / 3%	17% / 2% / 5%

a. Unable to determine CKD risk category for 6 subjects due to missing renal risk data.
b. Adjusted for body surface area.

Renal Outcomes By D:A:D Risk Scores

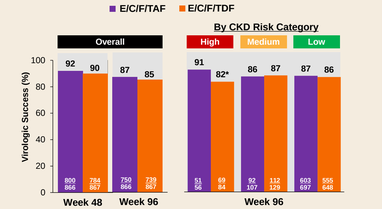
	High Risk for CKD [1]		Medium Risk for CKD [2]		Low Risk for CKD [3]	
	E/C/F/TAF n=56	E/C/F/TDF n=84	E/C/F/TAF n=107	E/C/F/TDF n=129	E/C/F/TAF n=697	E/C/F/TDF n=648
Median baseline $eGFR_{CG}$	88 mL/min	87 mL/min	98 mL/min	100 mL/min	121 mL/min	120 mL/min
Median change in $eGFR_{CG}$ at Week 4	-3 mL/min	-7 mL/min	-4 mL/min	-8 mL/min	-8 mL/min	-11 mL/min
Median change in $eGFR_{CG}$ at Week 96 [4,5]	**2 mL/min**	**-6 mL/min**	**5 mL/min**	**-7 mL/min**	**-3 mL/min**	**-8 mL/min**
Incident CKD [6]	0	**4.8%** (4)	0	**2.3%** (3)	0.1% (1)	**1.1%** (7)
Discontinuations due to renal AEs	0	2.4% (3) [7]	0	0.8% (3) [8]	0	0.7

1. CKD risk score ≥5. 2. CKD risk score: 0-4. 3. CKD risk score: <0. 4. **P =0.004** (High risk: TAF vs TDF). 5. **P <0.001** (Low risk: TAF vs TDF). 6. CKD defined as post-baseline $eGFR_{CG}$ <60 mL/min and/or UACR >30 mg/g for >3 months (with BL $eGFR_{CG}$ ≥70 mL/min and UACR <30 mg/g). TAF: isolated UACR elevation ([N =1], 38 year-old Black female with elevated UACR (36-73 mg/g) and $eGFR_{CG}$ >120 mL/min during study). TDF: isolated decreased $eGFR_{CG}$ (N =5), isolated UACR elevation (N =8), both decreased $eGFR_{CG}$ and UACR elevation (N =1). 7. Renal AEs: Fanconi Syndrome (N =1, nephropathy (N =1), renal failure (N =1). 8. Renal AEs: Decreased $eGFR_{CG}$ (N =1 [an incident CKD case]), elevated creatinine (N =1 [an incident CKD case]), renal failure (N =1).

Incident CKD: 0.1% (1) TAF vs 1.6% (14) TDF

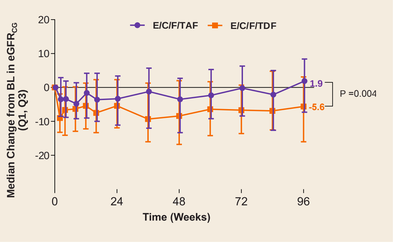
In the E/C/F/TDF arm, 1 Fanconi Syndrome in the high risk group led to discontinuation

Efficacy by D:A:D CKD Risk Category
HIV-1 RNA <50 copies/mL at Week 96

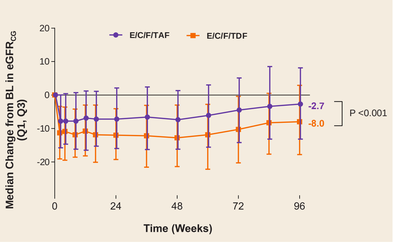


* Higher rates of E/C/F/TDF discontinuations due to AEs (5% vs 2%) and non-virologic reasons (7% vs 2%) led to a lower rate of virologic success.

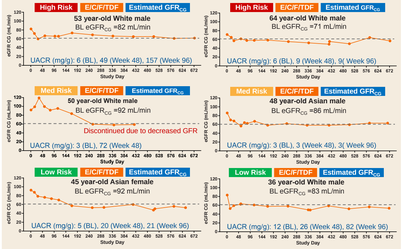
High Risk for CKD
Changes in $eGFR_{CG}$ Through Week 96



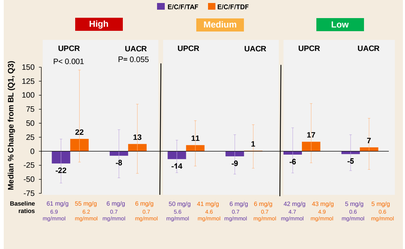
Low Risk for CKD
Changes in $eGFR_{CG}$ Through Week 96



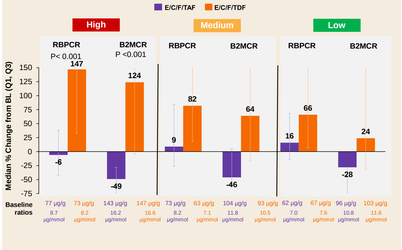
Incident CKD on TDF
Defined by Post-Baseline $eGFR_{CG}$ <60 mL/min for >3 Months



Changes (%) in Proteinuria and Albuminuria at Week 96



Changes (%) in Tubular Proteinuria at Week 96



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