Efficacy and Safety of Tenofovir Alafenamide (TAF) Versus Tenofovir Disoproxil Fumarate (TDF) in Treatment-Naïve Asian Adults: Week 144 results

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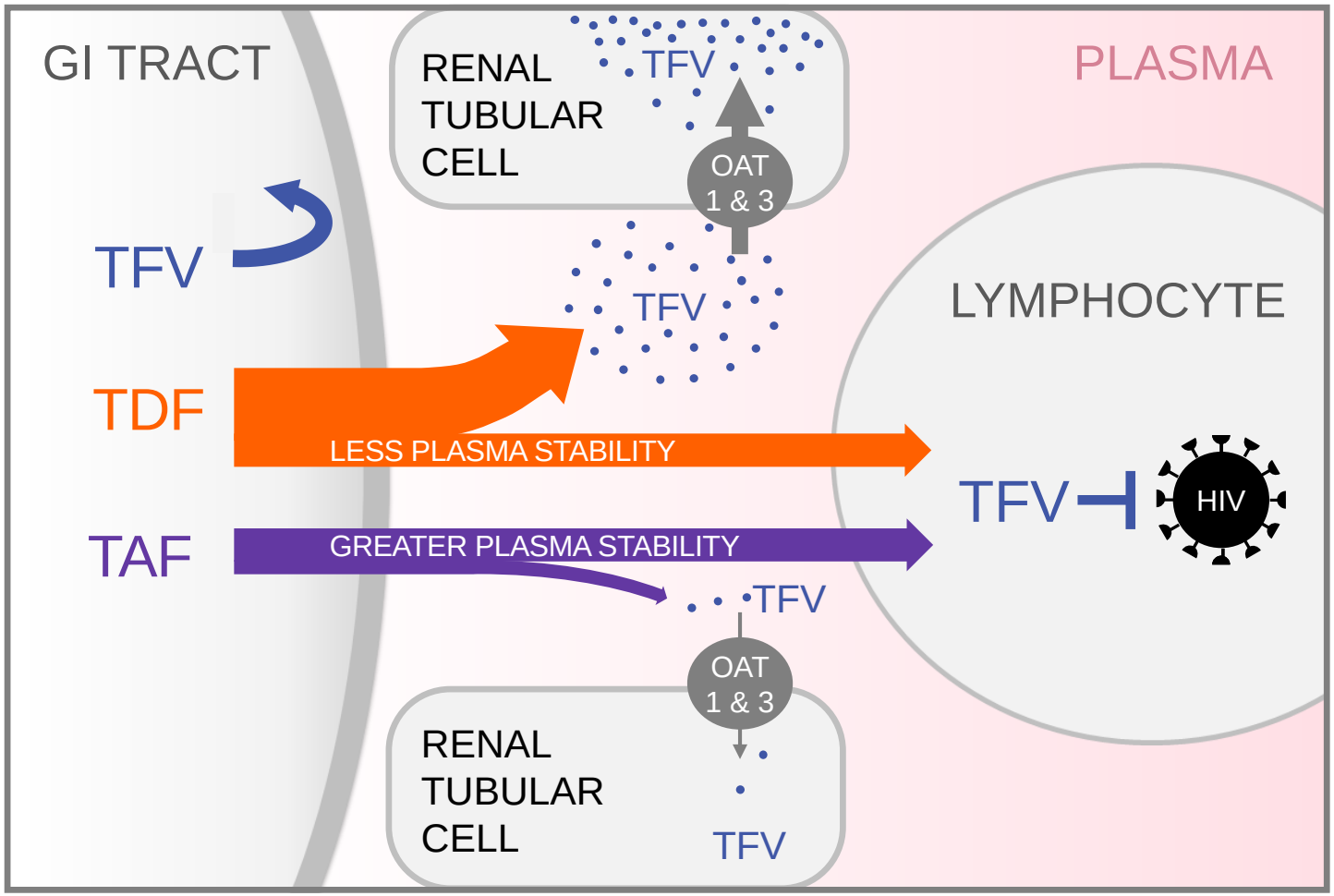
Introduction

- There are limited long term data on the efficacy and safety of contemporary antiretroviral regimens in HIV-infected Asian adults
- The Week 144 efficacy and safety of elvitegravir 150mg, cobicistat 150mg and emtricitabine 200mg (E/C/F), co-formulated with tenofovir alafenamide (TAF) 10mg or tenofovir disoproxil fumarate (TDF) 300mg in treatment-naïve adults from 2 randomized, double-blind phase 3 clinical trials (Studies 104 and 111) have been reported[1]
  - TAF has non-inferior antiviral efficacy to TDF[2]
  - Due to >90% reduction in plasma tenofovir (TFV) levels, TAF has an improved renal and bone safety profile relative to TDF[2]
- Previously, we described Week 96 efficacy and safety of E/C/F/TAF and E/C/F/TDF in HIV-infected Asian adults enrolled in Studies 104 and 111*
- Here we now describe efficacy and safety of these two guideline recommended regimens in Asian adults through Week 144

*Kim YS et al. Korea Society for AIDS, 2017. Poster # P-31

Prodrug Pharmacology

Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide



TAF results in >90% lower TFV plasma levels[2,3,4]

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

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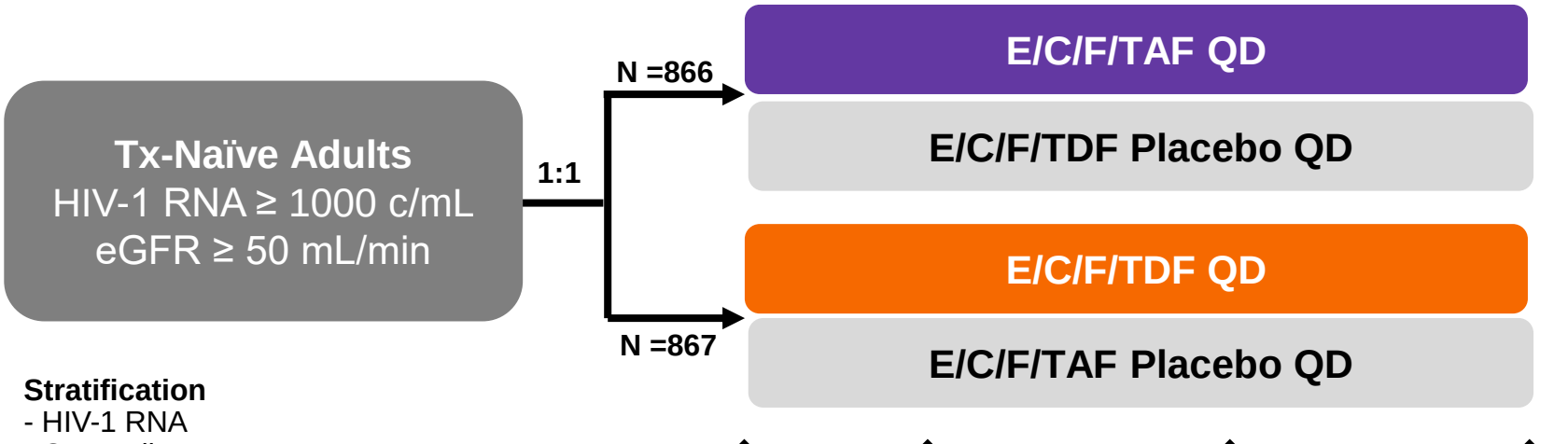
Study Design



Stratification
- HIV-1 RNA
- CD4 cell count
- Geographic region

GS-US-292-0104 was conducted in North America, Europe, Australia and Asia

GS-US-292-0111 was conducted in North America, Europe, and Latin America

- The primary endpoint of the main study was HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot algorithm
- The primary analysis compared efficacy by treatment with a non-inferiority margin of 12%

Asian and Non-Asian Sub-Analysis

ClinicalTrials.gov Identifier: NCT01780506 and NCT01797445

QD=once daily

‡

Methods

- In Studies 104 and 111, treatment-naïve adults (N=1,733) with HIV-1 RNA ≥1,000 copies/mL, estimated glomerular filtration rate by Cockcroft-Gault ($eGFR_{CG}$) ≥50 mL/min, and genotypic sensitivity to elvitegravir, emtricitabine and tenofovir disoproxil fumarate were randomized (1:1) to initiate E/C/F/TAF or E/C/F/TDF, and followed for 144 weeks

- This sub-analysis examines the efficacy and safety of E/C/F/TAF compared to E/C/F/TDF in Asian and non-Asian adults
  - At study entry, participants self-identified (on an enrollment questionnaire) as Asian or non-Asian (White, Black, American Indian/Alaskan, native Hawaiian/Pacific Islander)
  - This study was not randomized by Asian versus Non-Asian race

‡

Methods

- Key endpoints for this race sub-analysis included:
  - **Virologic outcome (HIV-1 RNA <50 copies/mL) at Week 144**
  - Changes in CD4 cell count
  - Adherence rates by pill count
  - **Adverse events (AEs) and discontinuation due to AEs**
  - **Changes in eGFR$_{CG}$**
  - **Changes in quantitative proteinuria**
    - Urine protein to creatinine ratio (UPCR), urine retinol binding protein to creatinine ratio (RBP:CR), and urine beta-2-microglobulin to creatinine ratio (β2M:CR)
  - Changes in spine and hip bone mineral density (BMD)
  - Changes in fasting lipids

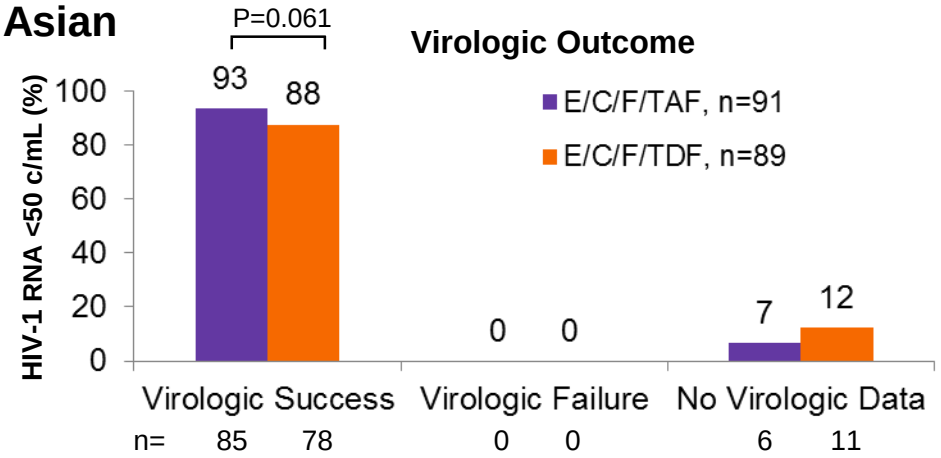
‡

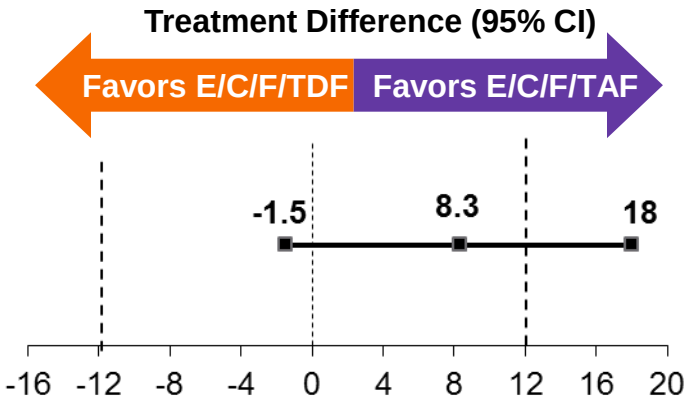
Baseline Characteristics

	Asian		Non-Asian	
	E/C/F/TAF n=91	E/C/F/TDF n=89	E/C/F/TAF n=775	E/C/F/TDF n=778
Median age, years	30	31	33	35
Male	55%	64%	88%	88%
Geography: Ex-US	89%	83%	33%	34%
Median Body Mass Index, kg/m^2	22	22	25	25
Median HIV-1 RNA, log_{10} copies/mL	4.58	4.75	4.57	4.57
>100,000 copies/mL	26%	33%	22%	21%
Median CD4 cell count, cells/μL	340	336	417	417
<200 cells/μL	15%	17%	13%	13%
Median $eGFR_{CG}$, mL/min	109	105	117	116
Dipstick proteinuria (1+ to 4+)	8%	8%	10%	10%
Diabetes mellitus	1%	1%	3%	5%
Hypertension	3%	2%	15%	19%
Median total cholesterol to HDL ratio	3.5	3.7	3.6	3.6

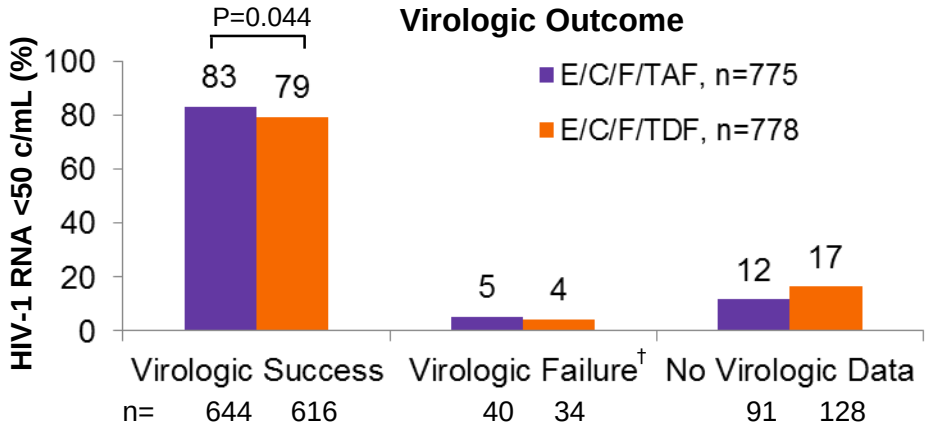
Virologic Outcome (HIV-1 RNA <50 c/mL) at Week 144

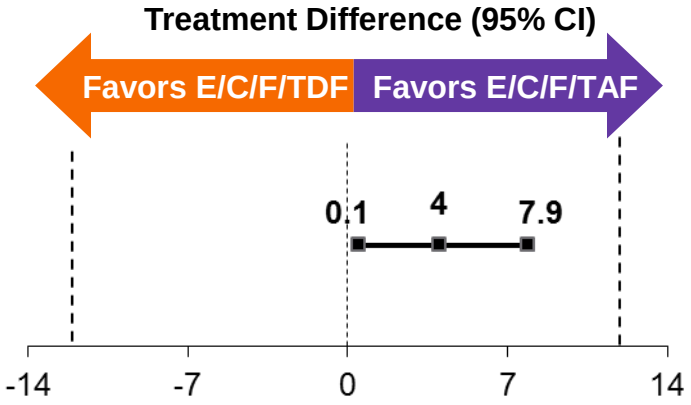
Asian





Non-Asian





†Emergent resistance in non-Asians was 1.2% E/C/F/TAF vs 0.9% E/C/F/TDF[5]

CI, confidence interval

‡

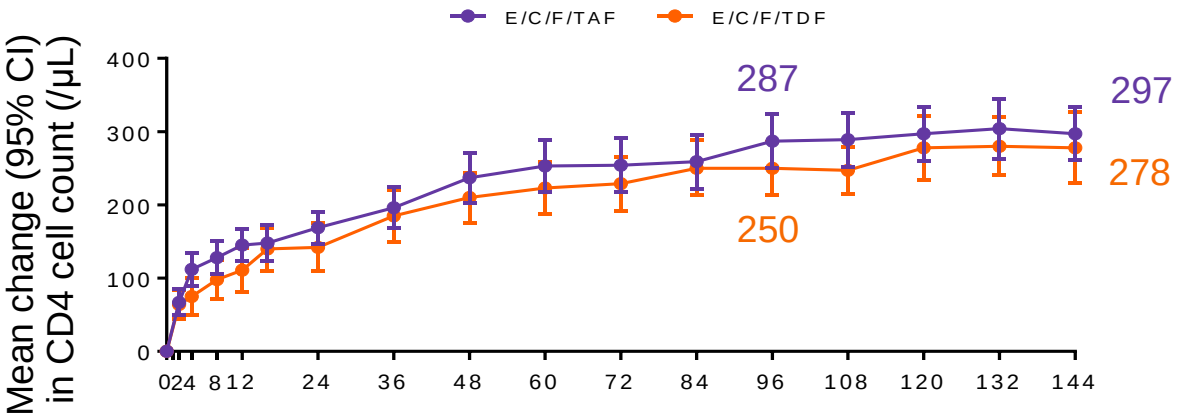
Adherence Rate by Pill Count up to Week 144

	Asian		Non-Asian	
	E/C/F/TAF n=91	E/C/F/TDF n=89	E/C/F/TAF n=775	E/C/F/TDF n=778
Mean adherence rate	99%	99%	96%	96%
Adherence rate of ≥95%*	91%	92%	73%	74%

*Differences between E/C/F/TAF and E/C/F/TDF in mean adherence rate and the proportion of participants with an overall adherence rate of ≥95% within the same racial group were not statistically different.

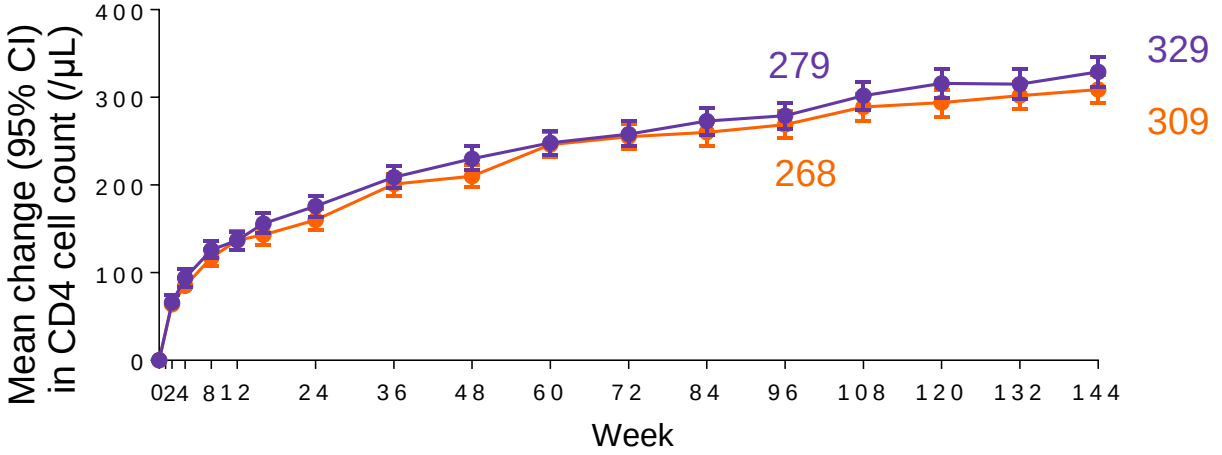
Changes in CD4 Count through Week 144

Asian



Mean baseline CD4 cell counts: 360 /µL for E/C/F/TAF and 359/µL for E/C/F/TDF

Non-Asian



Mean baseline CD4 cell counts: 360/µL for E/C/F/TAF and 359/µL for E/C/F/TDF

Adverse Events through Week 144

	Asian		Non-Asian	
	E/C/F/TAF n=91	E/C/F/TDF n=89	E/C/F/TAF n=775	E/C/F/TDF n=778
Adverse events in ≥ 15% of participants in either group, %*				
Nasopharyngitis	23%	14%	13%	14%
Upper respiratory tract infection	20%	15%	20%	20%
Nausea	14%	18%	18%	19%
Diarrhea	13%	14%	25%	26%
Headache	11%	11%	20%	16%

*Adverse Events (AEs) include all grades, regardless of relatedness to study drugs.

‡

Adverse Events Leading to Study Drug Discontinuation

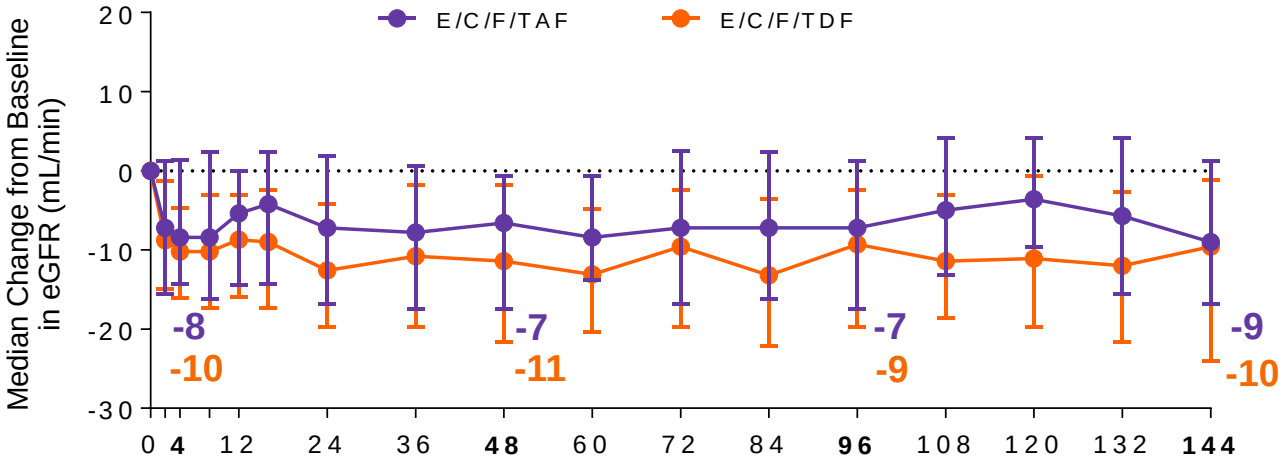
	Asian		Non-Asian	
	E/C/F/TAF n=91	E/C/F/TDF n=89	E/C/F/TAF n=775	E/C/F/TDF n=778
Any grade 3 or 4 adverse events (AE), %	2%	2%	2%	2%
Discontinuations due to AE, % (n)	1% (1)	2% (2)	1% (10)	4% (27)
Renal discontinuations, n	0	0	0	12*

* Renal tubular disorder (3), renal failure (2), glomerular filtration rate decreased (1), nephropathy (1), Fanconi Syndrome acquired and glycosuria (1), proteinuria (1), SCr increased (2), Bladder spasm (1). P<0.001. Details on 12 renal AEs leading to discontinuation of E/C/F/TDF have been presented.[6]

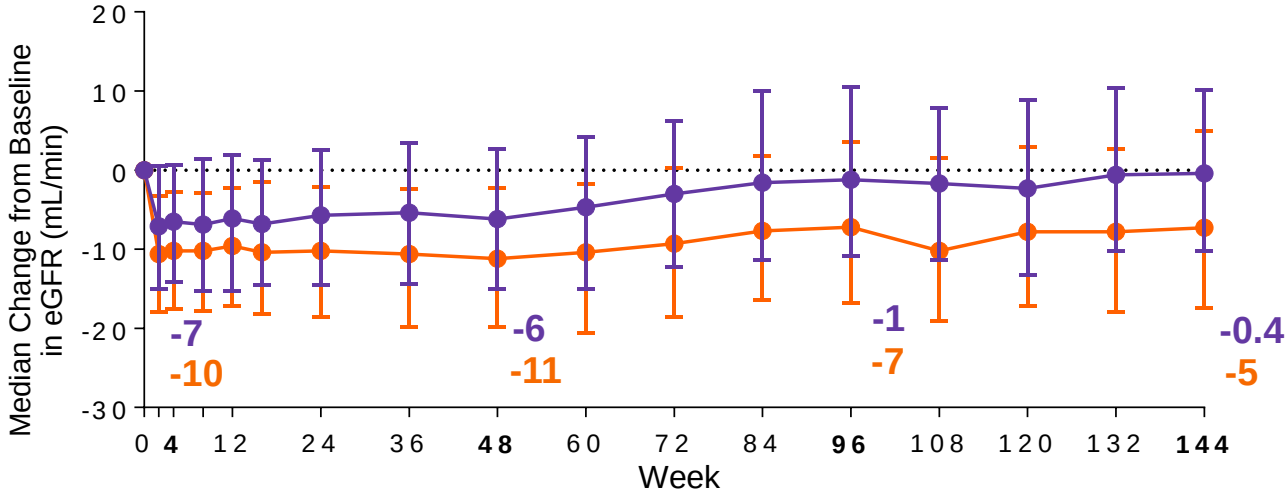
E/C/F/TAF was well-tolerated by Asian, as well as non-Asian, adults with low rates of discontinuation due to AEs

Changes in $eGFR_{CG}$ through Week 144

Asian

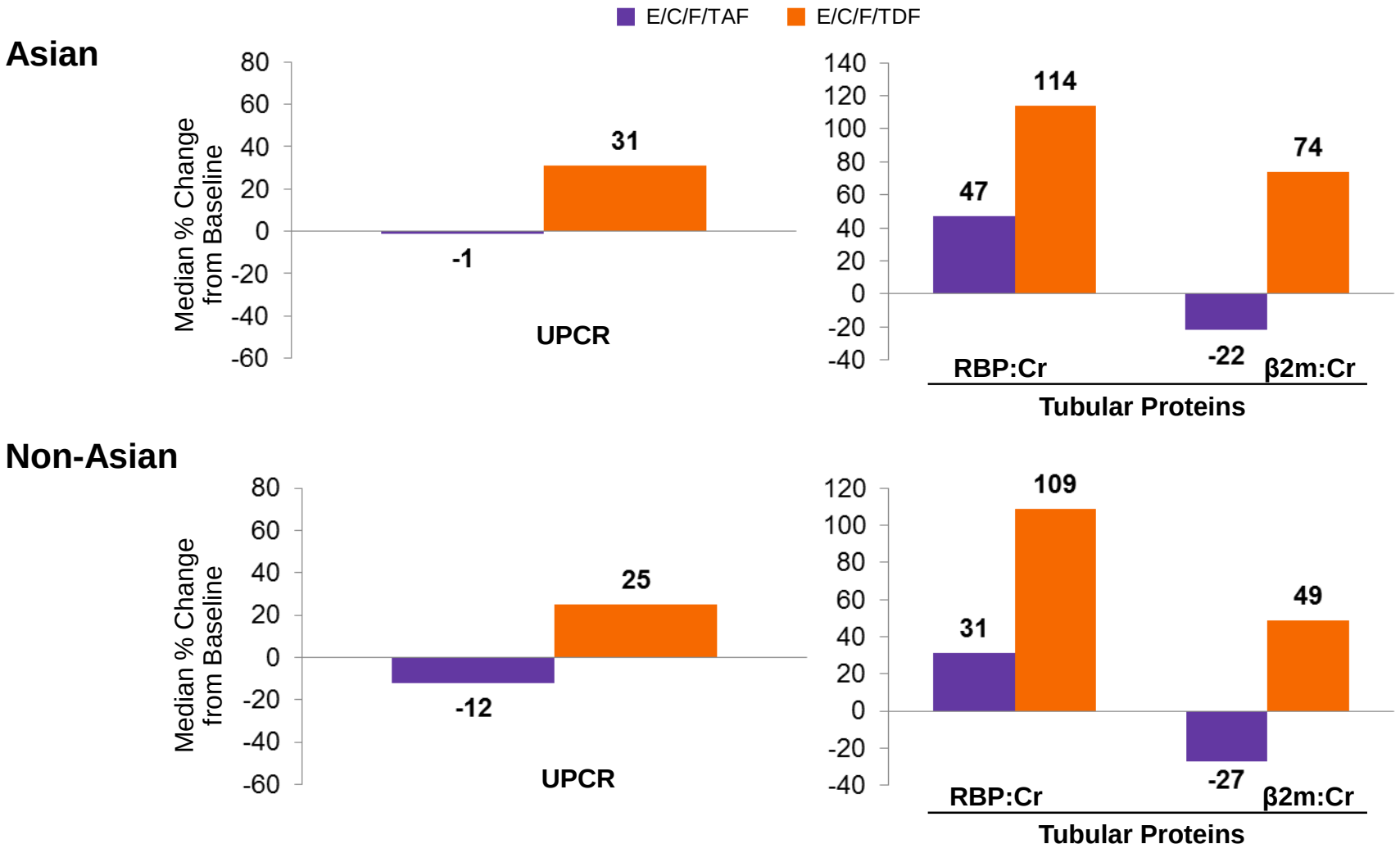


Non-Asian



Early decreases in eGFR related to COBI's inhibition of SCr secretion stabilized after Week 4

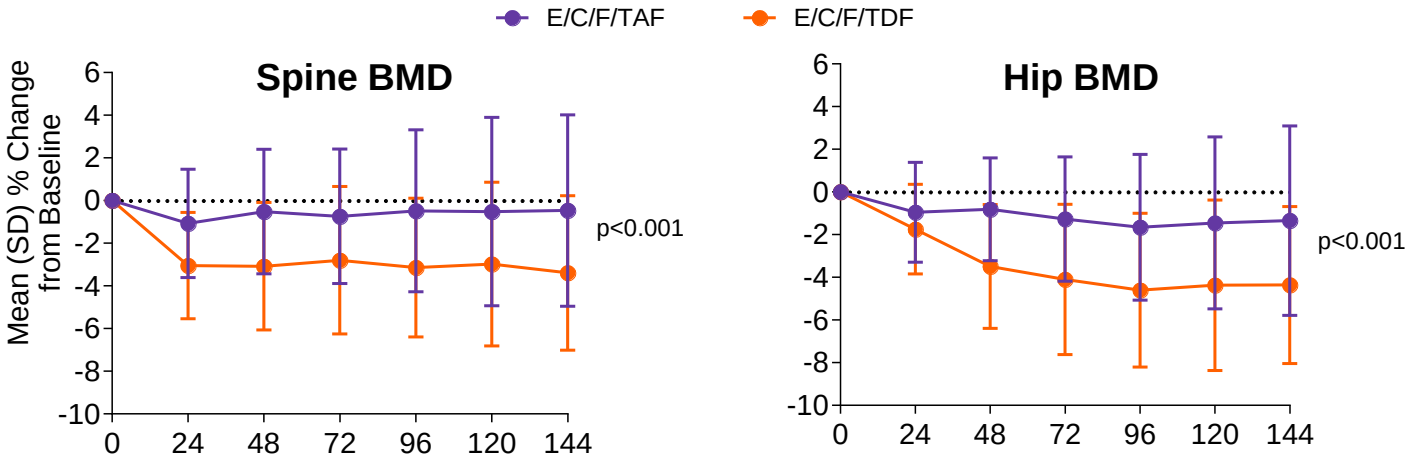
Changes in Quantitative Proteinuria



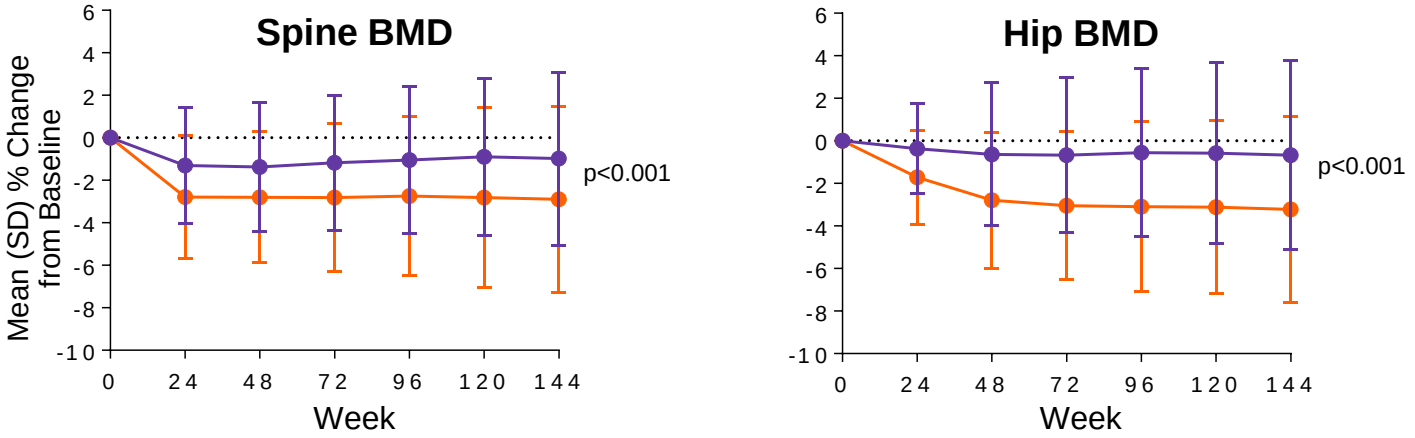
Asian adults treated with TAF had significantly less increase or decrease in tubular proteinuria vs increases for TDF

DXA Scan: Percent Changes through Week 144

Asian

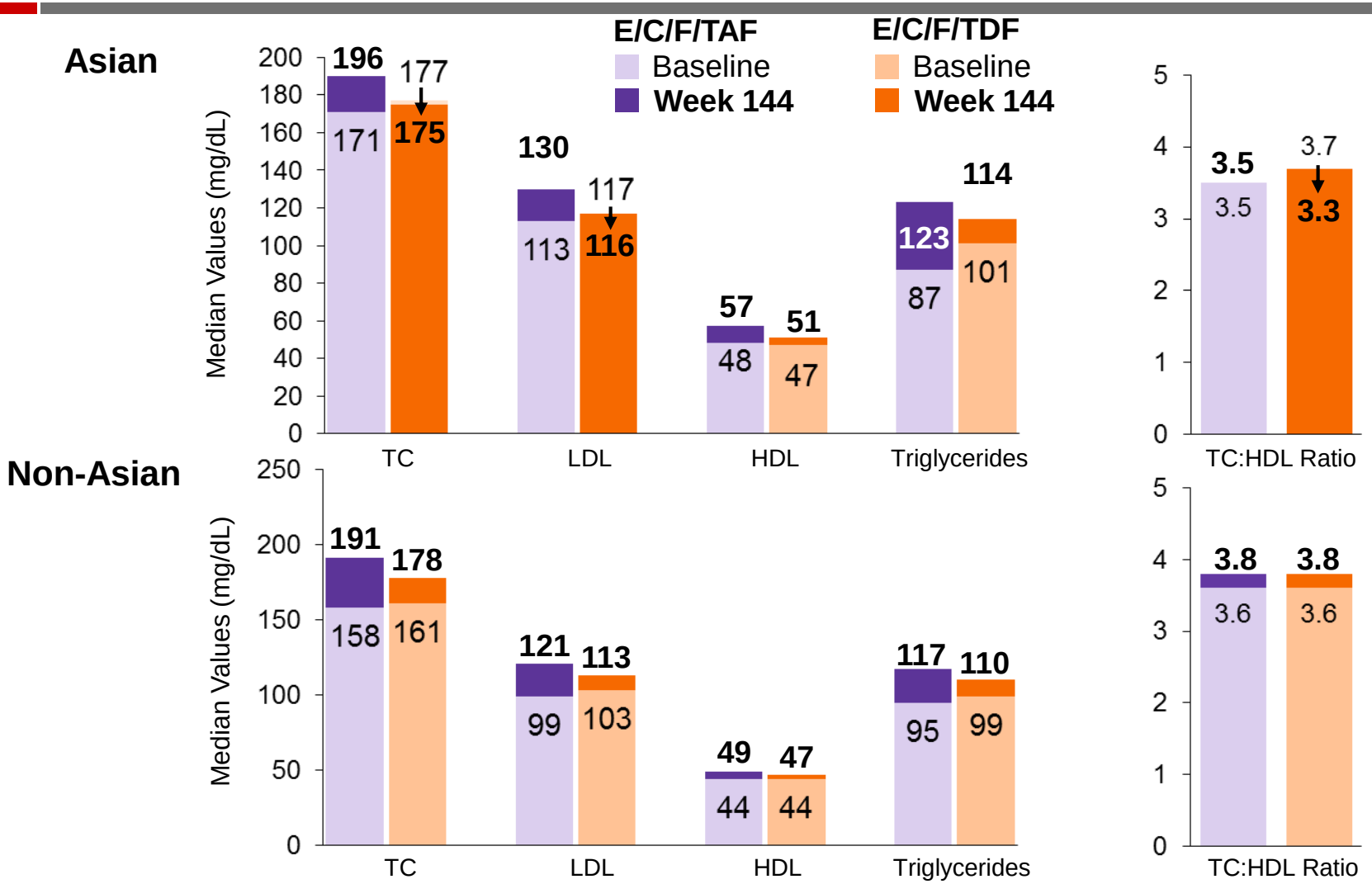


Non-Asian



DXA, dual-energy X-ray absorptiometry; Q, quartile

Fasting Lipids at Baseline and Week 144



- No difference in rate of initiation of lipid-modifying agents (E/C/F/TAF: 5.5% ; E/C/F/TDF: 5.8%) in overall study population*

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

*Arribas J, et al. CROI 2017. Seattle, WA. Poster #453

Conclusions

E/C/F/TAF compared to E/C/F/TDF in treatment-naïve adults through Week 144

- Asian adults (91 TAF and 89 TDF)
  - High and non-inferior efficacy (93 % vs 88 %) with no emergent resistance
  - Low rates of discontinuations due to AEs (1% vs 2%)
  - No proximal renal tubulopathy or discontinuations due to renal AEs
  - Less tubular proteinuria demonstrating less impact on tubular function
  - Significantly less spine and hip BMD loss
  - Increases in total and LDL cholesterol on TAF were balanced by increases in HDL cholesterol with no numerical differences in the total cholesterol to HDL ratios

E/C/F/TAF is highly effective, safe, and well tolerated in Asian adults supporting use as first line therapy for the treatment of HIV

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