

ARV Therapies and Therapeutic Strategies

REPORTING ON IAS 2015

Comprehensive Expert Review and Discussion of Key Presentations

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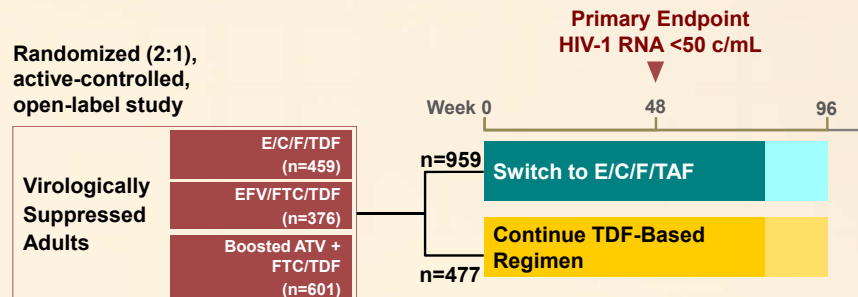
Switching From a Tenofovir Disoproxil Fumarate (TDF)-Based Regimen to a Tenofovir Alafenamide (TAF)-Based Regimen: Data in Virologically Suppressed Adults Through 48 Weeks of Treatment

Anthony Mills, Jaime Andrade-Villanueva, Giovanni DiPerri, Jan Van Lunzen, Ellen Koenig, Richard Elion, Matthias Cavassini, Jose Valdez-Madruga, Jason Brunetta, David Shamblaw, Edwin DeJesus, Andrew Plummer, YaPei Liu, and Scott McCallister

Abstract TUAB0102

Switch to E/C/F/TAF in Virologically Suppressed Adults

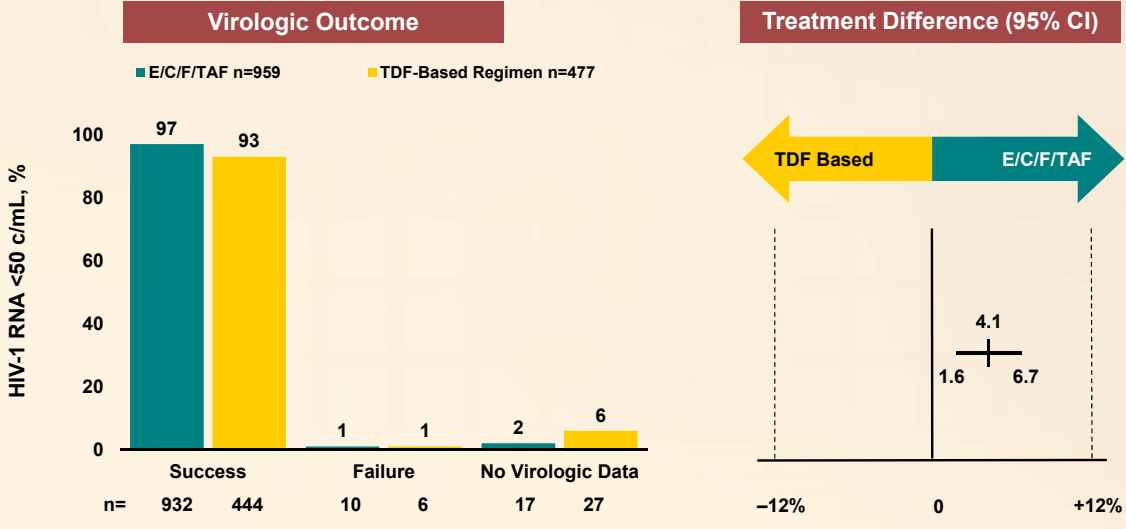
- ❖ All patients
 - ◆ HIV-1 RNA <50 copies/mL for ≥96 weeks on stable TDF-based regimen
 - ◆ Estimated GFR >50 mL/min
- ❖ E/C/F/TAF = EVG 150 mg, COBI 150 mg, FTC 200 mg, TAF 10 mg
- ❖ E/C/F/TDF = EVG 150 mg, COBI 150 mg, FTC 200 mg, TDF 300 mg



*Boosted by RTV or COBI

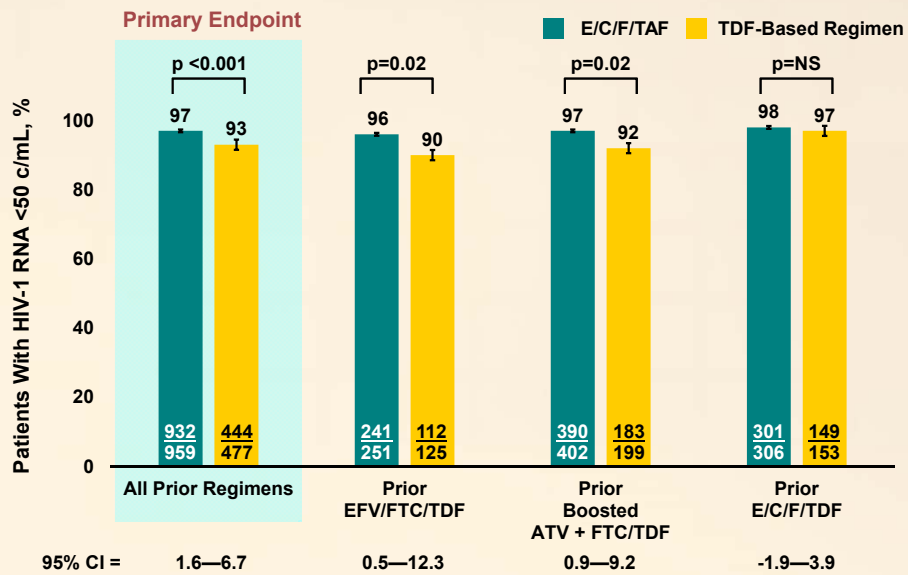
Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

Switch to E/C/F/TAF in Suppressed Adults: Results



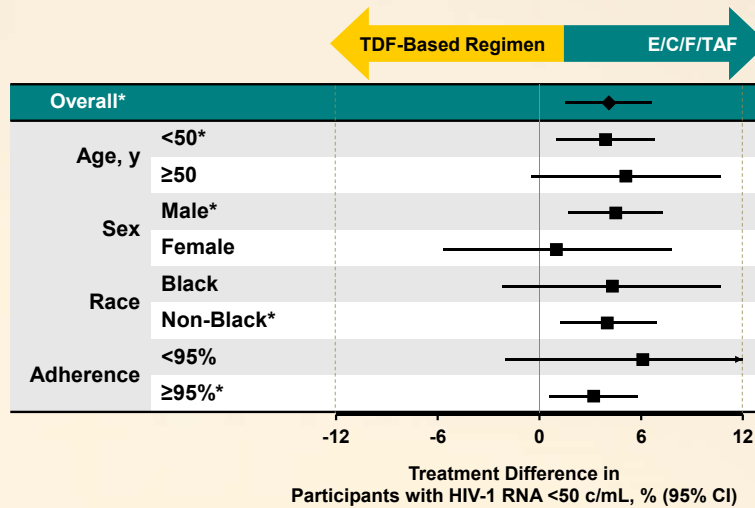
Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

Switch to E/C/F/TAF in Suppressed Adults: Virologic Outcome by Prior Treatment



Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

GS-US-292-0109 Virologic Outcome, Differences by Subgroup



*Statistically significant difference favoring E/C/F/TAF treatment.

Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

GS-US-292-0109 AEs Leading to Discontinuation

	E/C/F/TAF n=959	TDF-Based Regimen n=477
Participants %	0.9	2.5
Renal Events	<ul style="list-style-type: none"> Acute renal failure[†] Interstitial nephritis[‡] 	<ul style="list-style-type: none"> Chronic kidney disease Elevated serum creatinine Fanconi syndrome, mild jaundice Increased creatinine Nephretic colic (nephrolithiasis)
All Other Events	<ul style="list-style-type: none"> Depression Leg swelling, impaired concentration Memory loss, speech disturbance, lack of motivation Nausea, vomiting, headache Panic attack Reiter syndrome Suicide attempt 	<ul style="list-style-type: none"> Abnormal dreams Depression, insomnia, irritability Depression, insomnia, nightmares Elevated bilirubin Icterus (n=2) Increased forgetfulness

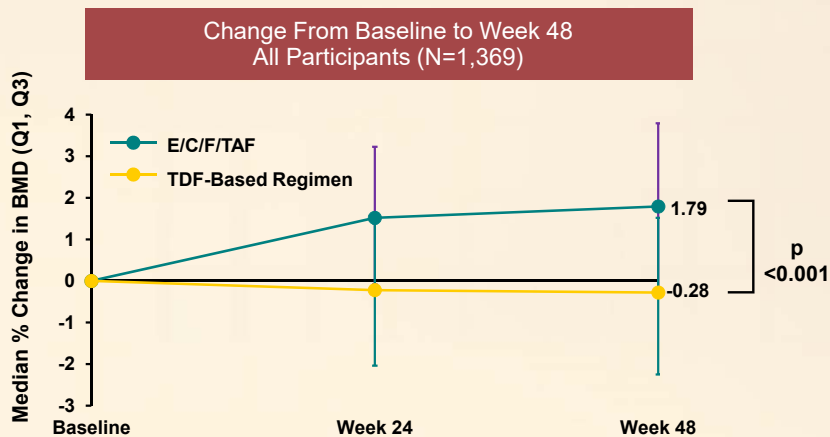
[†]After cancer chemotherapy, participant hospitalized with neutropenia, sepsis, and multi-system organ failure

[‡]Recurrent hematuria on treatment, subsequent off-treatment diagnosis of Hodgkin's Lymphoma

Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

GS-US-292-0109 DXA Scan Results: Spine BMD

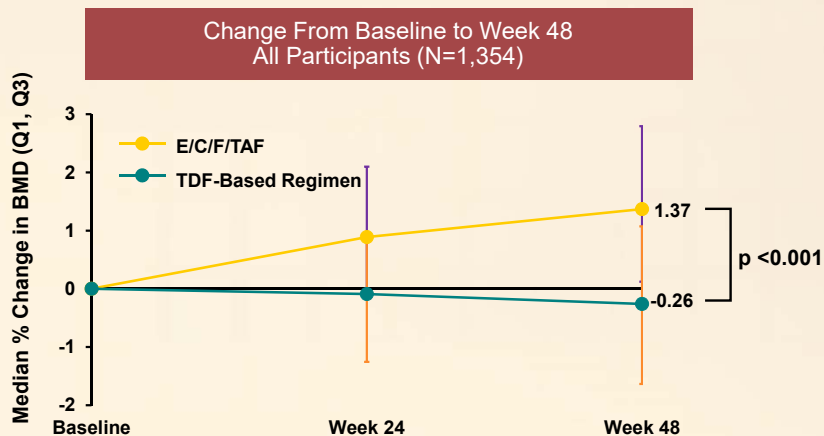
- ❖ Regardless of prior treatment regimen, differences between arms were statistically significant
- ❖ More than 2% difference between the arms at Week 48



Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

GS-US-292-0109 DXA Scan Results: Hip BMD

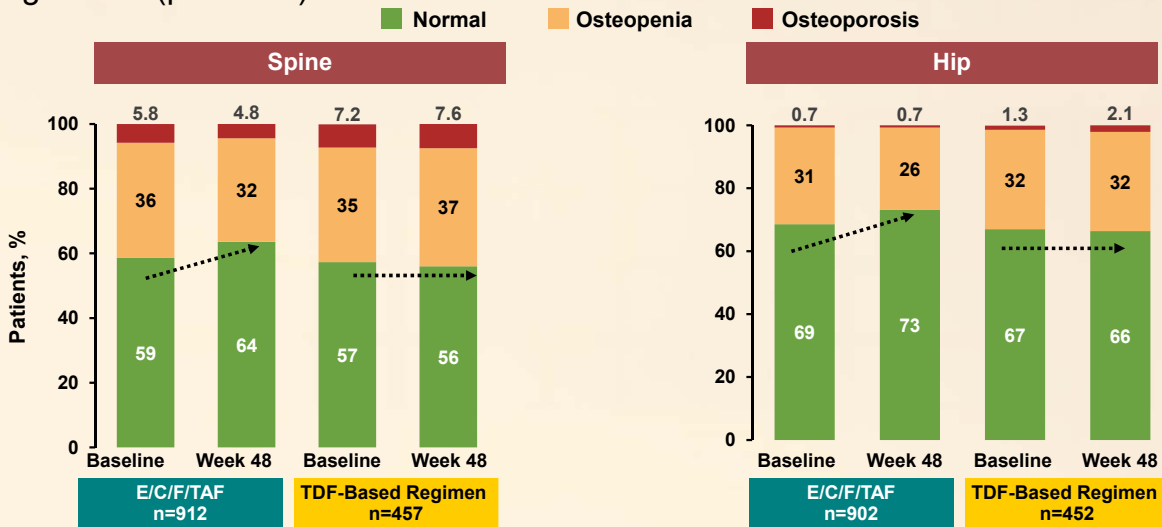
- ❖ Regardless of prior treatment regimen, differences between arms were statistically significant
- ❖ More than 1.6% difference between arms at Week 48



Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

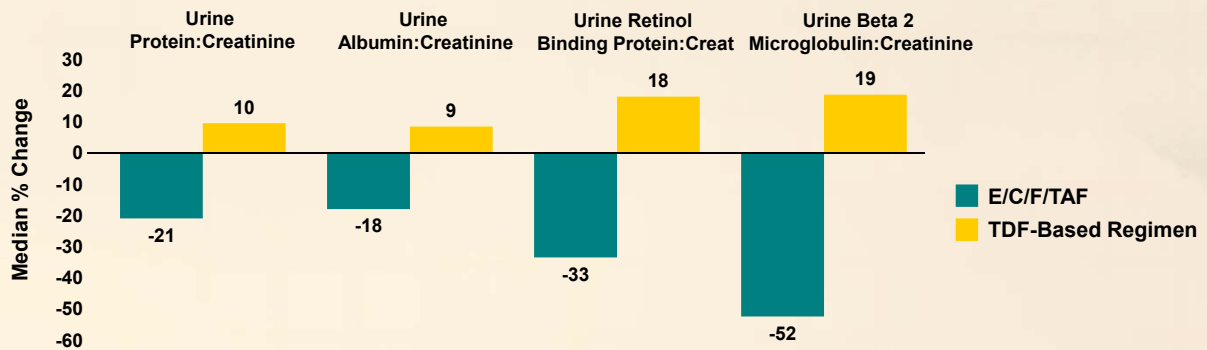
GS-US-292-0109 Change in Diagnosis of Osteopenia or Osteoporosis (Defined by T-Score)

- ❖ Differences between E/C/F/TAF and TDF-based regimens were statistically significant ($p < 0.001$)



Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

Switch to E/C/F/TAF in Suppressed Adults: Effect on Tubular Proteinuria



- ❖ Statistically significant improvements for participants who switched from either E/C/F/TDF or from boosted ATV + FTC/TDF
 - ◆ Serum creatinine ($p < 0.001$); eGFR ($p < 0.001$)
 - ◆ Fractional excretion of phosphate, FEPO₄ ($p = 0.05$); fractional excretion of uric acid, FEUA ($p < 0.001$)
- ❖ Changes began by Week 2 and persisted to Week 48

Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

Week 48 Conclusions

- ❖ Study GS-292-0109 is the largest randomized switch study conducted in HIV-positive virologically suppressed adults
- ❖ Participants who switched to E/C/F/TAF were significantly more likely to maintain virologic success
 - ◆ Had significant improvements in spine and hip BMD
 - ◆ Had significant reductions in osteopenia/osteoporosis
 - ◆ Had significant improvements in proteinuria and other markers of renal function

Mills A, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0102.

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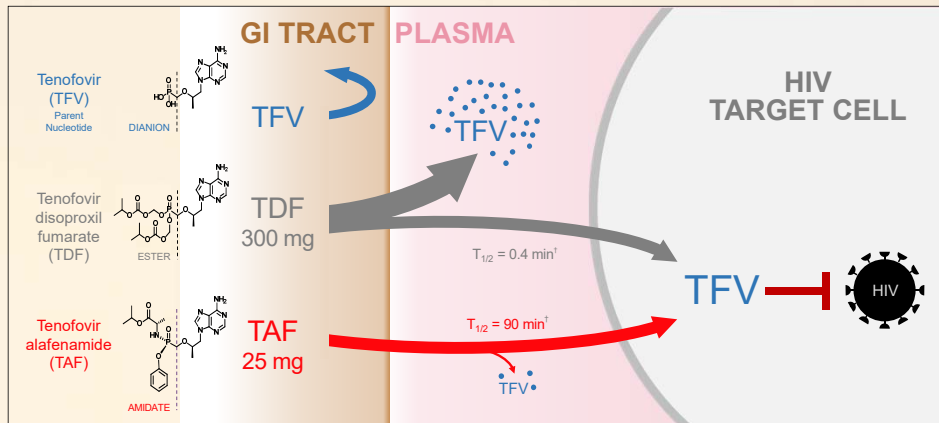
Subjects with Renal Impairment Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide Have Improved Renal and Bone Safety through 48 Weeks (Study GS-US-292-0112)

Samir K. Gupta, Anton Pozniak, Jose Arribas, Frank A. Post, Mark Bloch, Joseph Gathe, Paul Benson, Joseph Custodio, Michael Abram, Xuelian Wei, Andrew Cheng, Scott McCallister, Marshall W Fordyce

Abstract TUAB0103

Tenofovir Alafenamide (TAF): Novel Prodrug of Tenofovir

- ❖ 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV



[†] $T_{1/2}$ based on in vitro plasma data.

1. Lee W et al. Antimicrob Agents Chemo 2005;49(5):1898-1906.
 2. Birkus G et al. Antimicrob Agents Chemo 2007;51(2):543-550.
 3. Babusis D, et al. Mol Pharm 2013;10(2):459-66.
 4. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-5. 5. Sax P, et al. JAIDS 2014. 2014;67(1):52-8. 6. Sax P, et al. Lancet 2015;385:2606-15.
- Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

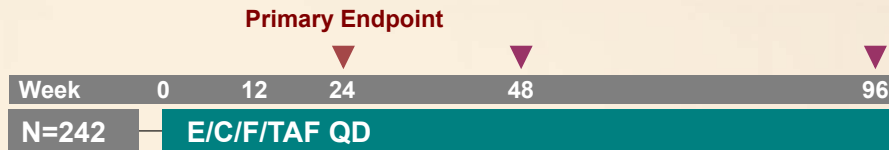
Background

- ❖ GS-US-292-0112 is an ongoing, single-arm, open-label Phase 3 study of HIV-1-infected participants with mild-moderate renal impairment (eGFR_{CG} 30-69 mL/min) who switched to E/C/F/TAF
- ❖ In the overall cohort, there were no changes in actual GFR, but there were reductions in total and tubular proteinuria and improvements in bone mineral density¹
- ❖ We present today the 48-week analysis of renal and bone safety markers in the two subgroups of participants on TDF-and non-TDF-containing regimens before switching to E/C/F/TAF

1. Pozniak A, et al. CROI 2015. Abstract 795

Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Study GS-US-292-0112 – Switch to FTC/TAF in Subjects with Renal Dysfunction (Stable eGFR CG 30–69 mL/min): Design



- ❖ Phase 3, 96-week, multicenter, open-label study of virologically suppressed adults switching from TDF- or non-TDF-containing regimens to E/C/F/TAF
- ❖ Eligibility: stable eGFR_{CG} (30–69 mL/min)
- ❖ Primary endpoint: change from baseline in eGFR at Week 24
 - ◆ Actual GFR assessed with iohexol clearance in a participant subset
- ❖ Week 48 data are presented here by pre-switch TDF use (within-group comparisons, not between group comparisons)

Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Study GS-US-292-0112 - Switch to FTC/TAF in Subjects with Renal Dysfunction (Stable eGFR CG 30–69 mL/min): Baseline Characteristics

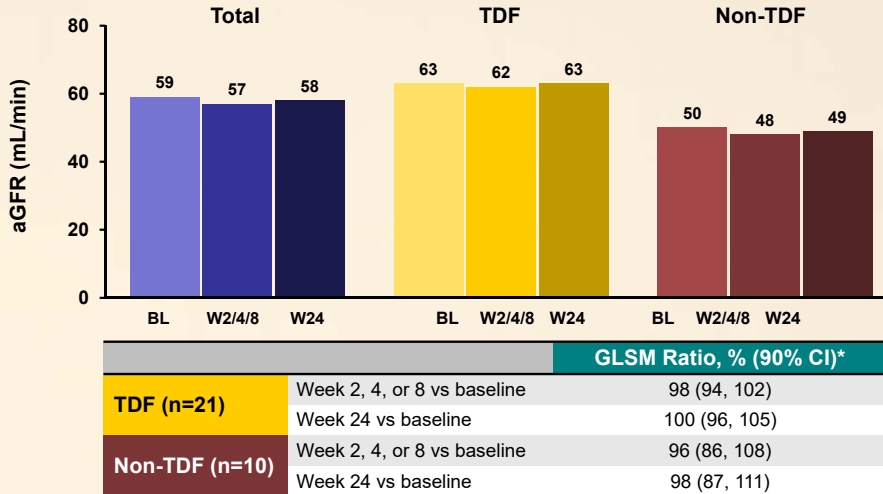
Primary Endpoint

Week	0	12	24	48	96
N=242	E/C/F/TAF QD				

	Total N=242	TDF n=158	Non-TDF n=84
Median age, years	58	59	58
≥ 65 years, %	26	22	33
Female, %	21	23	17
Black or African descent, %	18	22	12
Median CD4 count, cells/μL	632	661	585
Hypertension, %	40	34	49
Diabetes, %	14	13	14
Median eGFR _{CG} , mL/min	56	58	53
eGFR _{CG} ≥60 mL/min, %	34	40	24
Dipstick proteinuria, %			
Grade 1	23	27	16
Grade 2	10	10	10
Grade 3-4	0	0	0

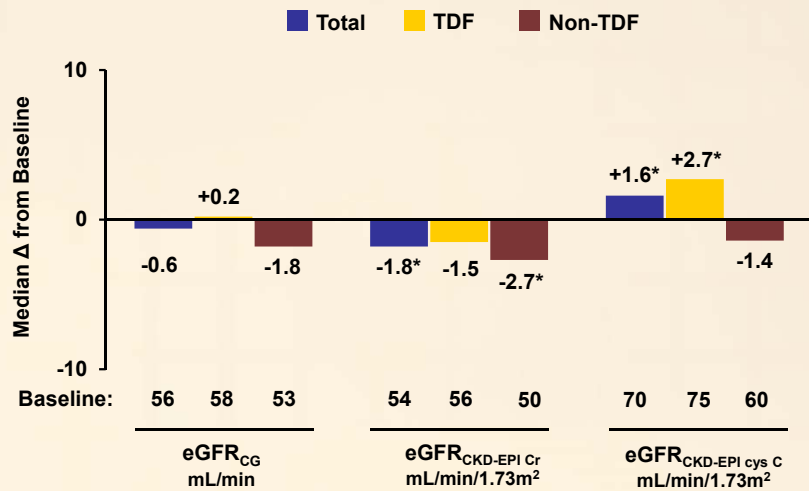
Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Switch to FTC/TAF in Pts with Renal Dysfunction: Actual GFR by Iohexol Clearance (1^o Endpoint)



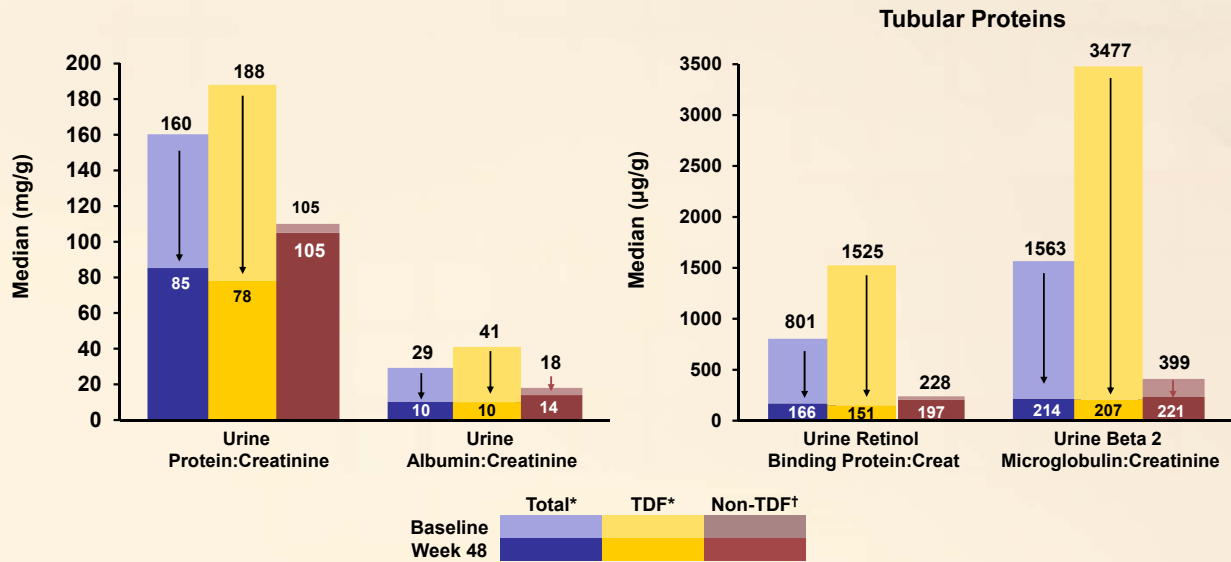
*Lack of alteration boundary: 80–125% (GLSM).
 Actual GFR unaffected by E/C/F/TAF switch, regardless of previous regimen
 Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Estimated GFR: Change from Baseline to Week 48



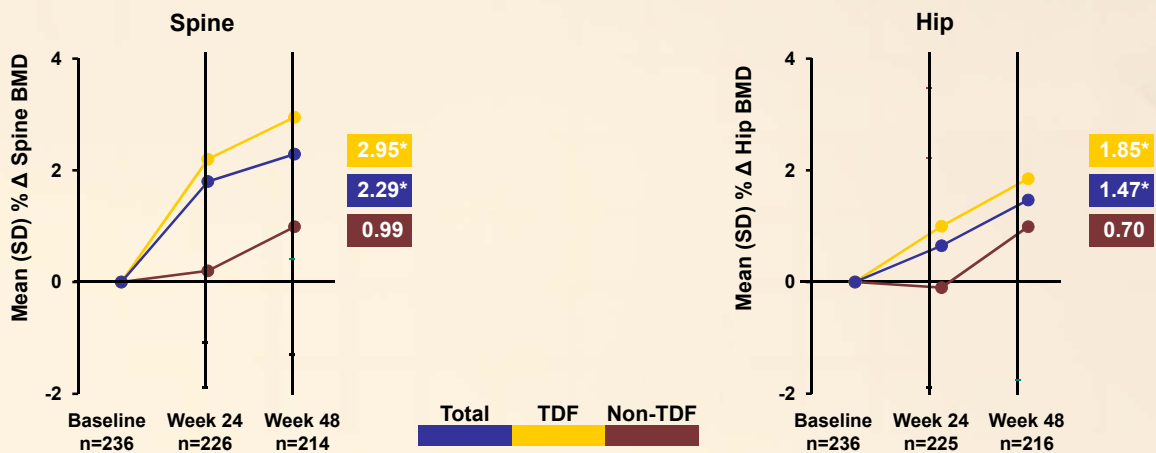
*p<0.05 by two-sided Wilcoxon signed-rank test.
 Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Switch to FTC/TAF in Pts with Renal Dysfunction: Proteinuria From Baseline to Week 48



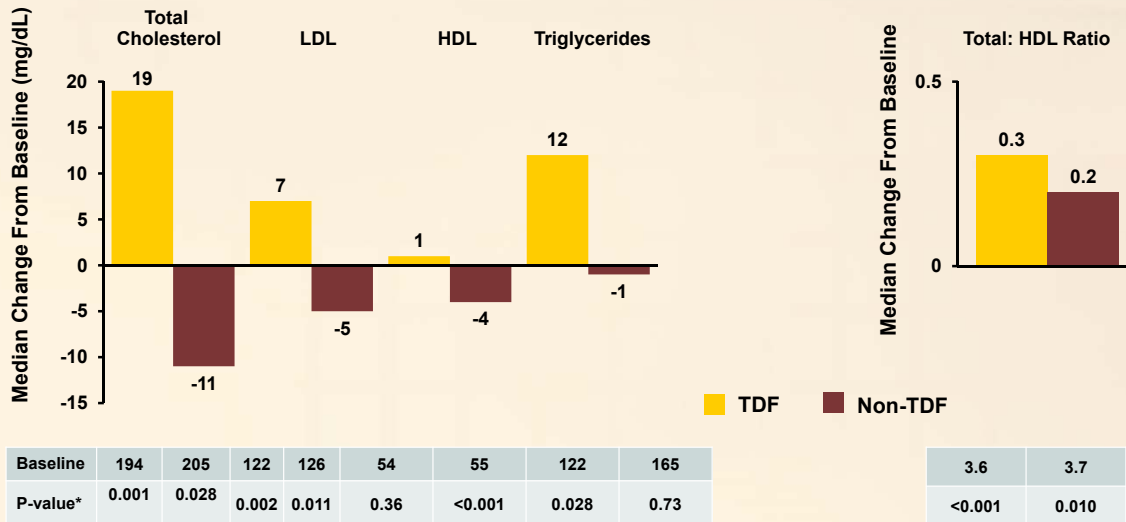
*All Total and TDF changes statistically significant; †all non-TDF changes not statistically significant.
Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Switch to FTC/TAF in Pts with Renal Dysfunction: Change in BMD from Baseline to Week 48



*p<0.05 by two-sided Wilcoxon signed-rank test.
Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Switch to FTC/TAF in Pts with Renal Dysfunction: Fasting Lipids at Week 48



*Wilcoxon signed-rank test.

Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.

Conclusions

- ❖ Participants on TDF at time of switch had
 - ◆ No change in actual GFR
 - ◆ Significant improvements in urinary markers of renal function
 - ◆ Significant improvements in BMD
 - ◆ Significant increases in lipids
 - ◆ Consistent with independent effect of circulating TFV on reducing cholesterol levels
- ❖ Participants not on TDF at time of switch had
 - ◆ No changes in actual GFR
 - ◆ Stable urinary markers of renal function and BMD
 - ◆ Significant decreases in cholesterol fractions
- ❖ These 48 week data support the renal and bone safety of once daily, single-tablet E/C/F/TAF for adults with HIV and renal impairment (eGFR_{CG} 30–69 mL/min)

Gupta S, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUAB0103.