“It is a Time to Switch”

Switching A New Backbone for Aging Patients and Those with Comorbidities

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Disclosure

I have received conference travel grants from:

- Pfizer, Meiji, Siam, Mylan, MSD, Janssen

Speaker Bureau

- Pfizer, Meiji, Mylan, Janssen, GSK, Zuellig Pharma, Gilead

Outlines

- General information: Tenofovir alafenamide (TAF) vs. Tenofovir disoproxil fumarate (TDF)
- Switching to TAF in HIV aging population
- Switching to TAF in PLWH with comorbidities

General Information
TAF vs. TDF

The recommended initial combined 3-drug ART for adults

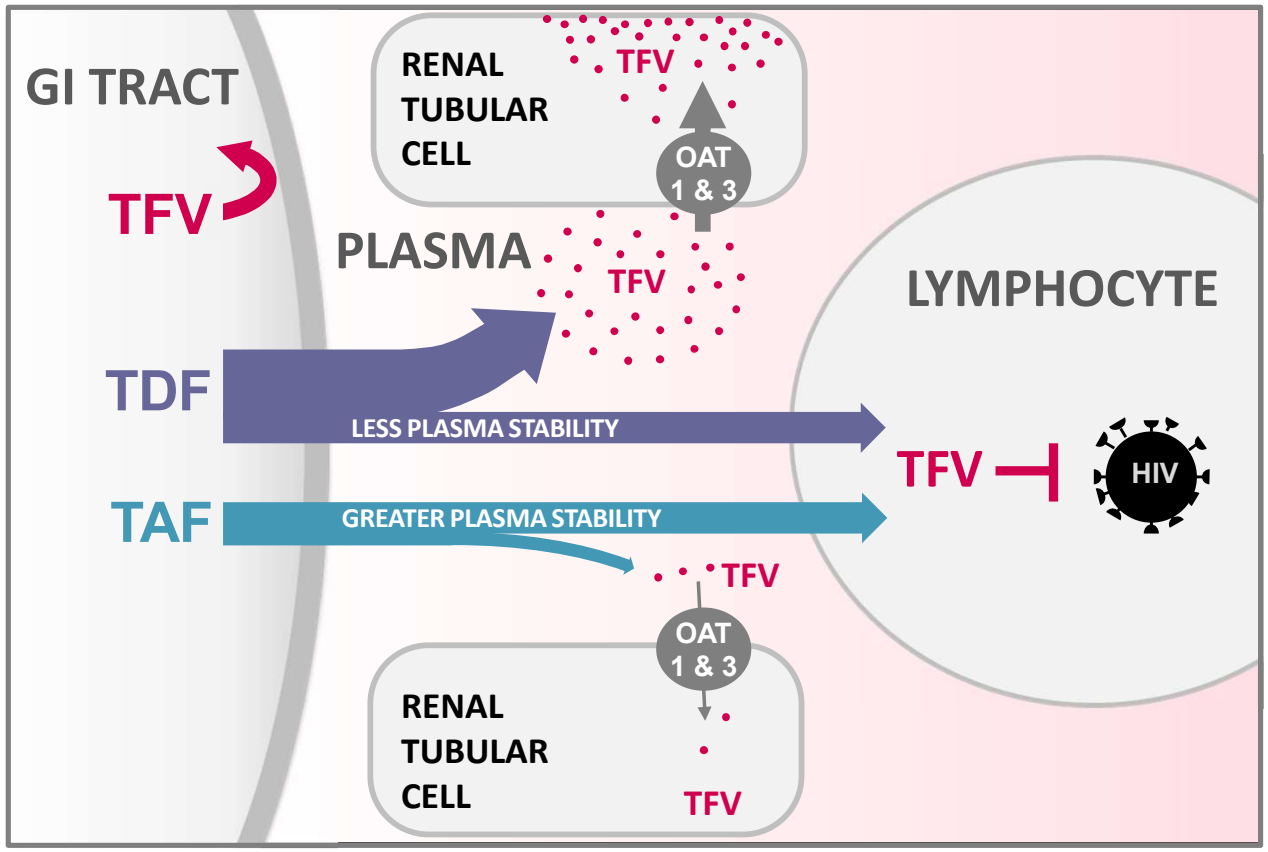
DHHS (2021)		EACS (2020)		WHO (2021)		Thai (2020/2021)	
Backbone	3rd drug	Backbone	3rd drug	Backbone	3rd drug	Backbone	3rd drug
TDF/3TC	DTG	TDF/3TC	DTG	TDF/3TC	DTG	TDF/3TC	DTG
TDF/FTC	BIC	TDF/FTC	BIC	TDF/FTC		TDF/FTC	
TAF/3TC		TAF/FTC	RAL			TAF/3TC	
TAF/FTC		ABC/3TC*				TAF/FTC	
ABC/3TC*							

* Used with DTG in a single-tablet regimen

TAF vs. TDF

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/what-start-initial-combination-regimens-antiretroviral-naive.
https://www.eacsociety.org/media/guidelines-10.1_30032021_1.pdf.
https://www.who.int/publications/i/item/9789240031593.
http://www.thaiaidssociety.org/images/PDF/thai_aids_guidelines_2020_2021.pdf.

Tenofovir Alafenamide (TAF) – A Novel Prodrug of Tenofovir



TAF results in 80-90% lower TFV plasma levels compared to TDF

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

1. Sax P, et al. Lancet 2015;385:2606-15. 2. Ruane P, et al. J Acquir Immune Defic Syndr 2013;63:449-5. 3. Data on file

TDF and TAF based combination regimens: Tablet dimensions

FTC/TDF-based

E/C/F/TDF
elvitegravir 150 mg /cobicistat 150 mg /emtricitabine 200 mg /tenofovir disoproxil fumarate 300 mg
20.0 mm x 10.0 mm
~1400 mg

RPV/FTC/TDF
rilpivirine 25 mg /emtricitabine 200 mg /tenofovir disoproxil fumarate 300 mg
19.0 mm x 8.5 mm
~1200 mg

FTC/TDF
emtricitabine 200 mg /tenofovir disoproxil fumarate 300 mg
19.0 mm x 8.5 mm
~1000 mg

EFV/FTC/TDF
efavirenz 600 mg /emtricitabine 200 mg /tenofovir disoproxil fumarate 300 mg
20 mm x 10.4 mm
~1600 mg

FTC/TAF-based

E/C/F/TAF
elvitegravir 150 mg /cobicistat 150 mg /emtricitabine 200 mg /tenofovir alafenamide 10 mg
19.0 mm x 8.5 mm
~1100 mg

RPV/FTC/TAF
rilpivirine 25 mg /emtricitabine 200 mg /tenofovir alafenamide 25 mg
15.4 mm x 7.3 mm
~700 mg

FTC/TAF
emtricitabine 200 mg /tenofovir alafenamide 25 mg
12.5 mm x 6 mm
~225 mg

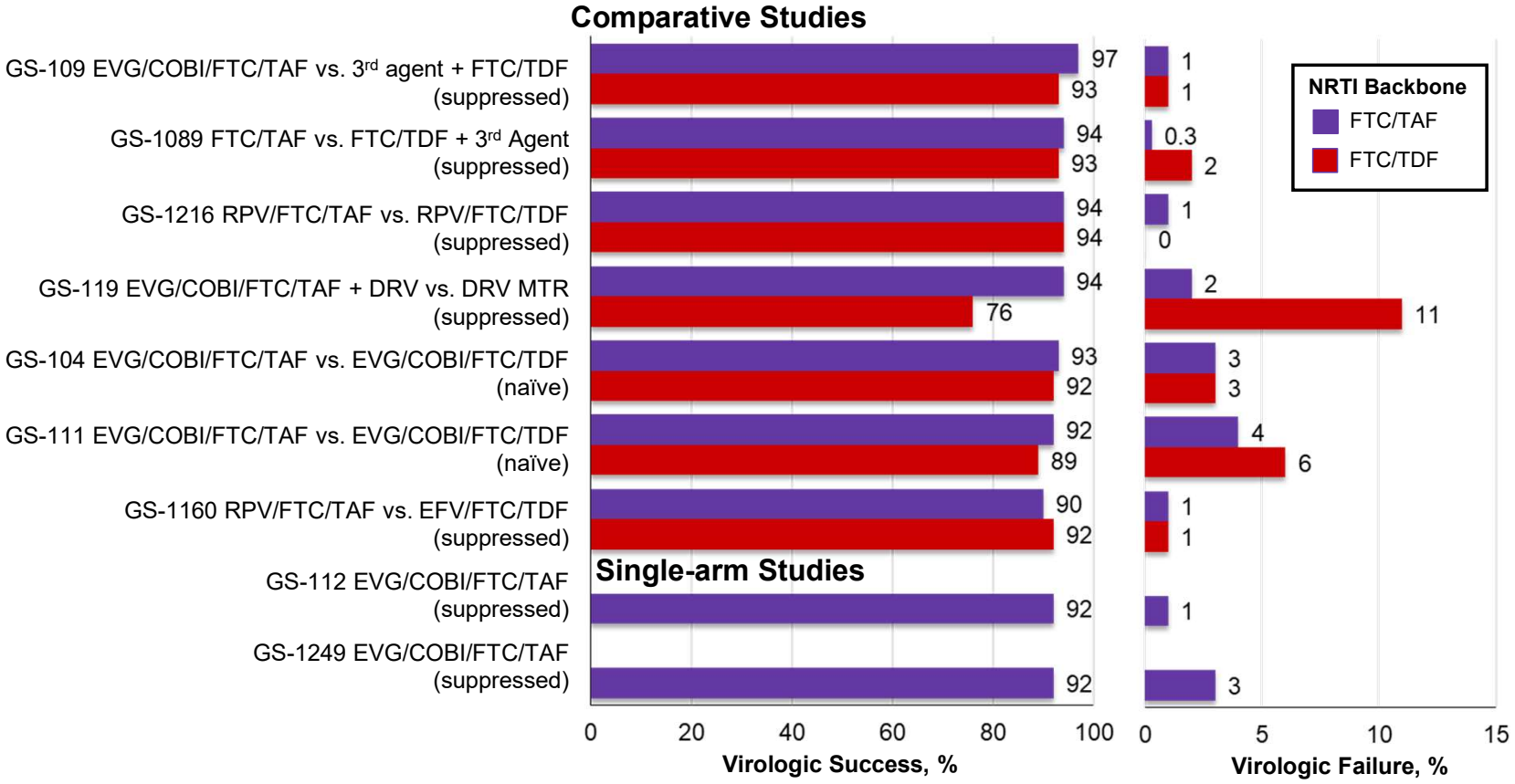
B/F/TAF
bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg
15 mm x 8 mm
~721 mg

Tablet size is not intended to compare clinical efficacy and safety, indications, dosing regimens, or treatment adherence.

Gilead Sciences Inc. Data on File

Virological Outcomes for TAF Portfolio at Week 48* by FDA Snapshot Analysis

Not all regimens have been compared head-to-head in a clinical trial.
Inclusion/exclusion criteria vary depending on the clinical trial.



MTR – multi-tablet regimen
See slide notes for references

* Week 48 was the primary endpoint for the studies depicted, except for Studies 112, 119, and 1249 which had Week 24 primary endpoints.

Resistance Summary for TAF Portfolio at Week 48

Study Type	Studies	Resistance	RAMs		
			NRTI	NNRTI	INSTI
MDR	**E/C/F/TAF 119 (n=89)**	0%	-	-	-
Virologically Suppressed (n=2,360)	**E/C/F/TAF 109, 112, 1249 (n=1,273)**	0.1% (n=1)	0.1% (n=1; M184V)	-	-
	FTC/TAF 1089 (n=333)	0.3% (n=1)	0.3% (n=1; M184V)	-	-
	RPV/FTC/TAF 1160, 1216 (n=754)	0%	-	-	-
Naïve	**E/C/F/TAF 104 & 111 (n=866)**	0.8% (n=7)	0.8% (n=7)	-	0.6% (n=5)

- No resistance was detected in study of multi-drug resistant population
- Rare resistance emergence observed in virologically suppressed studies (0-0.3%)
  - 2 cases of M184V and no INSTI resistance
- In ART-naïve studies, rare resistance emergence observed (<1%)

MDR – multi-drug resistance; RAMs – resistance-associated mutations

Abram M, et al. CROI 2016. Boston, MA. Poster #496
Gallant J, et al. Lancet HIV 2016;3(4):e158-65

Common Adverse Drug Reactions (ADR) at Week 48 of TAF-based Products

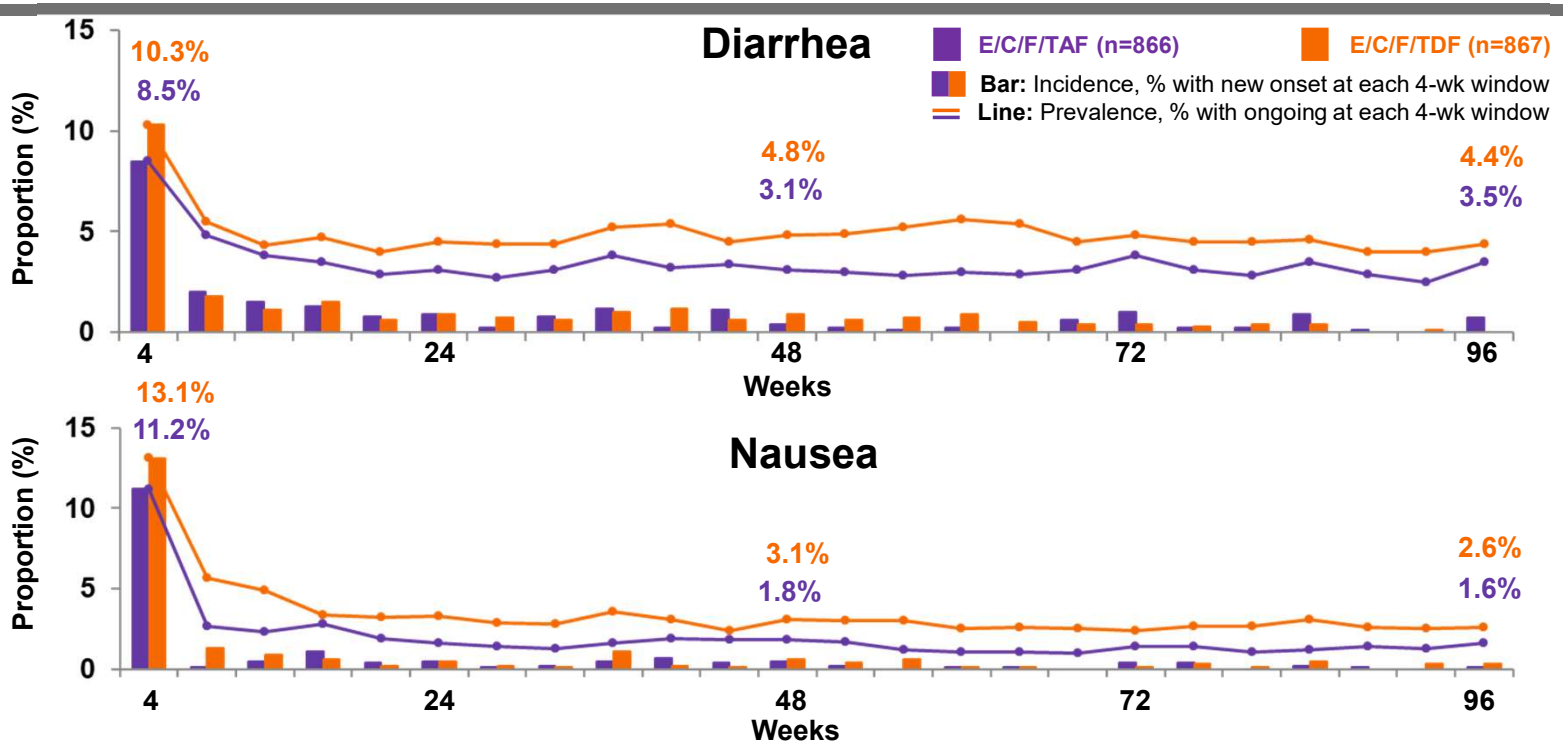
ADR Source: Grades & Prevalence:	**USPI[1-3]** Grades 1-4 or 2-4	**Clinical Trials[4]*** Grades 1-4
F/TAF	***Grades 1-4 in ≥10%*** nausea (10%)	**1089 vs F/TDF (≥1%)** Nausea and diarrhea (1%)
E/C/F/TAF		**109 vs 3rd agent + F/TDF (≥2%)** diarrhea (3%), nausea (2%) **104/111 vs E/C/F/TDF (≥5%)** nausea (10%), diarrhea (7%), headache (6%)
R/F/TAF	***Grades 2-4 in ≥2%*** **(RPV component)** depressive disorders (5%) insomnia (3%) headache (3%)	**1160 vs EFV/FTC/TDF (≥1%)** headache (2%), flatulence (1%), insomnia (1%) **1216 vs RPV/FTC/TDF (≥1%)** None

* Only Studies 104 and 111 were in ART-naïve subjects. All other studies were of virologically suppressed subjects.

1. Genvoya US Prescribing Information, Gilead Sciences, Inc. April 2017
2. Odefsey US Prescribing Information, Gilead Sciences, Inc. April 2017
3. Descovy US Prescribing Information, Gilead Sciences, Inc. April 2017
4. Data on file. Gilead Sciences.

Incidence and Prevalence of Diarrhea and Nausea

Studies 104 and 111: ART-naïve Adults



The majority of diarrhea (78%) or nausea (85%) occurred within the first 4 weeks and were mostly Grade 1 on E/C/F/TAF

There were no discontinuations in the E/C/F/TAF arm for either diarrhea or nausea

Segal-Maurer S, et al. ADR Workshop 2016. NYC. P19

Studies 104 and 111: ART-Naïve Adults, Week 144 Combined Analysis

Week 144 Safety Summary*

Participants, n (%)	E/C/F/TAF n=866	E/C/F/TDF n=867	p-value†
Any Adverse Event (AE)	**817 (94.3)**	**833 (96.1)**	**—**
Grade 3 or 4 AE	140 (16.2)	137 (15.8)	—
Serious AE	121 (14.0)	124 (14.3)	—
Death	4 (0.5)**	5 (0.6)‡	—
AE-related discontinuations	11 (1.3)	29 (3.3)	0.01

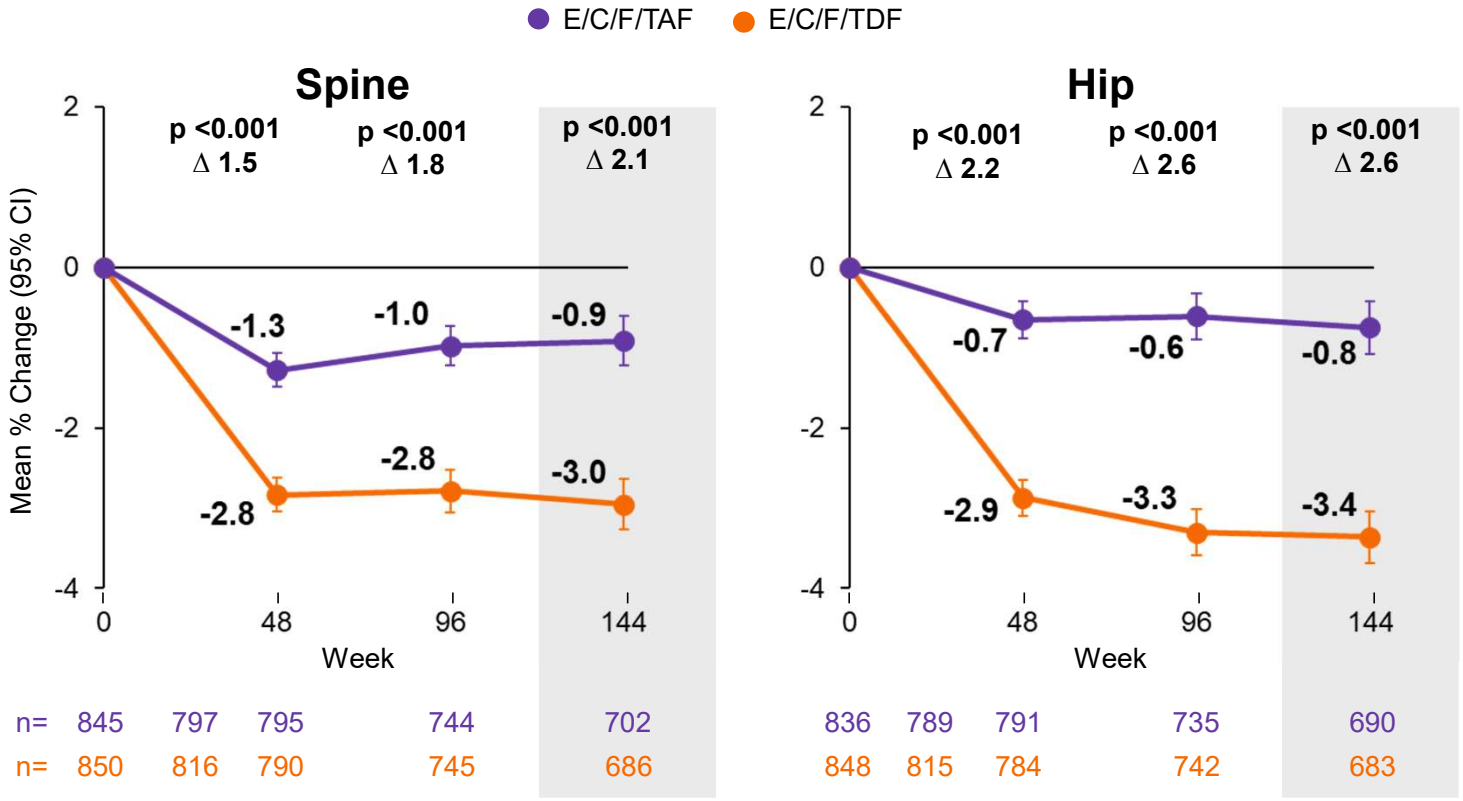
* Safety analysis set included all participants who received ≥1 dose
† Calculated using Fisher's exact test to compare treatment groups
** Stroke (n=2), alcohol intoxication (n=1), suicide (n=1)
‡ Alcohol and drug intoxication (n=1), myocardial infarction (n=2), cardiac arrest (n=1), unknown (n=1)

AEs leading to discontinuations were significantly less on E/C/F/TAF compared to E/C/F/TDF at Week 144

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

Studies 104 and 111: ART-Naïve Adults, Week 144 Combined Analysis

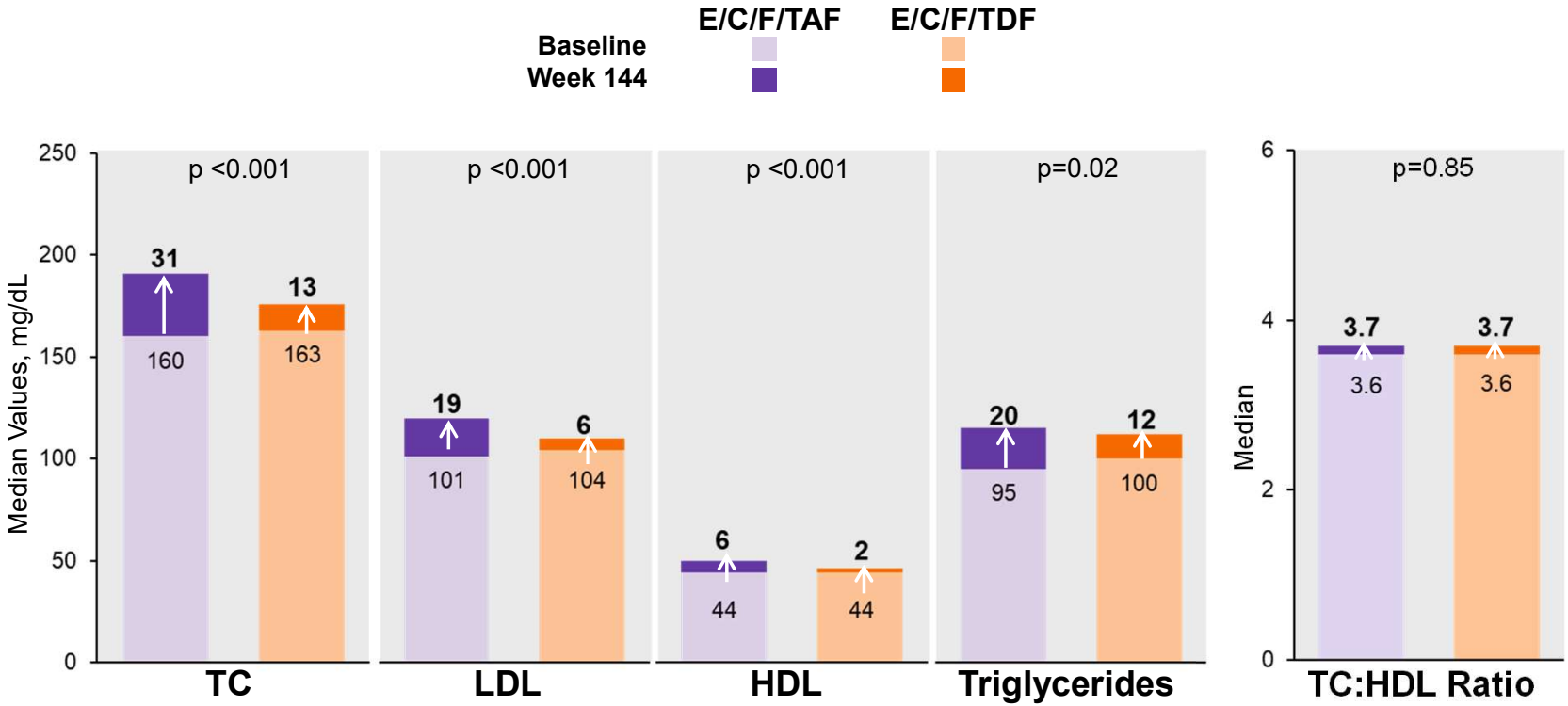
Results: Change in Spine and Hip BMD through Week 144



Through Week 144, significantly greater losses in spine and hip BMD in TDF group

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

Fasting Lipids through Week 144*



- Participants on E/C/F/TAF had greater increases in TC, LDL, HDL, and TG than those on E/C/F/TDF
- No difference in TC:HDL ratio

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

Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in 8 Randomized Comparative Clinical Trials

Variable	OR	(95% CI)	*P* Value
CD4 count (<200 vs ≥200 cells/all)	4.36	(3.6–5.27)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	1.98	(1.65–2.37)	<.001
BMI			
Normal vs overweight	1.54	(1.27–1.87)	<.001
Normal vs obese	1.66	(1.29–2.15)	<.001
Sex (female vs male)	1.54	(1.21–1.96)	<.001
Race (black vs non-black)	1.32	(1.10–1.59)	.003
Third ART agent			
BIC/DTG vs EFV	1.82	(1.24–2.66)	.002
EVG/c vs EFV	1.36	(1.04–1.78)	.026
RPV vs EFV	1.51	(1.03–2.20)	.035
ATV/r vs EFV	0.92	(.59–1.45)	.73
NRTI			
TAF vs ZDV	1.75	(1.04–2.95)	.034
TDF vs ZDV	1.19	(.76–1.87)	.44
ABC vs ZDV	0.93	(.47–1.8)	.82
TAF vs ABC	1.9	(1.25–2.88)	.003
TDF vs ABC	1.29	(.79–2.11)	.31
TAF vs TDF	1.47	(1.14–1.90)	.003

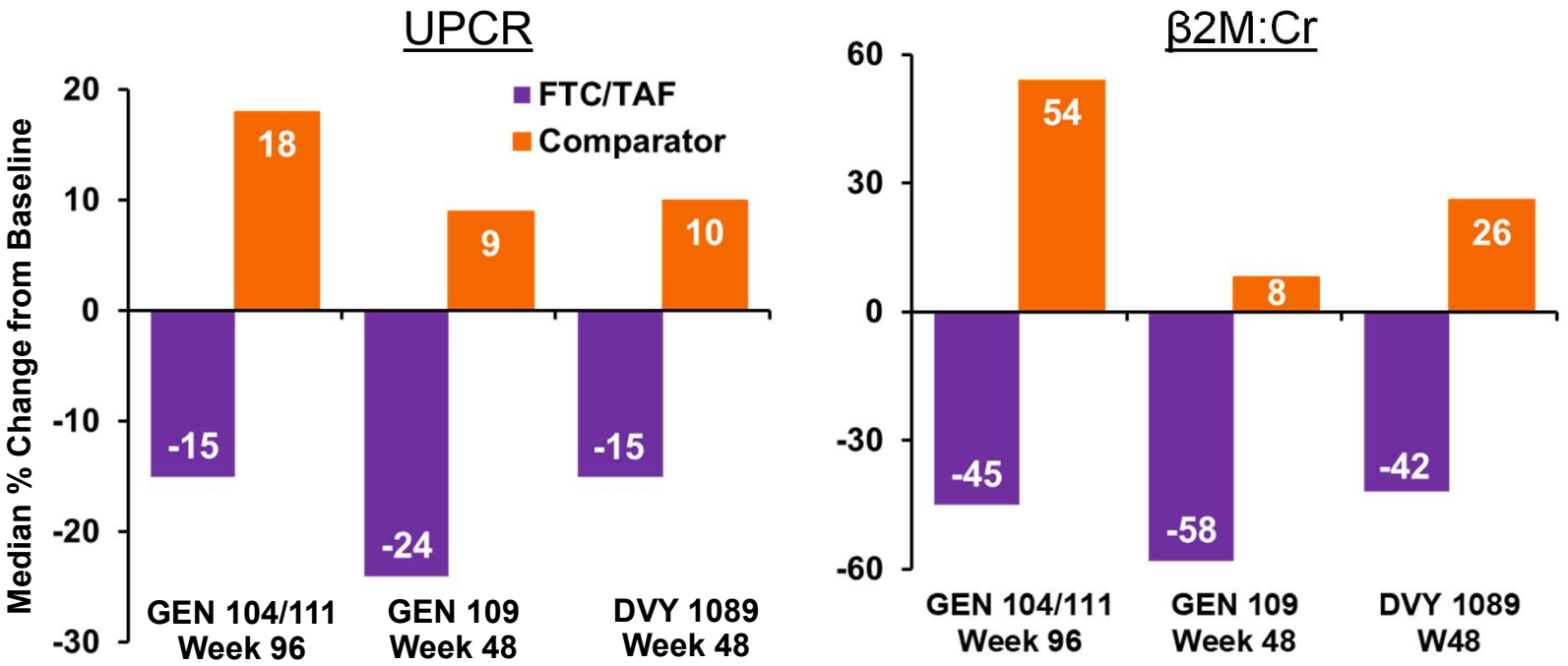
TAF was associated with ≥ 10% weight gain compared to TDF

Sax P, et al. Clin Infect Dis 2019 Oct 14;ciz999. doi: 10.1093/cid/ciz999

Switching to TAF in HIV aging population

Study GEN 104/111, GEN 109 and DVY 1089: Aging Analyses

Renal Biomarkers: Median Change (%) in ≥ 50 Years of Age

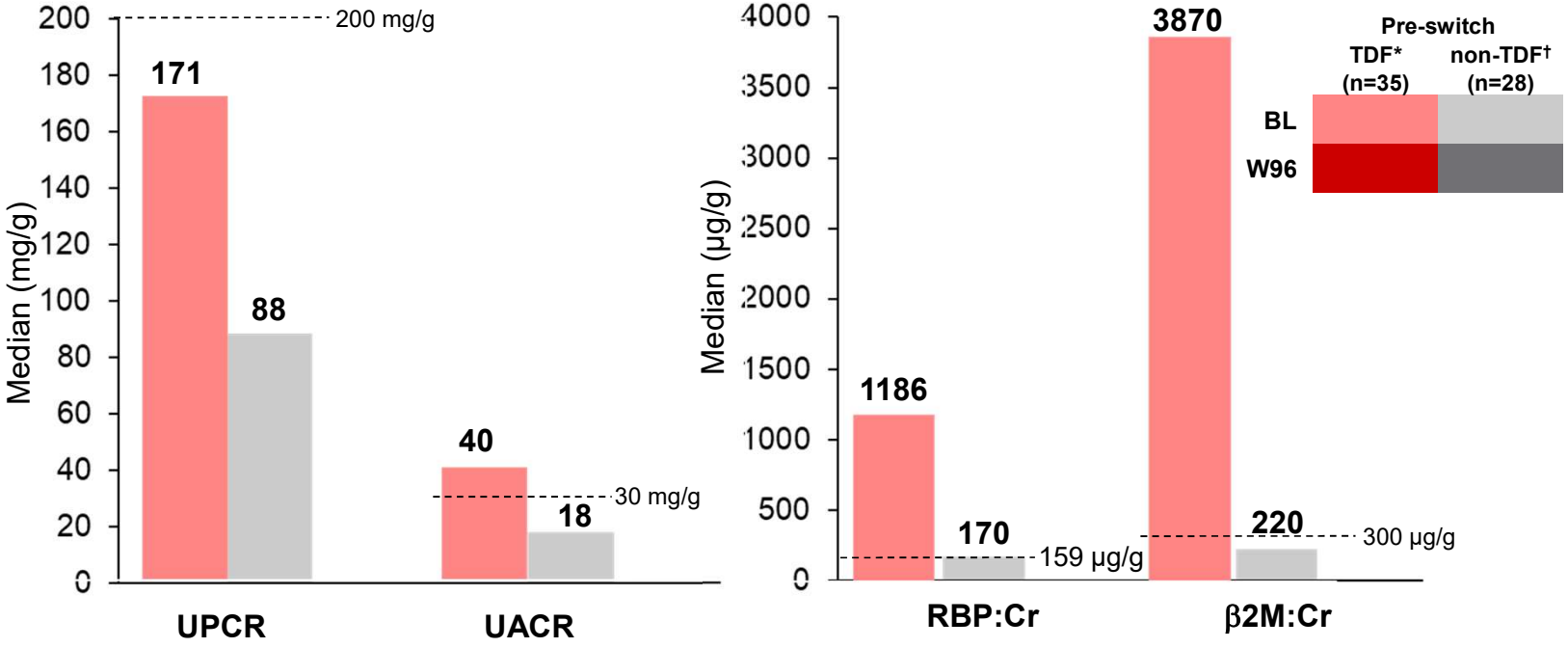


Switching to FTC/TAF-based regimens resulted in improvements in renal biomarkers and eGFR in subjects ≥50 years old

Ward D, et al. HIV and Aging 2016. Washington, DC. #33
Goldstein D, et al. HIV and Aging 2016. Washington, DC. #32
Daar E, et al. ID Week 2016. New Orleans. Oral #952

UPCR: urine protein to creatinine ratio
β2M:Cr: β2-microglobulin to creatinine ratio

Quantitative Proteinuria at Baseline and W96 in Subjects ≥ 65 years of Age



For all 4 proteinuria measures:

- Pre-switch TDF regimens were associated with elevations vs. non-TDF regimens

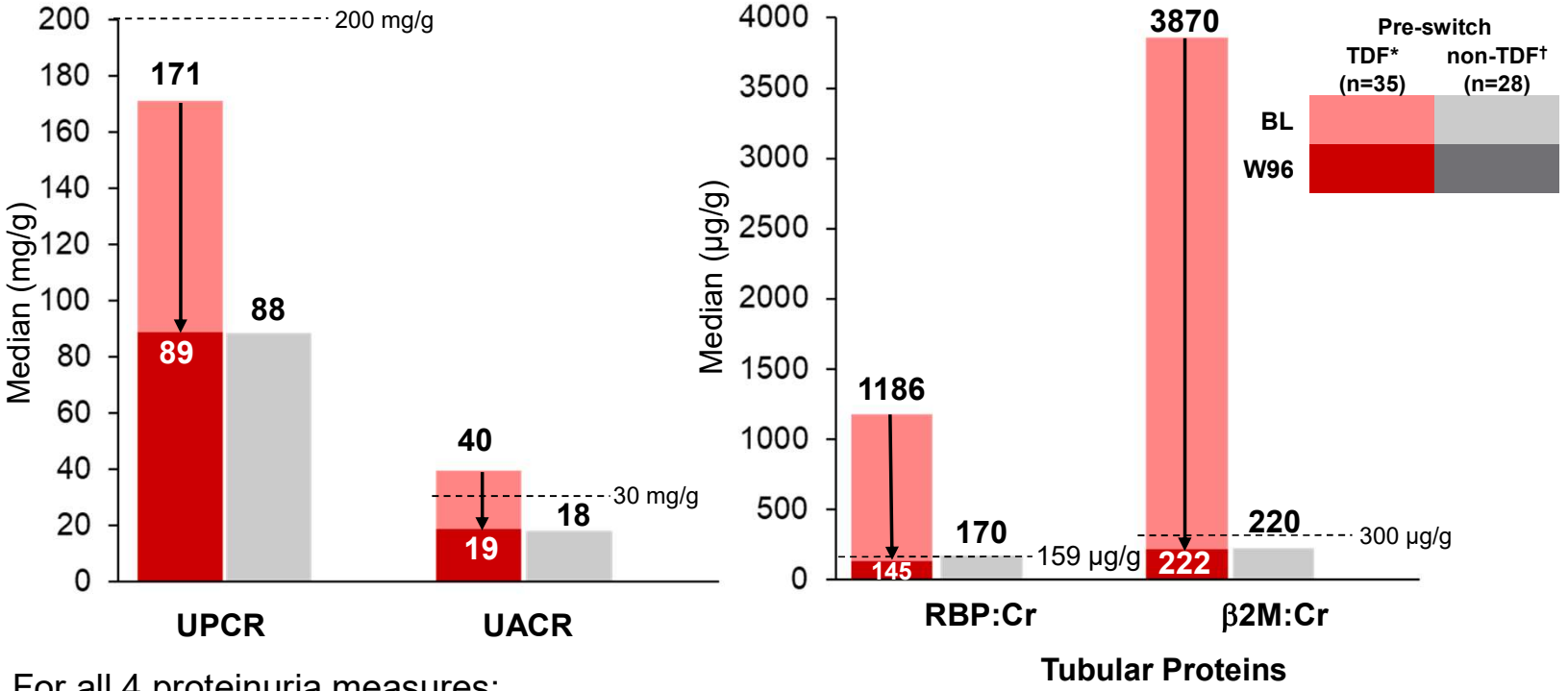
UPCR = Urine Protein:Creatinine Ratio; UACR = Urine Albumin: Creatinine Ratio
RBP:Cr = Retinol Binding Protein: Creatinine Ratio; β-2M:Cr = β-2-microglobulin:Creatinine Ratio

Martorell C, et al. HIV and Aging 2016. Washington, DC. Poster #36

*** All changes statistically significant**
† All changes not statistically significant

Study 112: Suppressed Adults with Renal Impairment W96 - 65 Years of Age Sub-Analysis

Quantitative Proteinuria at Baseline and W96 in Subjects ≥ 65 years of Age



For all 4 proteinuria measures:

- Pre-switch TDF regimens were associated with elevations vs. non-TDF regimens
- Significant decreases observed with switch from TDF to TAF regimens

UPCR = Urine Protein:Creatinine Ratio; UACR = Urine Albumin: Creatinine Ratio
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Martorell C, et al. HIV and Aging 2016. Washington, DC. Poster #36

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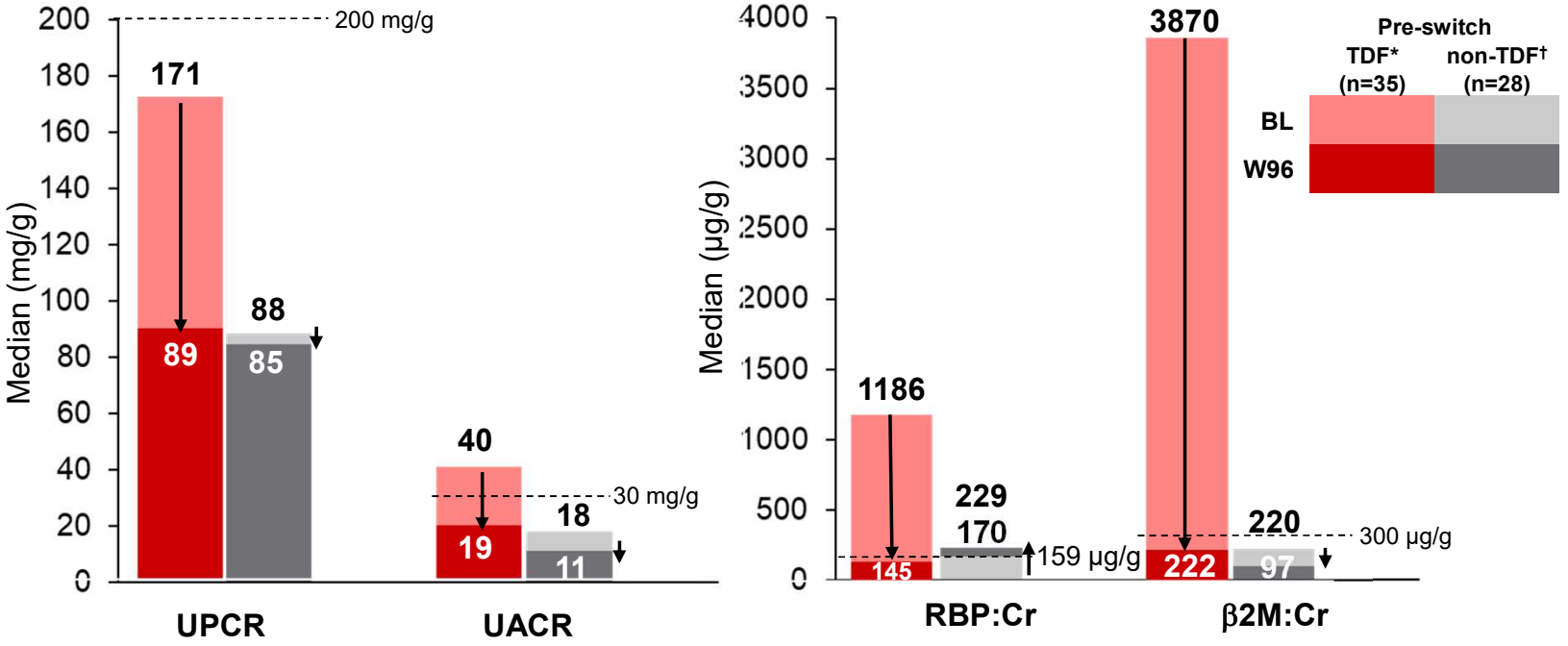
Quantitative Proteinuria at Baseline and W96 in Subjects ≥ 65 years of Age



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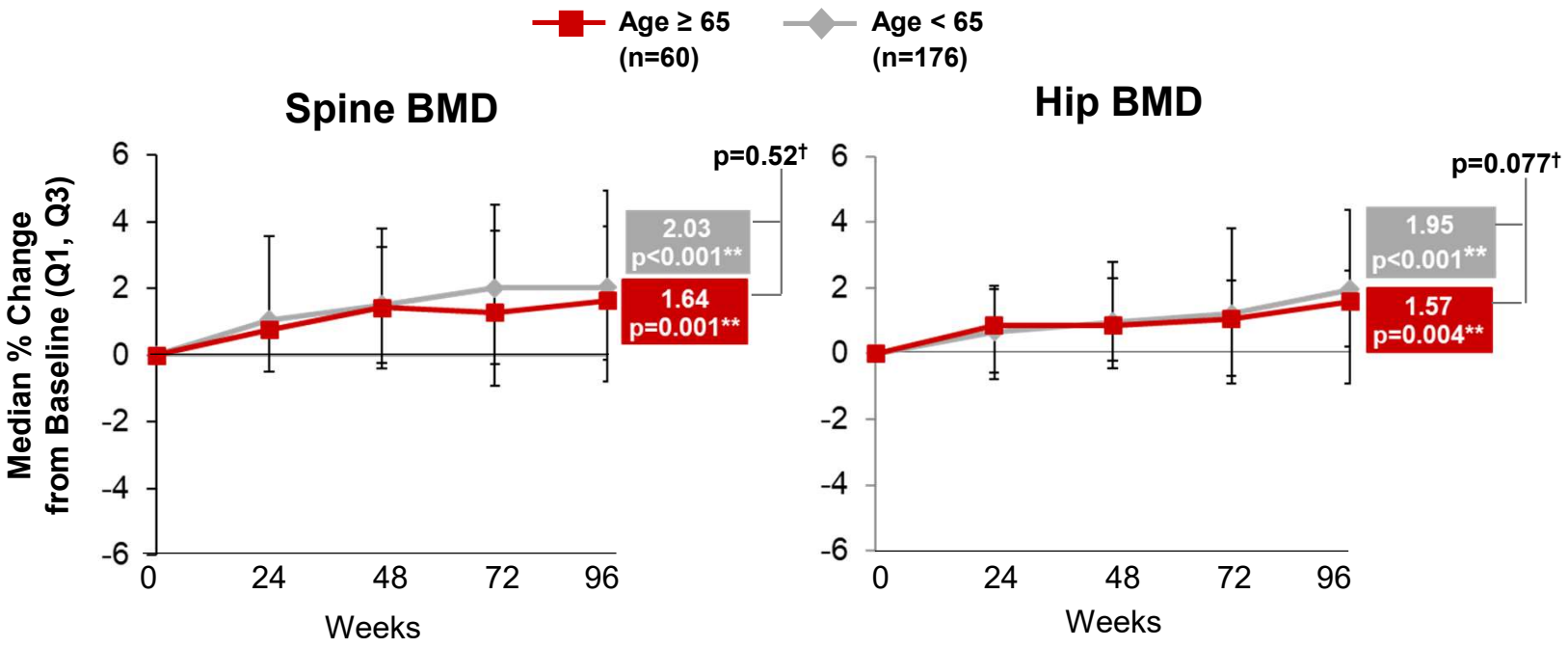
Martorell C, et al. HIV and Aging 2016. Washington, DC. Poster #36

*** All changes statistically significant**
† All changes not statistically significant

Study 112: Suppressed Adults with Renal Impairment Week 96 - ≥ 65, < 65 Aging Analysis

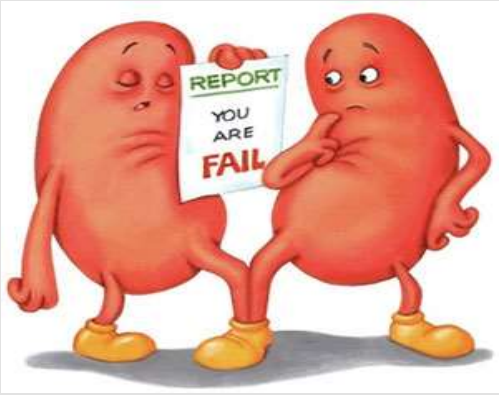
Median % Change in Spine and Hip BMD by Age*

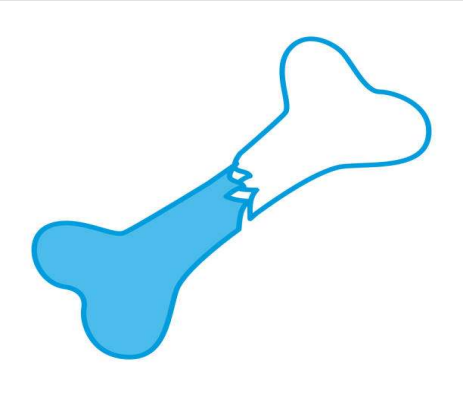


- **Regardless of age, switching to E/C/F/TAF resulted in similar significant increases in spine and hip BMD, were driven mainly by subjects switching from a TDF-containing regimen**

Martorell C, et al. HIV and Aging 2016. Washington, DC. Poster #36

Switching to TAF in PLWH with comorbidities





Switch to TAF for Renally Impaired Patients

FDA Approved Creatinine Clearance Cut-offs (eGFR, mL/min)

TAF-based Antiretrovirals			TDF-based Antiretrovirals			
FTC/TAF (25 mg)	R/F/TAF (25 mg)	E/C/F/TAF (10 mg)	TDF 300 mg	FTC/TDF (300 mg)	R/F/TDF (300 mg)	E/C/F/TDF (300 mg)
≥30			≥50			≥70

- TAF-based antiretrovirals are approved for HIV infection in patients with creatinine clearance of ≥30 mL/min, which is an improvement over TDF-based antiretrovirals.
- TAF (25 mg) is approved for HBV infection in patients with creatinine clearance of ≥15 mL/min.

US Prescribing Information: 2017

Renal Outcomes By D:A:D Risk Scores at Week 96

Studies 104/111: Renal Risk Sub-analysis by D:A:D Risk Score

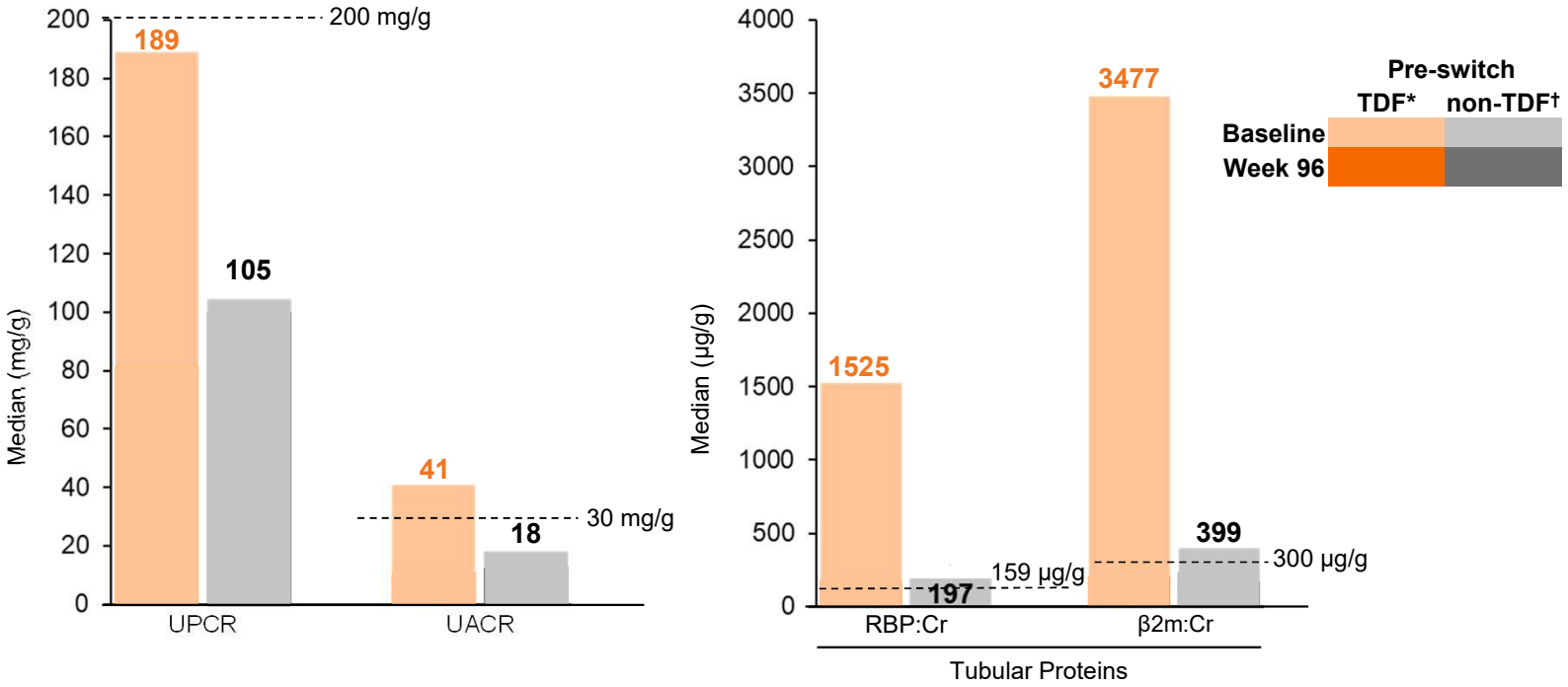
	High Risk for CKD [1]		Medium Risk for CKD [2]		Low Risk for CKD [3]	
	E/C/F/TAF n=56	E/C/F/TDF n=84	E/C/F/TAF n=107	E/C/F/TDF n=129	E/C/F/TAF n=697	E/C/F/TDF n=648
Median baseline $eGFR_{CG}$ (mL/min)	88	87	98	100	121	120
Median Δ in $eGFR_{CG}$ at Wk 4	-3	-7	-4	-8	-8	-11
Median Δ in $eGFR_{CG}$ at Wk 96 [4,5]	2	-6	5	-7	-3	-8
Incident CKD[6]	0	4.8% (4)	0	2.3% (3)	0.1% (1)	1.1% (7)
Renal AE Discontinuations	0	3.6% (3)[7]	0	2.3% (3)[8]	0	0

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's Syndrome (N =1 [an incident CKD case]), nephropathy (N =1), renal failure (N =1); 8. Renal AEs: Decreased GFR (N =1 [an incident CKD case]), elevated creatinine (N =1 [an incident CKD case]), renal failure (N =1).

- **Overall Incident CKD: 0.1% (1) TAF vs 1.6% (14) TDF**
- **Total Renal Discontinuations: E/C/F/TAF 0 vs. E/C/F/TDF 6; p = 0.03**

1. Wohl D, et al. CROI 2016. Boston, MA. #681
2. Wohl D, et al. JAIDS 2016;72:58-64.

Renal Biomarkers: Changes From Baseline to Week 96

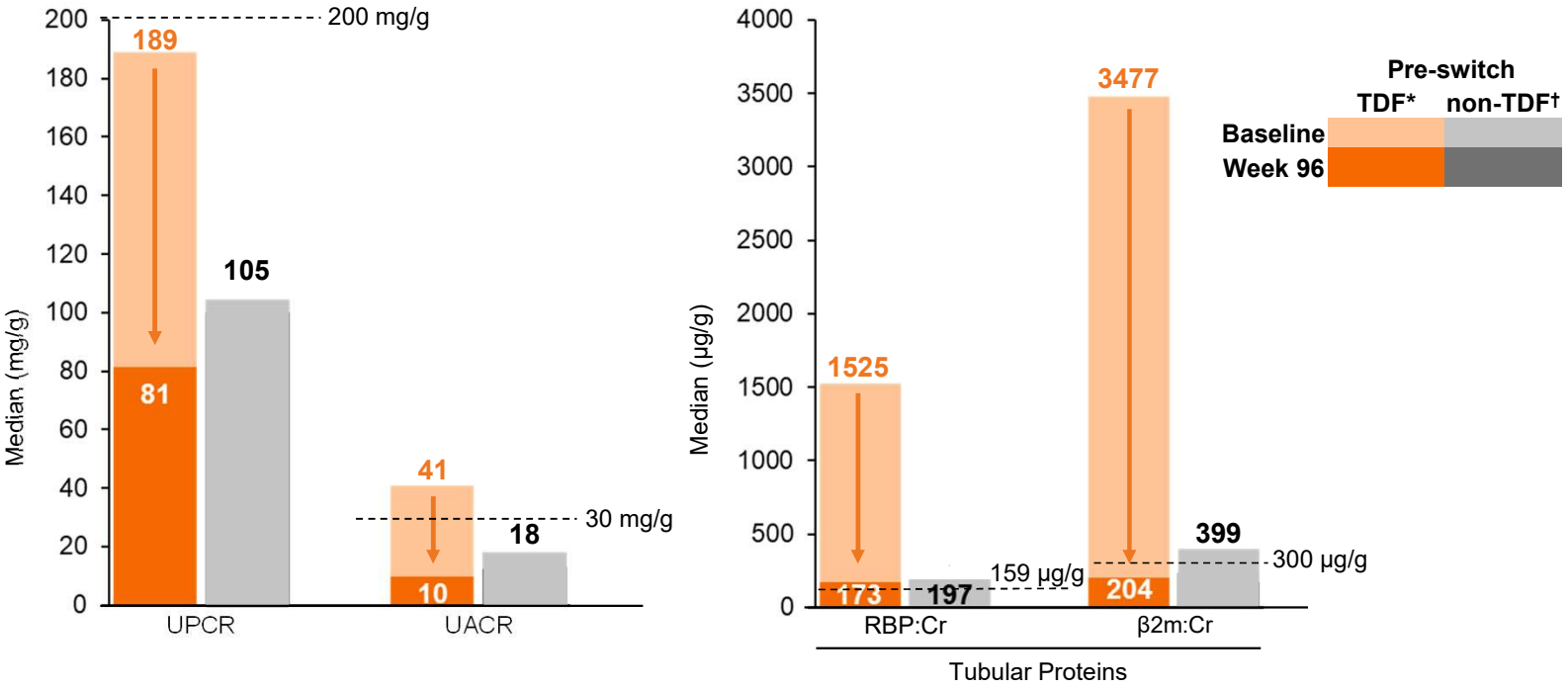


For all 4 proteinuria measures:

- Pre-switch TDF regimens were associated with elevations vs. non-TDF regimens

* All changes statistically significant; †All changes not statistically significant with exception of β2m:Cr. β2m, β2-microglobulin; RBP, retinol-binding protein.
Post F, et al. CROI 2016. Boston, MA. Poster #680.

Renal Biomarkers: Changes From Baseline to Week 96



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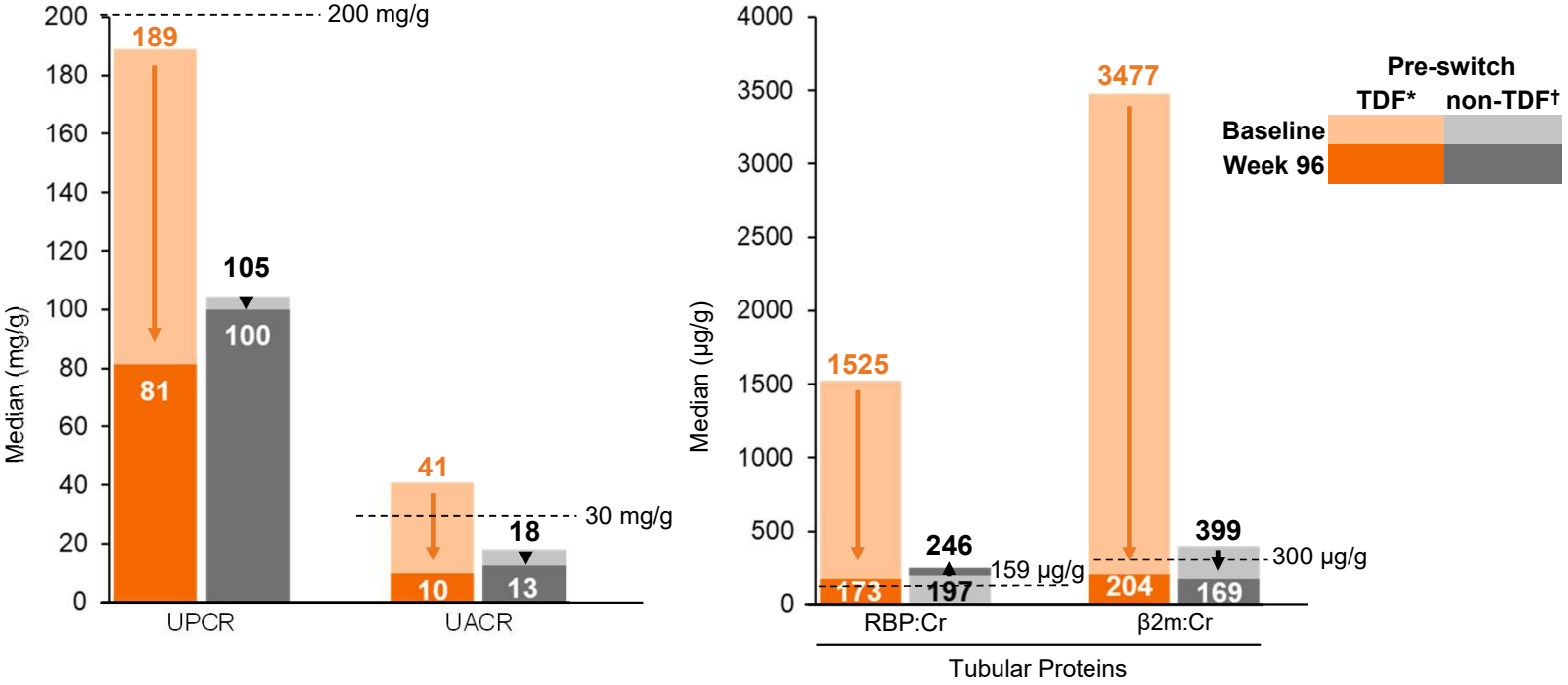

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Post F, et al. CROI 2016. Boston, MA. Poster #680.

Switch to TAF in Patients with Renal Injury or Fanconi Syndrome from TDF

- Four patients with a history of Fanconi Syndrome were treated with FTC/TAF without recurrence of Fanconi Syndrome with 2 years of follow-up on TAF-based regimens[1-4]

- Most patients with renal comorbidities in Swiss Compassionate Use Program had stable eGFR and an improvement in proximal renal tubulopathy markers when switching from TDF to TAF[5]
  - 2 with Fanconi Syndrome
  - 2 with proximal renal tubulopathy
  - 6 with CKD Stage ≥2

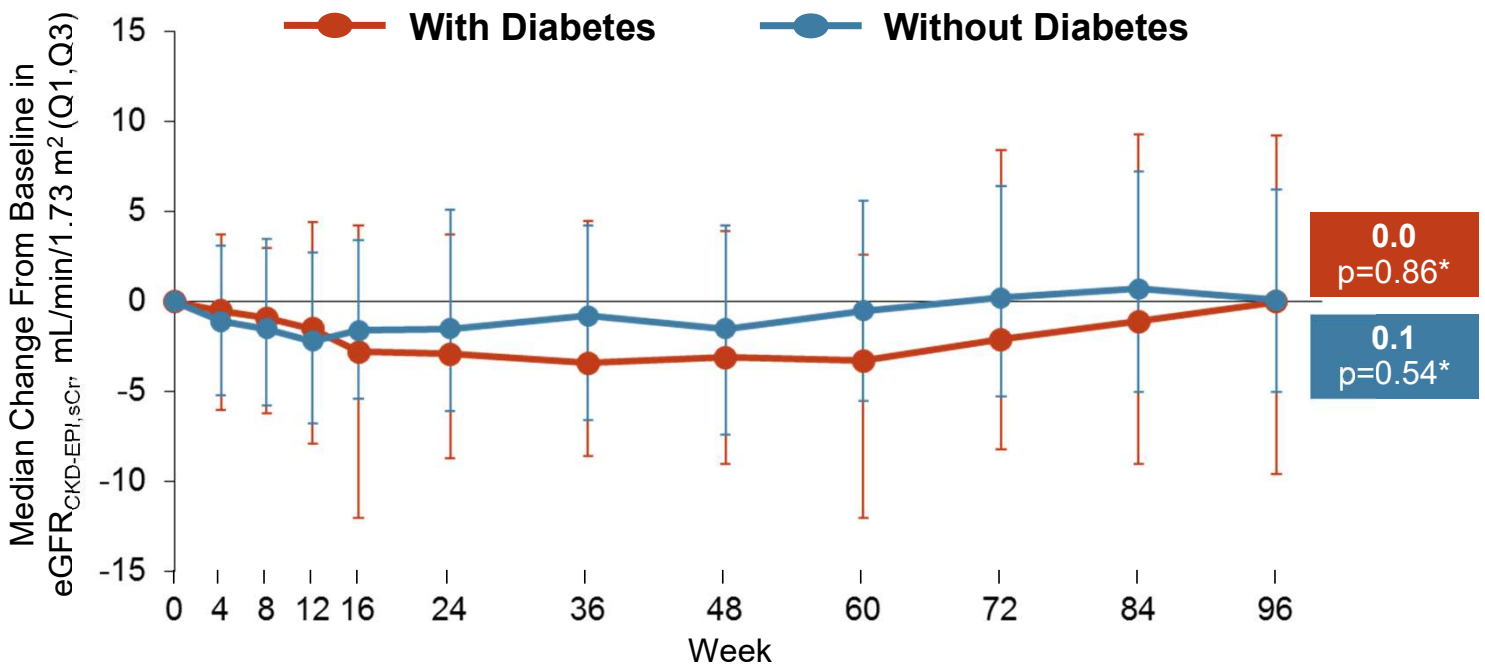
- One published case with two episodes of TDF-associated acute kidney injury who switched to TAF without worsening kidney function through 48 weeks[6]

1. Post F, et al. CROI 2016. Boston MA. #680
2. Garcia M, et al. *AIDS*. 2016;30:1487-1488.
3. Data on File, Gilead Sciences.
4. Karris MY. AIDS Research and Human Retroviruses 2017.doi: 10.1089/AID.2016.0180.
5. Walti LN, et al. Swiss Society of Infectious Diseases (SSI) 2016. Poster.
6. Mikula M, et al. *Antiviral Therapy* 2016;21:553-8.

DIABETICS

Study 112: HIV Suppressed Diabetics with Renal Impairment Switched to E/C/F/TAF

Changes in $eGFR_{CKD\text{-}EPI,sCr}$ through Week 96



*Baseline vs Week 96 (2-sided Wilcoxon signed-rank test).

Median, mL/min/1.73 m^2 (Q1, Q3)	Baseline	Week 96
With Diabetes (n=33)	53.0 (42.0, 62.4)	55.6 (41.4, 66.6)
Without Diabetes (n=209)	54.2 (46.3, 62.8)	55.1 (48.1, 63.8)

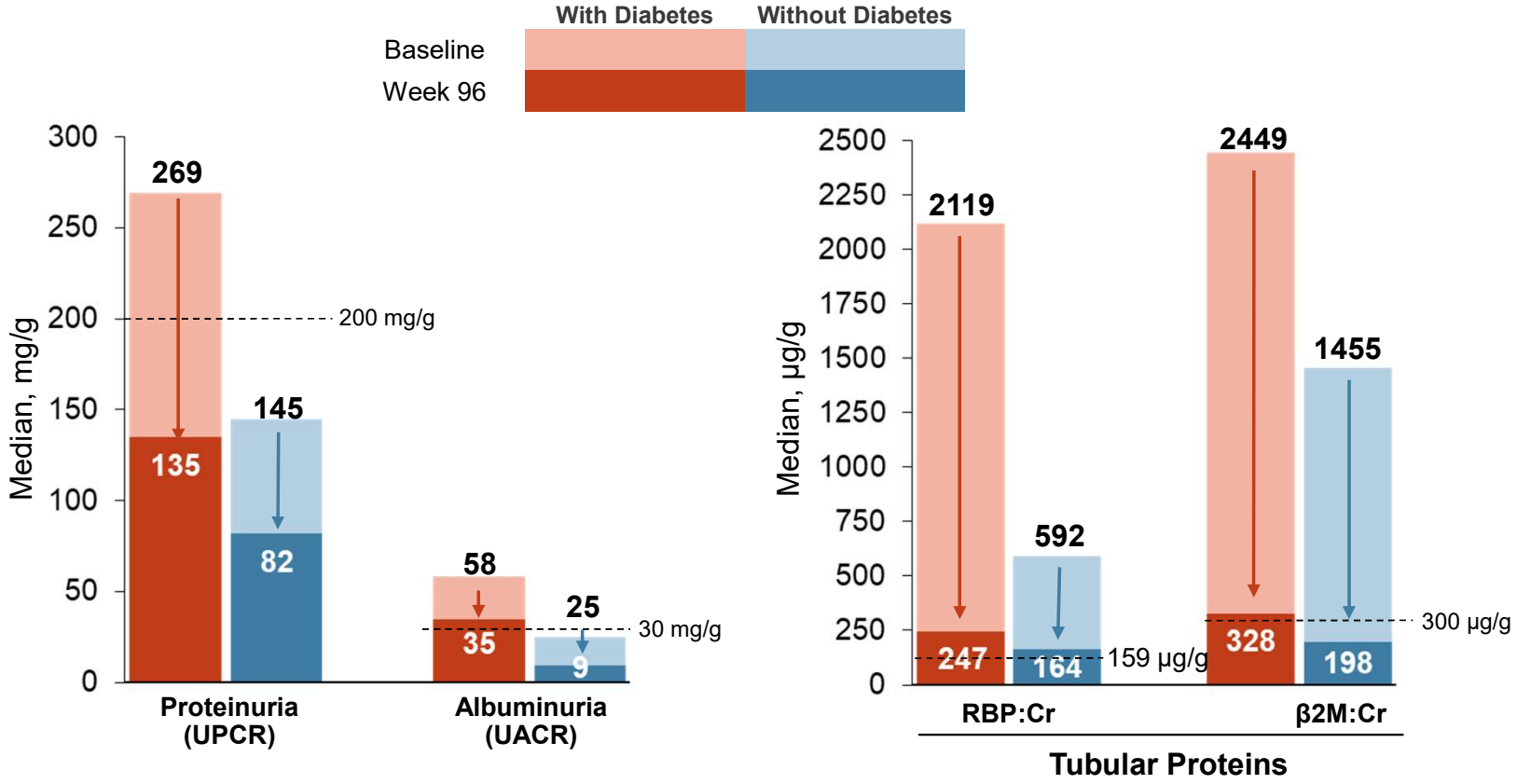
eGFR remained stable over two years after switching to E/C/F/TAF

Stein D, et al. ASM 2016. Boston MA. Oral

DIABETICS

Study 112: HIV Suppressed Diabetics with Renal Impairment Switched to E/C/F/TAF

Renal Biomarkers: Changes From Baseline to Week 96 in Diabetic Subjects



Statistically significant reductions in proteinuria and tubular proteinuria with a trend towards reduction in albuminuria

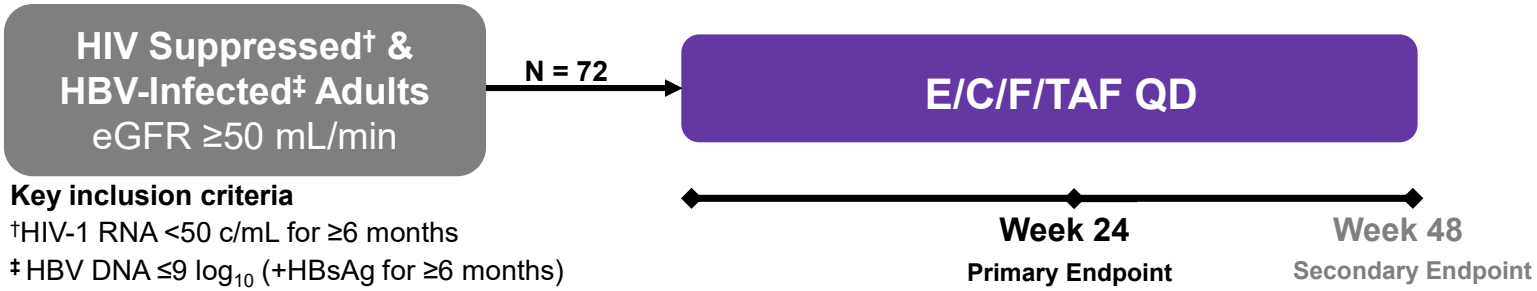
All changes statistically significant, with exception of UACR in diabetic patients (*P*= 0.09).

Stein D, et al. ASM Microbe 2016. Oral.

Study 1249: HIV/HBV Co-infected Adults on E/C/F/TAF

Switching to TAF in HBV-HIV co-infected individuals

Phase 3, 48-week, multicentered, single-arm, open label study



		N=72
Demographics	Median age, y (Q1, Q3)	51 (45, 55)
	Male, n (%)	66 (92)
	Asian, n (%)	7 (10)
	Black, n (%)	13 (18)
HIV	Median Cockcroft-Gault eGFR, mL/min (Q1, Q3)	95 (77, 117)
	TDF-based ART (TDF and FTC or 3TC), n (%)	69 (96)*
HBV	HBsAg+; HBeAg+, n (%)	71 (99)† ; 30 (42)
	ALT ≤ULN, n (%)	62 (86)

*3 patients received non-TDF-based antiretroviral therapy (ART): ABC/3TC+LPV/r; RAL+ATV+RTV; ATV+RTV only.
†1 patient was positive at screening, negative at baseline, positive at Week 12, and negative afterwards.

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ClinicalTrials.gov Identifier: NCT02071082

Study 1249: HIV/HBV Co-infected Adults on E/C/F/TAF

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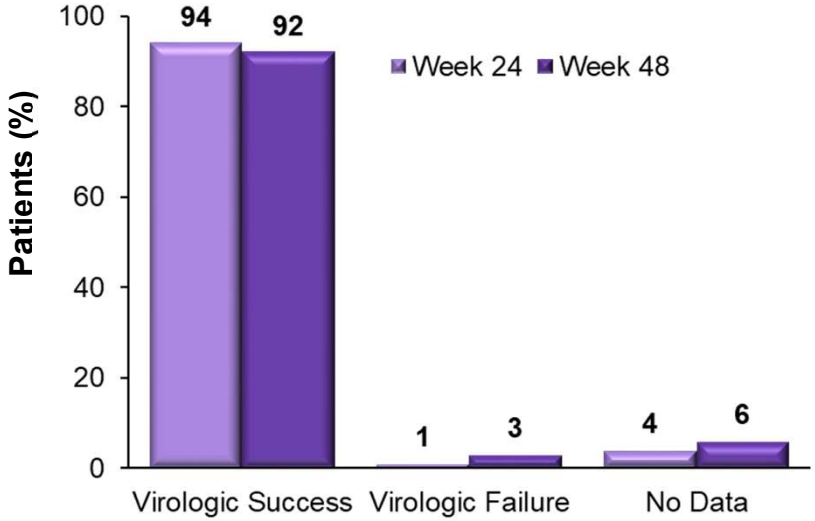
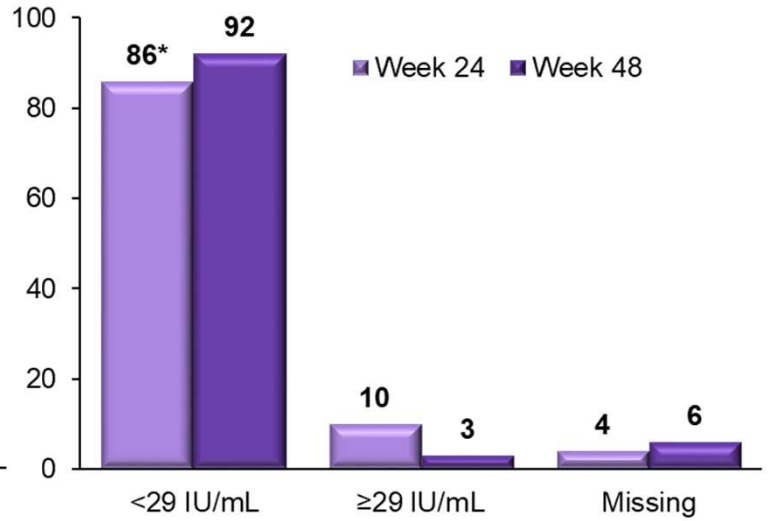
HIV-1 RNA <50 Copies/mL (FDA Snapshot)



HBV DNA <29 IU/mL (Missing=Failure)



*Note: 86% of patients had baseline HBV DNA <29 IU/mL

Switching to E/C/F/TAF maintained/achieved high rates of HIV and HBV suppression through 48 weeks

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Switch to TAF in PLWH with concurrent medications

Concomitant Drug Class: Drug Name	Effect on Concentration (↓ = decrease)	Clinical Comment
Protease Inhibitor: Tipranavir/ritonavir	↓TAF	Coadministration with FTC/TAF is not recommended.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓TAF	Consider alternative anticonvulsant.
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓TAF	Coadministration of FTC/TAF with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓TAF	Coadministration of FTC/TAF with St. John's wort is not recommended.

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Conclusions

Switching to TAF should be considered in specific populations:

- Efficacy is maintained for HIV treatment
- Well-tolerated and safe
- Better safety profile (kidney and bone)
- Adverse effects on lipids and weight gain
- Considering drug-drug interaction