14th Residential Course on Clinical Pharmacology of Antiretrovirals

Turin, 16-18 January 2019

SESSION II – TWO-DRUG REGIMEN FOR HIV INFECTION (Chair: C. Mussini, A. Castagna)

9:00 Trials evaluation **(D. Ripamonti)**

9:30 Two-drug regimen in HIV infection **(G. Di Perri)**

SESSION III - INSIGHTS ON CLINICAL PHARMACOLOGY OF ARVs (Chair: S. Khoo, A. D'Avolio)

10:00 Clinical pharmacology of new and upcoming ARV compounds **(M. Boffito)**

10:30 Case-based discussion on ARVs and DDIs in pregnancy **(D. Burger)**

11:00 Coffee break

11:30 Clinical pharmacology of TAF and Cobicistat: more data from the clinical ground **(S. Bonora)**

12:00 Case-based discussion: clinical pharmacology of INI + PI regimens **(M. Ferrara)**

12:30 The long-acting wave: perspectives and pipeline **(C. Flexner)**

13:00 Lunch

TAF vs TDF, *facts* from all the comparative trials

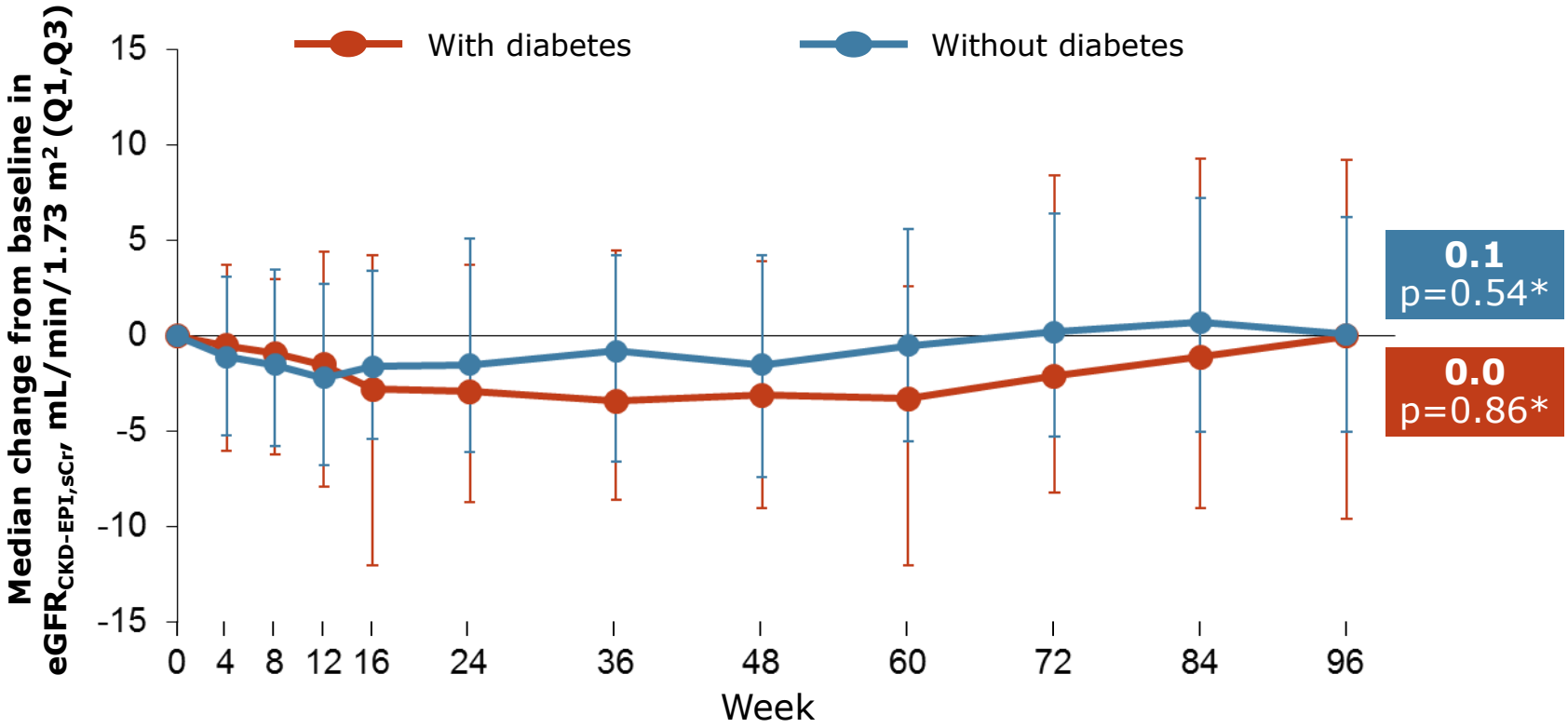
- ✓ TAF resulted non inferior to TDF as efficacy
- ✓ TAF resulted better tolerated in terms of tubular proteinuria (RBP) and proximal tubular toxicity
- ✓ TAF resulted better tolerated in term of decreases BMD and in prevalence of osteopenia/osteoporosis
- ✓ TAF showed a worse lipids trend as compared to TDF

How this bunch of information has changed my practice?

1. May I use TAF in patients with renal/bone disease?

Study 112: Suppressed diabetics adults with renal impairment switched to E/C/F/TAF

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



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**

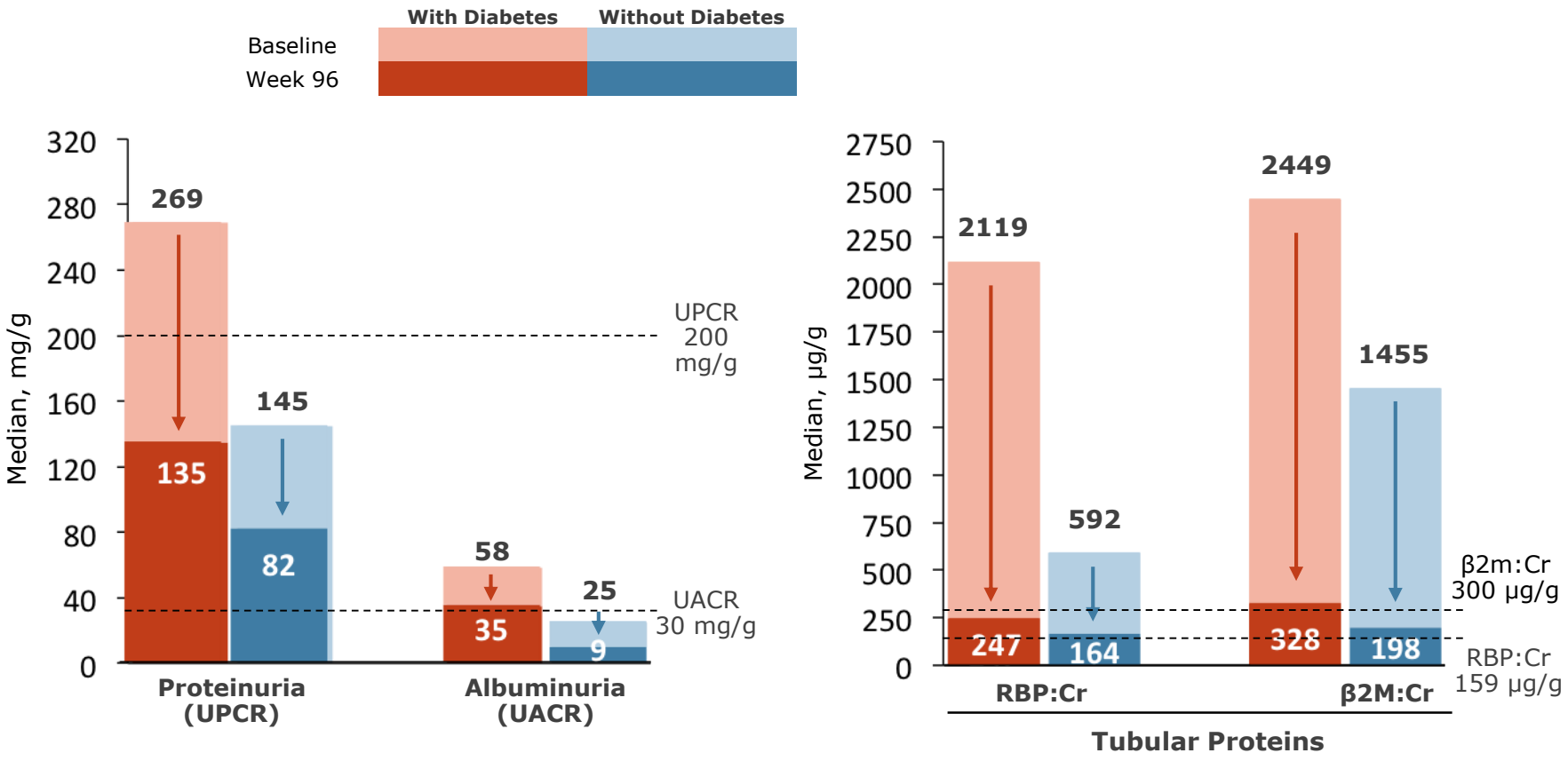
* Baseline vs Week 96 (2-sided Wilcoxon signed-rank test)

C, cobicistat; E, elvitegravir; F, emtricitabine; TAF, tenofovir alafenamide

Stein D et al. ASM 2016. Boston MA. # 371

Study 112: Suppressed diabetics adults with renal impairment switched to E/C/F/TAF

Changes in renal biomarkers at week 96



- **Significant reductions in proteinuria and tubular proteinuria (all p<0.05), with a reduction in albuminuria (p=0.09)***

* All changes statistically significant, with exception of UACR in diabetic patients (p=0.09)
β2-m, β2-microglobulin; C, cobicistat; Cr, creatinine; E, elvitegravir; F, emtricitabine; RBP, retinol-binding protein; TAF, tenofovir alafenamide; UACR, urine albumin–Cr ratio; UPCR, urine protein–Cr ratio

Stein D et al. ASM 2016. Boston MA. # 371

‡

Outcomes in Subjects with Low Baseline BMD Switched from TDF to TAF

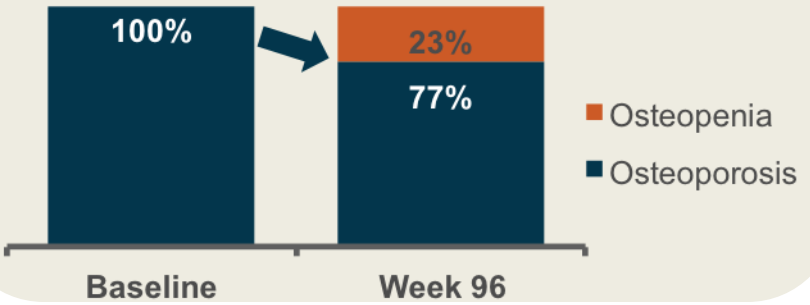
Analysis of outcomes and predictors of clinically significant BMD increases (≥5%) at W96 in the 214 subjects with low baseline BMD (T-score ≤ -2.0) in pooled TAF studies (E/C/F/TAF Studies 109 and 112)

Baseline T-score ≤ -2.0

- Significant BMD increases observed
  - Spine: +2.53% (p<0.001)
  - Hip: +2.39% (p<0.001)
- Proportion of low BMD participants experiencing ≥5% BMD increase
  - Spine: 27% (52/193)
  - Hip: 16% (32/195)

Baseline T-score ≤ -2.5

- 86 subjects with low baseline BMD also had osteoporosis*
  - 23% of these subjects improved to osteopenia by Week 96



- Factors predicting ≥5% BMD increase after a switch from TDF to TAF:
  - Urinary phosphate wasting ($FEPO_4$ ≥ 10%) or
  - High bone turnover (P1NP levels >1.72 $\log_{10}$ ng/mL)

Switching from TDF to TAF is an important treatment strategy to increase BMD in PLWHIV

* Subjects had osteoporosis at baseline and W96 follow-up BMD data

Brown T, et al. CROI 2017. Seattle, WA. Poster #683

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2. Is TAF simply **less harmful** for kidney/bone as compared to TDF, or **really harmless,** as ABC, FTC and 3TC are?

Switch from ABC/3TC to FTC/TAF in Suppressed Individuals

Phase 3, randomized, double-blind, double-dummy, active-controlled study in US and EU

ABC/3TC FDC + Third Agent
N=556*
- HIV-1 RNA <50 c/mL for ≥6 mo
- No CD4 criteria
- CrCL ≥50 mL/min
- No single tablet regimen allowed

1:1

n=280
- FTC/TAF† QD
- ABC/3TC Placebo QD
- Continue Third Agent‡

n=276
- ABC/3TC QD
- FTC/TAF† Placebo QD
- Continue Third Agent

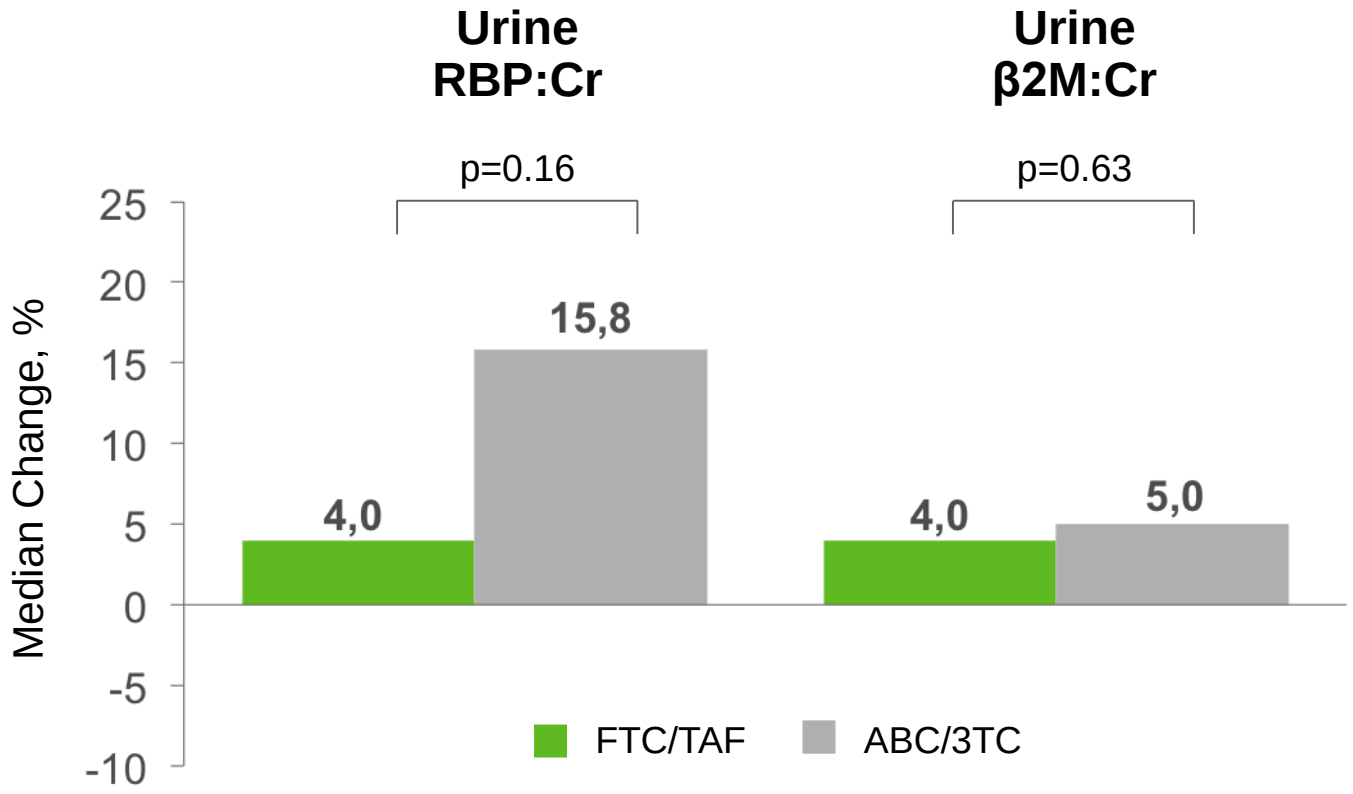
Week 0 — 48 — 96

1º Endpoint
HIV-1 RNA <50 c/mL
(snapshot analysis)

2º Endpoint

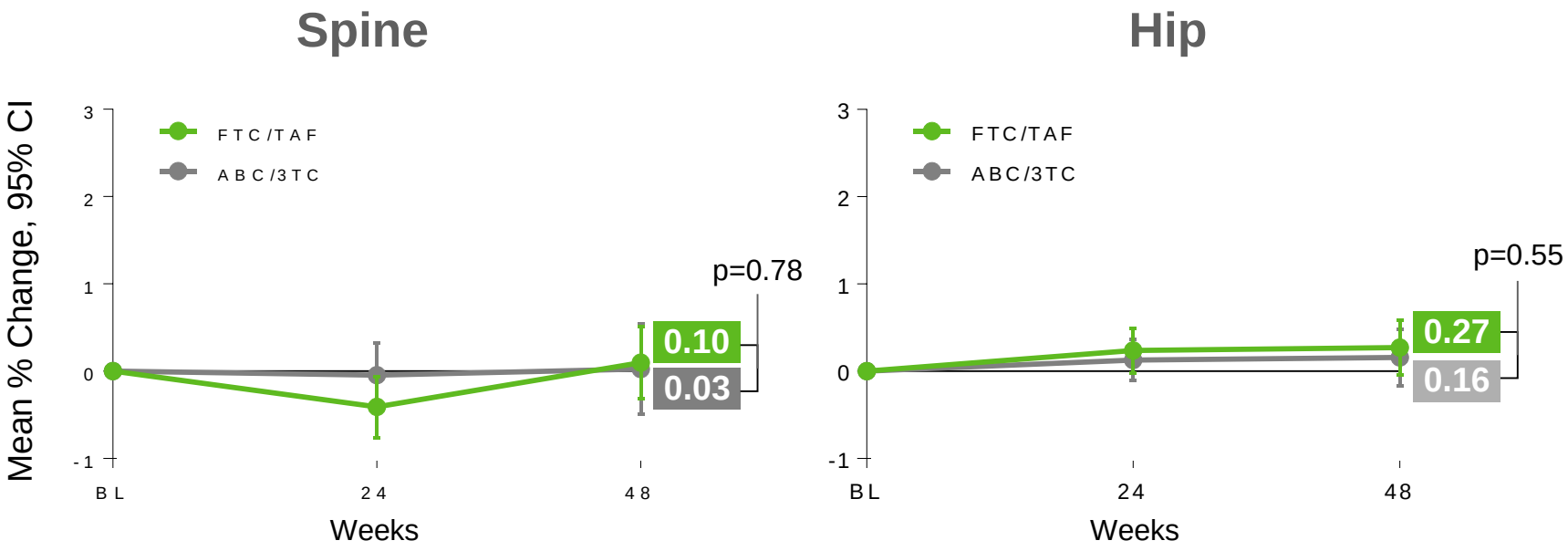
A. Winson, EACS 2017

Change in Renal Biomarkers



A. Winson, EACS 2017

Change in Bone Mineral Density



FTC/TAF, n	256	238	213	253	235	212
ABC/3TC, n	251	237	217	248	233	212

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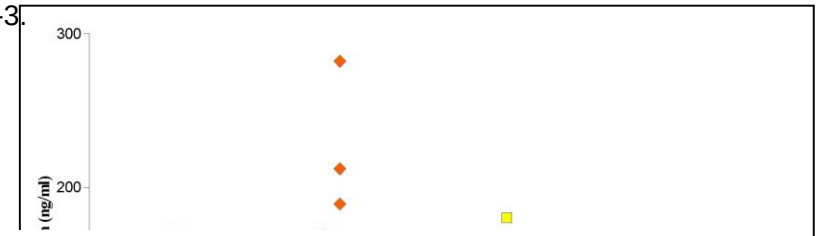
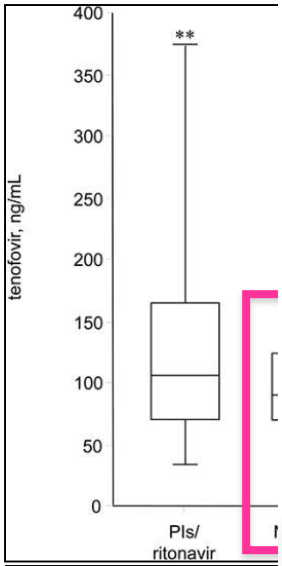
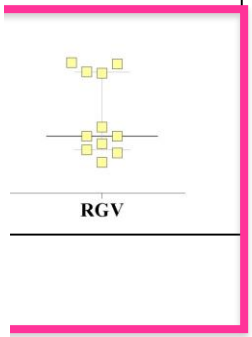


The TFV plasma level Contest





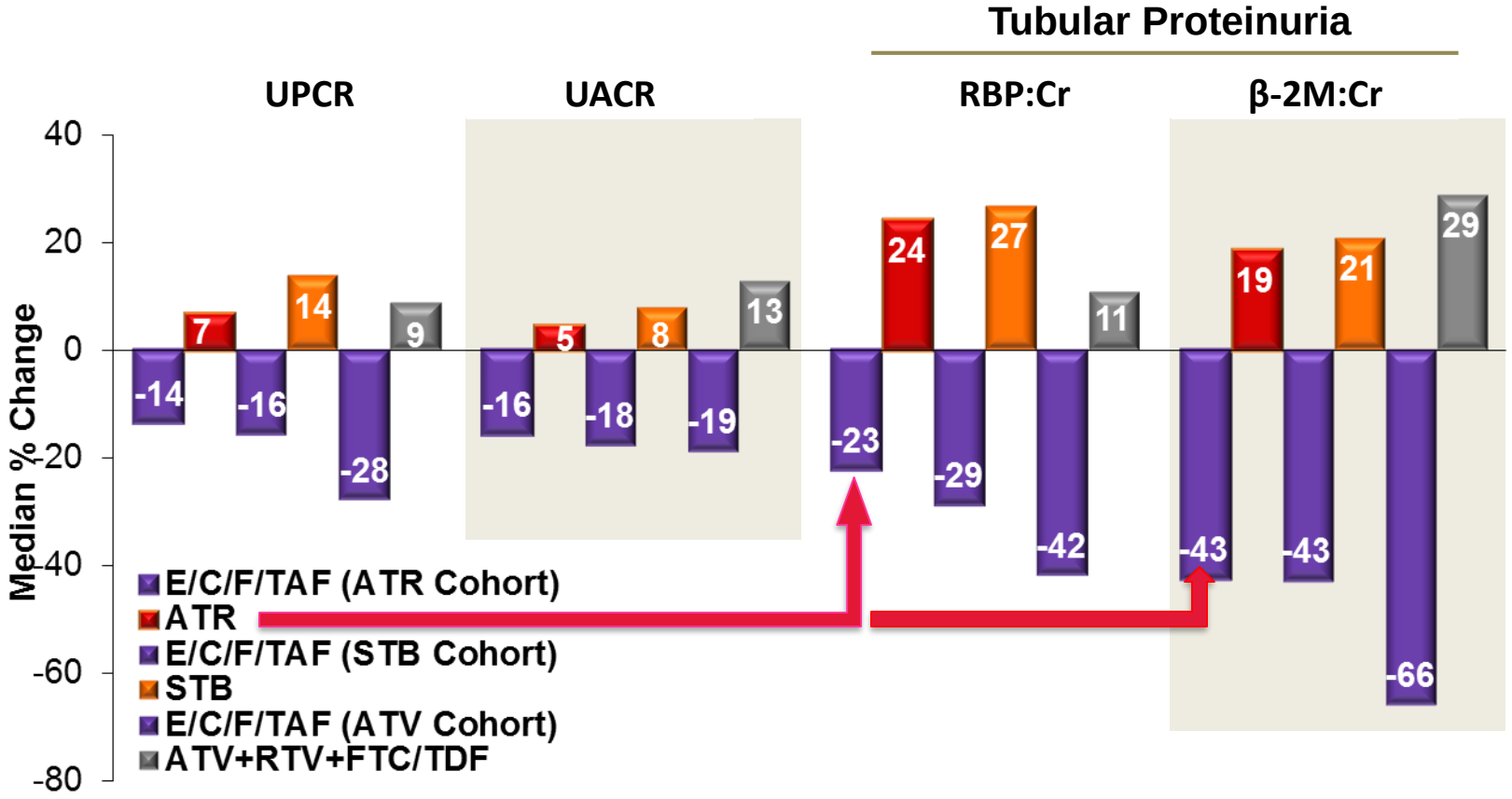
Effect of Cobicistat on Ter
(TDF): What Is True for TA
Cattaneo, Dario; PharmD,
Sara; Mazzali, Cristina; Giacomelli, Andrea; Milazzo, Laura; Meraviglia, Paola; Resnati, Chiara; Rizzardini, Giuliano; Clementi, Emilio; Galli, Massimo; Gervasoni, Cristina

JAIDS Journal of Acquired Immune Deficiency Syndromes. 77(1):86-92, January 1, 2018.

	(mean % CV)
	00 (50)
ATV+RTV (n=26)	3940 (30)
DRV+RTV (n=12)	4630 (16)
LPV/r (n=45)	3500 (27)
RPV/FTC/TDF (n=24)	3610 (21)
EFV/FTC/TDF (n=30)	2280 (19)

Ramanathan S, *et al.* CROI 2013; Atlanta, GA. #520

Changes in Quantitative Proteinuria at Week 48



All measures of proteinuria significantly decreased by Week 2 and persisted to Week 48 with switch to E/C/F/TAF

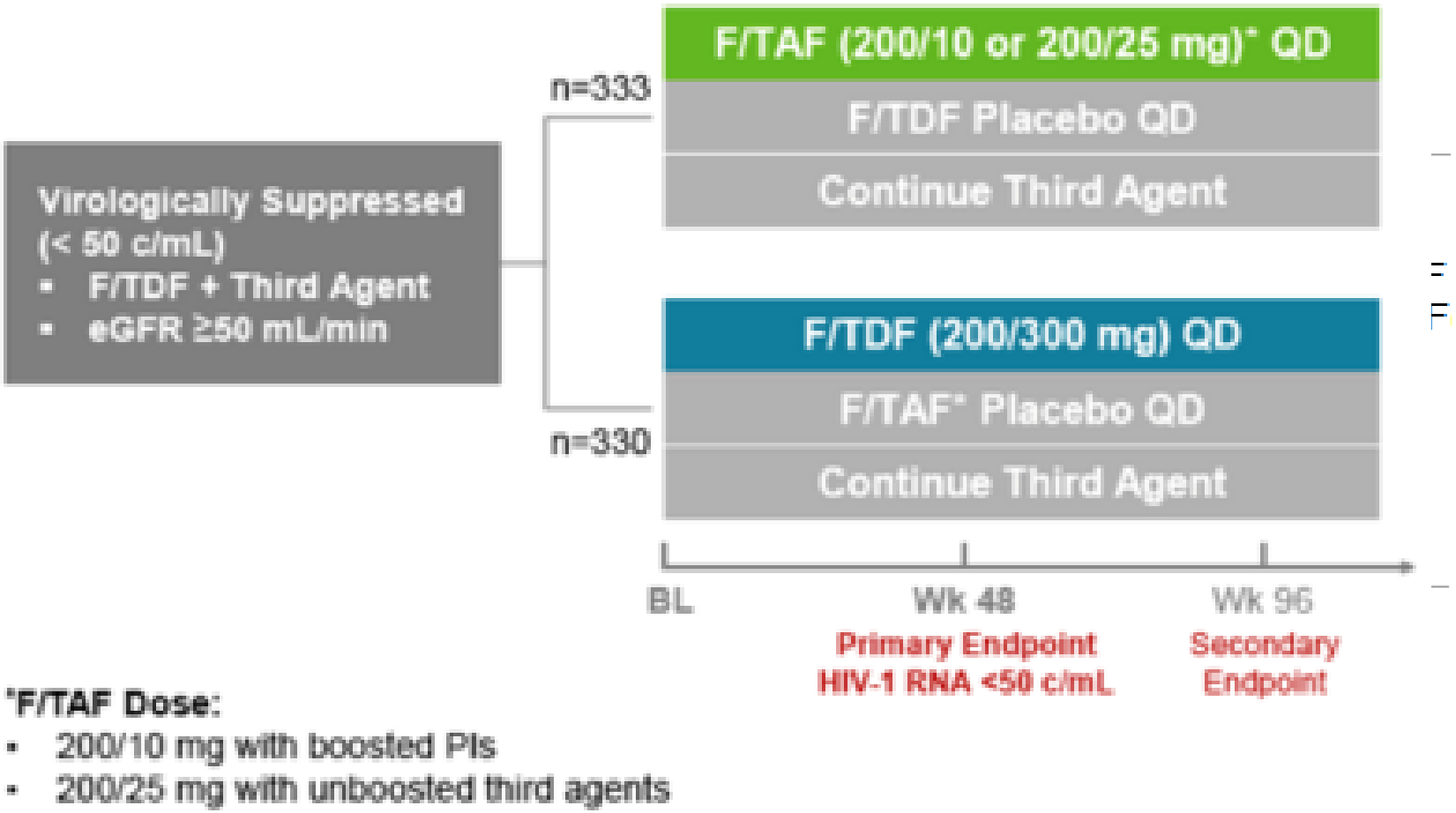
* Each difference between treatment arms was statistically significant ($p<0.001$).

UPCR = urine protein to creatinine ratio
UACR = urine albumin to creatinine ratio
RBP:Cr = retinol binding protein to creatinine ratio
β2M:Cr = beta-2-microglobulinemia to creatinine ratio

1. Shamblaw D, et al. ICAAC 2015, San Diego, CA. Oral
2. Thompson M, et al. ID Week 2015. San Diego, CA. Oral #725
3. Rijnders B, et al. EACS 2015. Barcelona, Spain. Oral # PS10/3

Switch from F/TDF to F/TAF

- Randomized, double-blind, double-dummy, active-controlled study

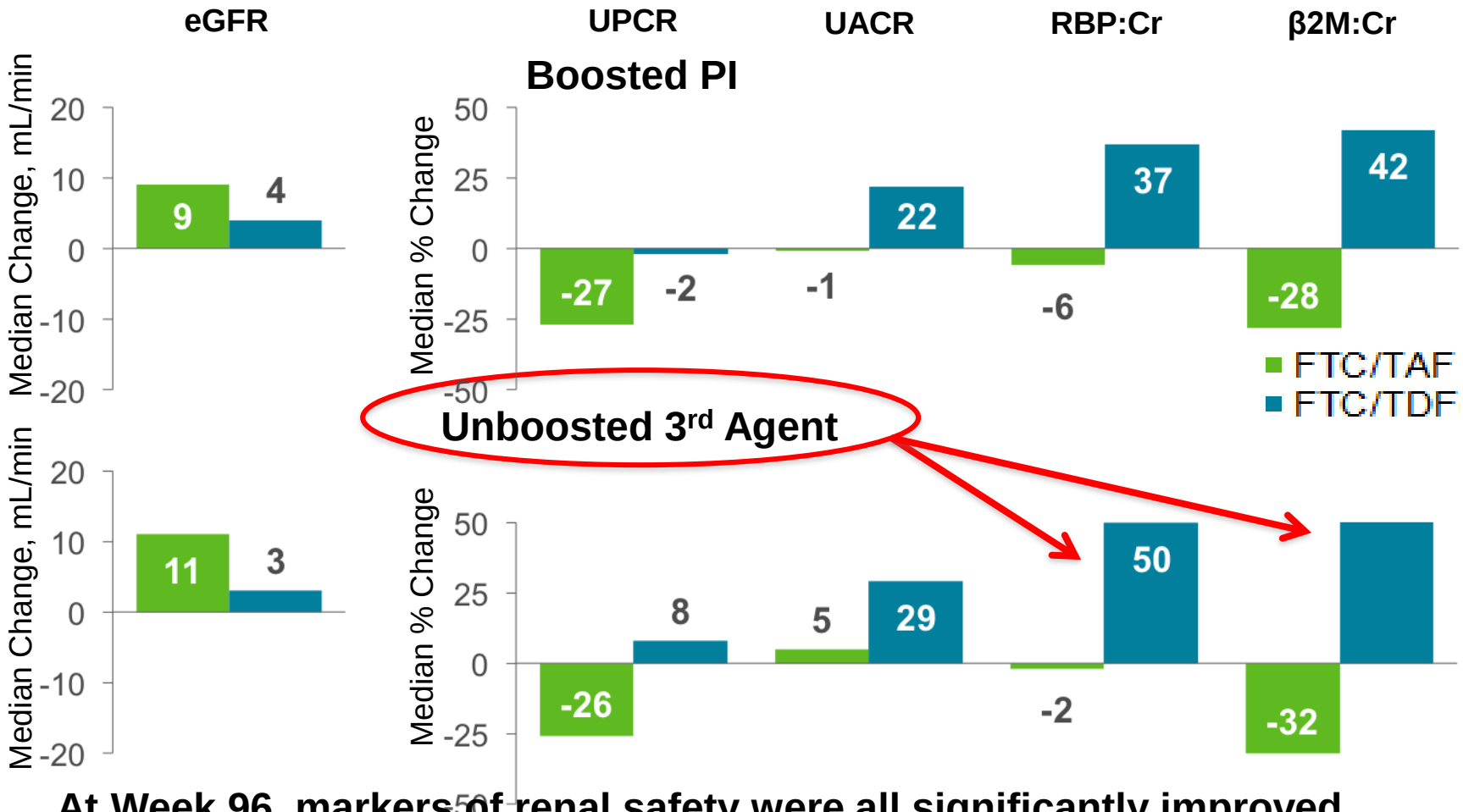


*F/TAF Dose:
- 200/10 mg with boosted PIs
- 200/25 mg with unboosted third agents

•*All dif
•eGFR,

Post et al. HIV MED 2017

Change in Renal Biomarkers by 3rd Agent



At Week 96, markers of renal safety were all significantly improved with switch to FTC/TAF, regardless of 3rd agent*

- *All differences between treatments were statistically significant ($p \leq 0.005$) regardless of 3rd agent
- eGFR, estimated glomerular filtration rate; Cr, creatinine; RBP, retinol-binding protein; β2M, β2-microglobulin.

Post et al. HIV MED 2017

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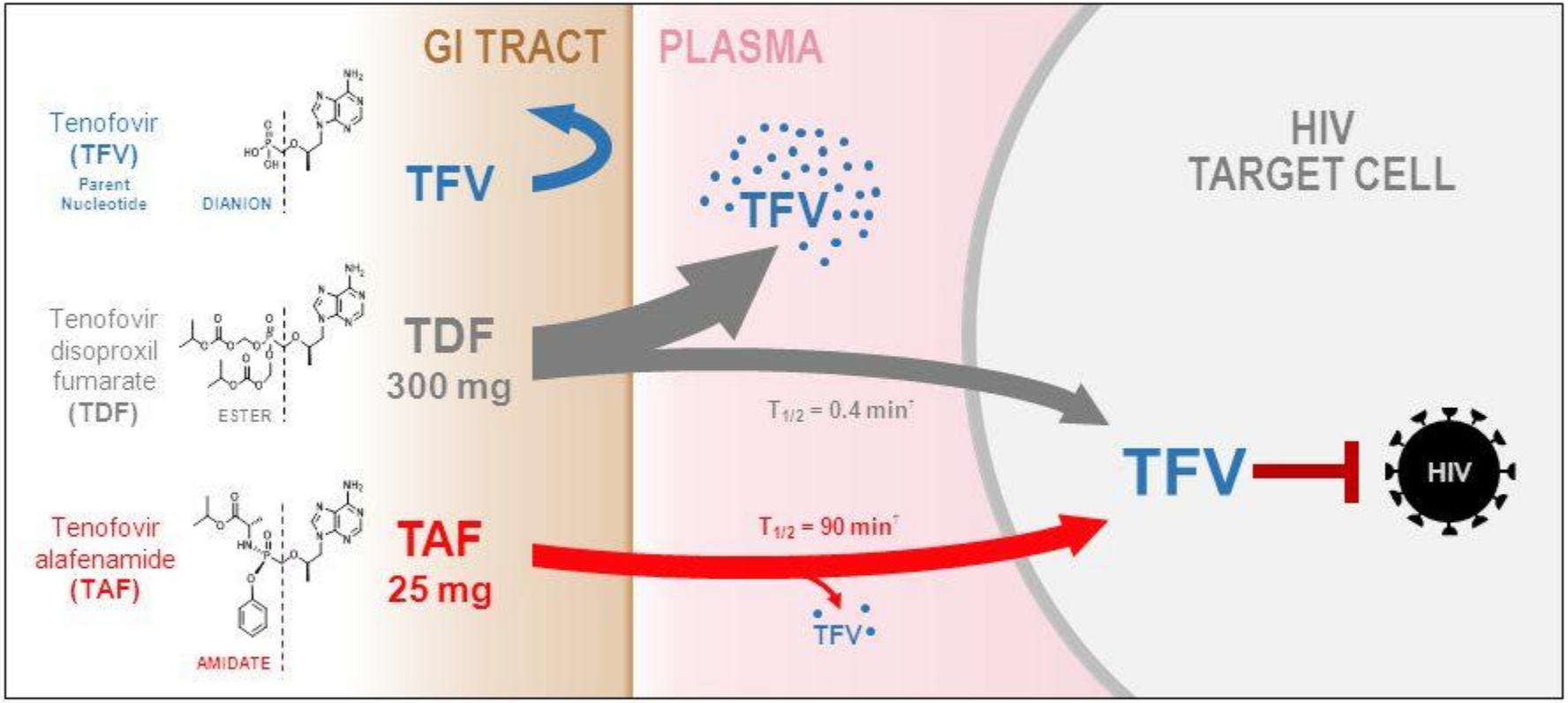
Some data gap or criticism still exist……

1. “Really full renal safety?”

Possibile residual renal effect, with very slow onset, not still captured in clinical trials?

The tubular damage is typical of the family drug (adefovir, cidofovir..) and even with TDF was reported and considered as a problem after many years of use.

Tenofovir Alafenamide (TAF): Novel Prodrug of Tenofovir

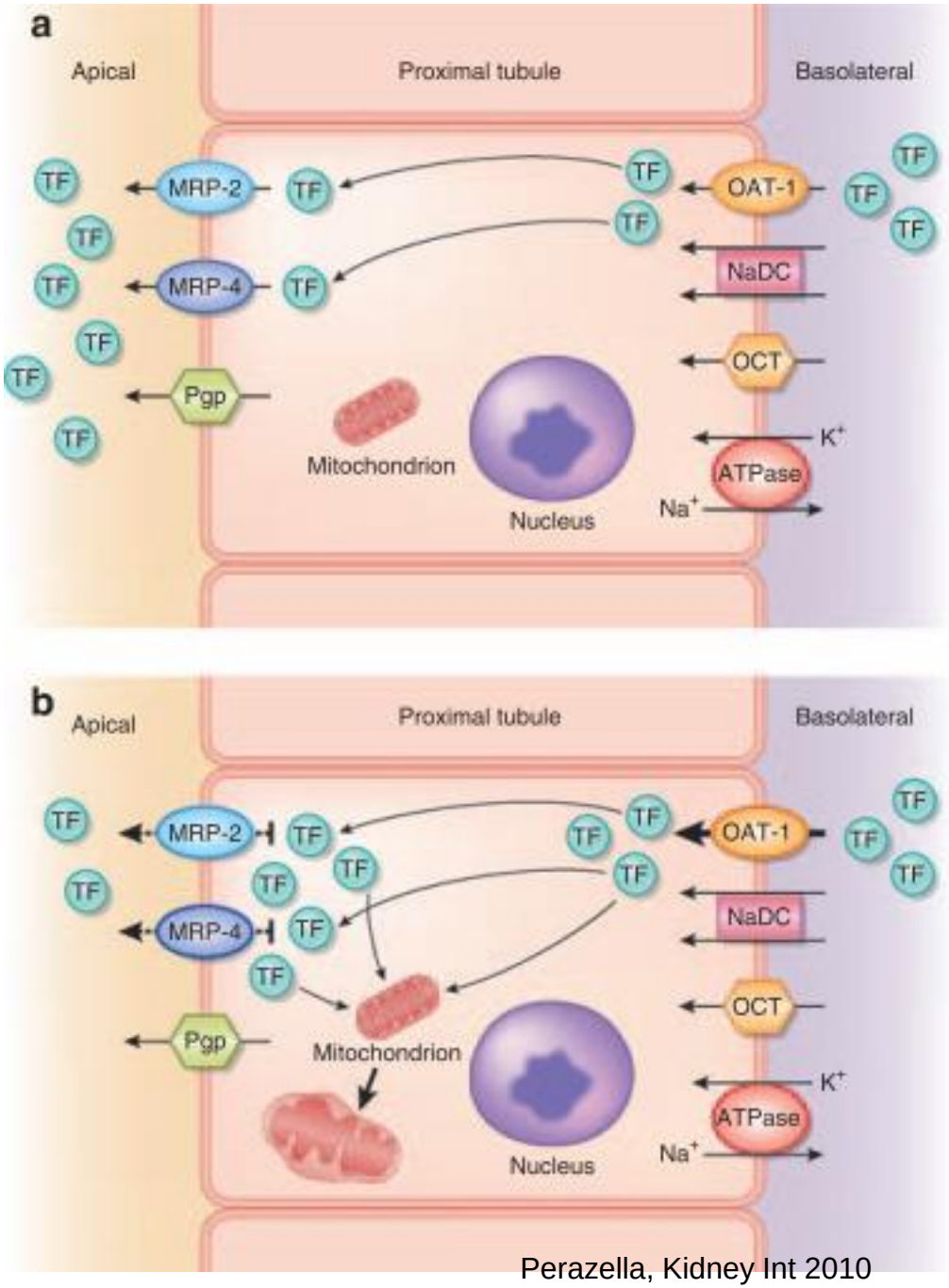


- **91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV**

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

1. Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. 2. Birkus G et al. *Antimicr 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.

Renal accumulation of TFV and the resulting effects on the function of the proximal tubule are caused by **highly efficient uptake** from plasma and **less rapid efflux** into urine.

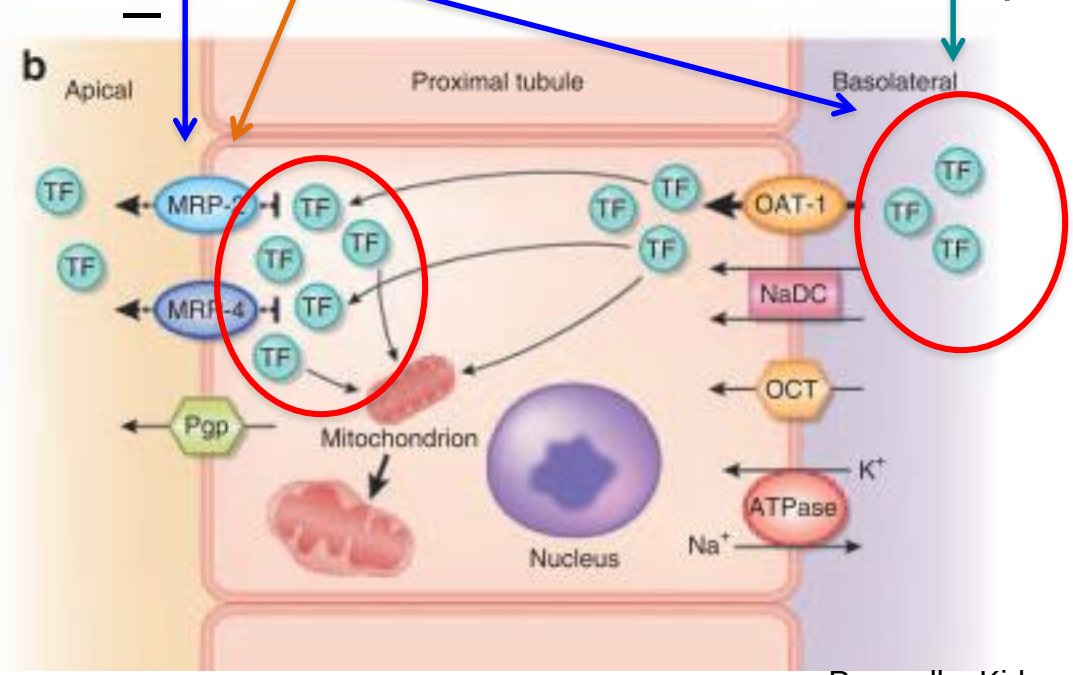


Perazella, Kidney Int 2010

Decrease of efflux:
- Age, gender,BMI
- Concomitant renal diseases
- Genetics

Decrease of efflux + increase of uptake (increase of plasma TFV):
- RTV based regimens

Increase of uptake (increase of plasma TFV):
- COBI-based



Perazella, Kidney Int 2010

Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients

José L. Casado[a], Carmen Santiuste[b], Monica Vazquez[c], Sara Bañón[a], Marta Rosillo[b], Ana Gomez[b], María J. Perez-Elías[a], Carmen Caballero[d], José M. Rey[b] and Santiago Moreno[a]

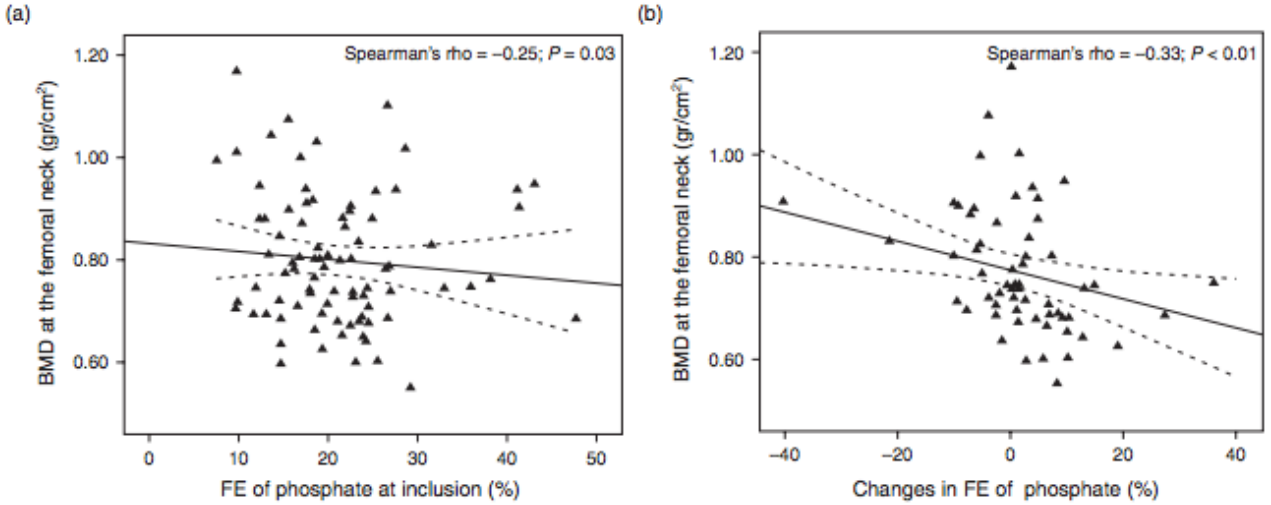


Fig. 2. (a) Correlation between phosphaturia (fractional excretion of phosphate) and bone mineral density at femoral neck at inclusion. (b) Bivariate correlation between bone mineral density at hip and changes in fractional excretion of phosphate (%) before inclusion.

Chronic abnormal phosphaturia explains, at least in part, progressive **bone loss during TDF therapy**.

These data suggest that **tubular dysfunction** leads to an altered equilibrium between phosphataemia, phosphaturia, and bone as **mechanism of progressive BMD decline**

AIDS 2016

Bone damage by TDF: beyond renal proximal tubulopathy?

Alternative or complementary mechanism(s) through which TDF affects the bone

Direct effect

•In vitro studies have shown an altered expression of the genes implicated in cell signaling and in amino acid metabolism in osteoclasts and osteoblasts exposed to physiological doses of TDF (Grisby et al, 2010)

Indirect effects:

•***Inhibition of Vitamin D hydroxylation*** to to 1,25-hydroxyvitamin D (Borderi, pers, comm.)

•Higher plasma TDF concentrations were associated with ***higher vitamin D–binding protein,*** which leads to lower free 1,25-hydroxyvitamin D, thus suggesting a functional vitamin D deficiency that would explain the increase in parathyroid hormone (Havens et al AAC 2013)

•TDF is able ***to inhibit the activity of Calcium-Sensing Receptor*** in a dose-dependent manner, promoting hyperparathyroidism (Mingione et al 2018)

Tenofovir clearance is reduced in HIV-positive patients with subclinical tubular impairment

Andrea Calcagno, Jessica Cusato, Letizia Marinaro, Marco Simiele, Manuela Lucchiari, Chiara Alcantarini, Maria C. Tettoni, Laura Trentini, Giulio Mengozzi, Antonio D'Avolio, Giovanni Di Perri and Stefano Bonora

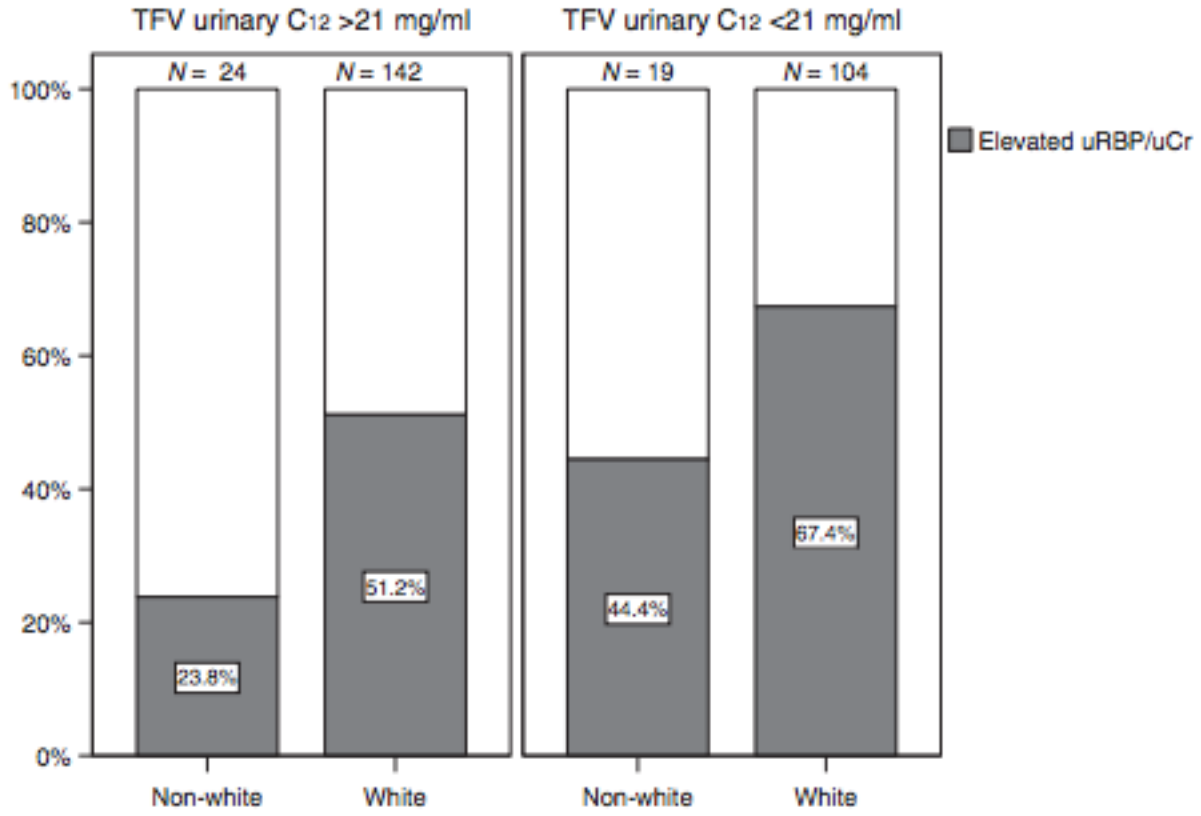
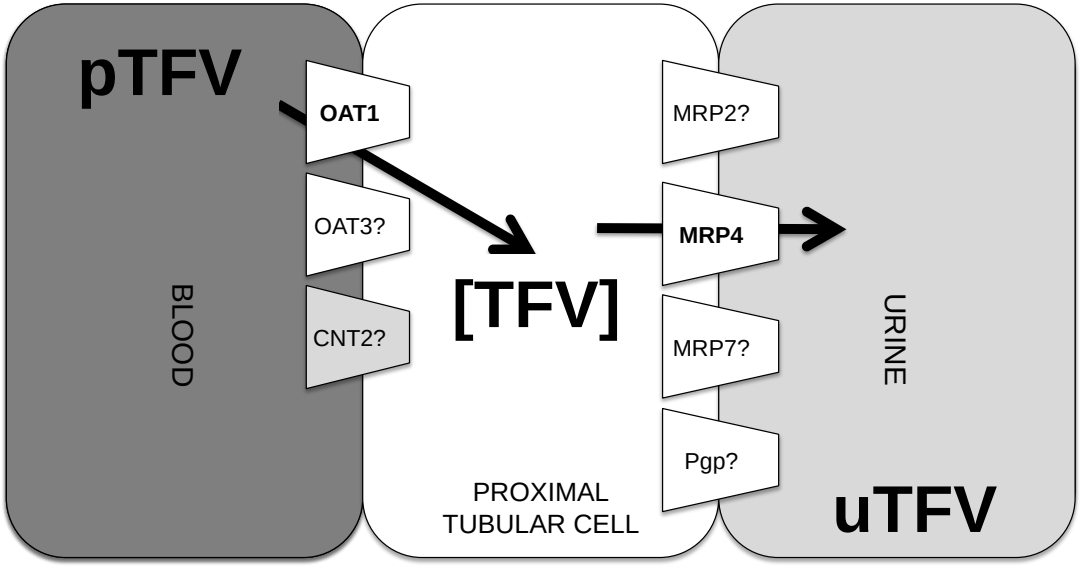


Fig. 2. Bars representing the prevalence of subclinical tubular dysfunction according to ethnicity and tenofovir urinary concentrations. TFV, tenofovir; urinary C_{12}, 12-h urinary concentration (mg/ml); uRBP/uCr, urinary retinal-binding protein/urinary creatinine. Tubular function was categorized using age-defined uRBP/uCr thresholds (<130 μg/g in patients aged <50 years and <172 μg/g in patients aged ≥50 years).

Clinical pharmacology of tenofovir clearance: a pharmacokinetic/pharmacogenetic study on plasma and urines

A Calcagno, J Cusato, L Marinaro, L Trentini, C Alcantarini, M Mussa, M Simiele, A D'Avolio, G Di Perri & S Bonora

ABCC10 GA/AA genotypes and protease inhibitor co-administration were independently associated with **the urinary to plasma tenofovir ratio**. Tenofovir clearance was associated with genetic polymorphisms in host genes and with co-administered drugs:



The Pharmacogenomics Journal volume 16, pages 514–518 (2016)

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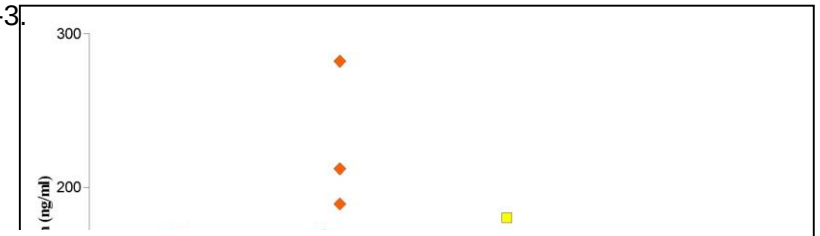

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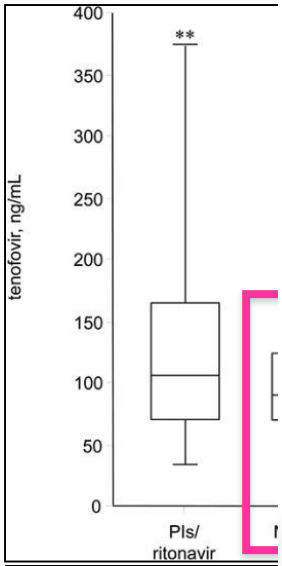

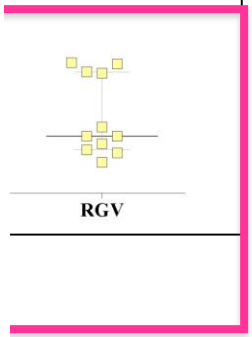

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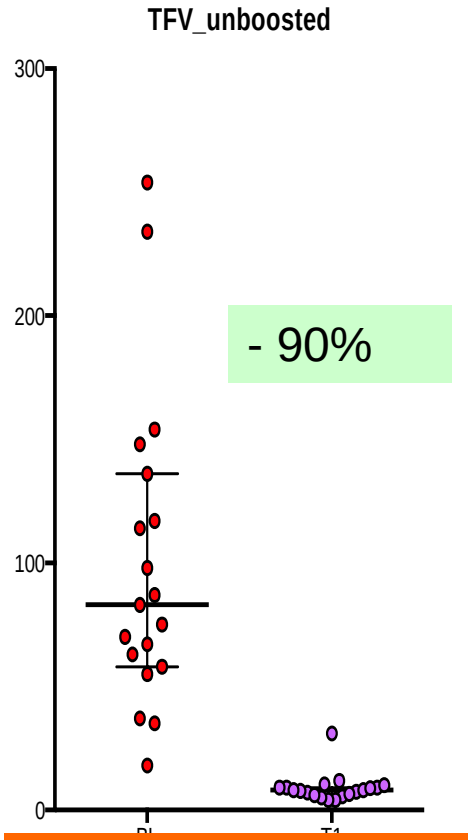
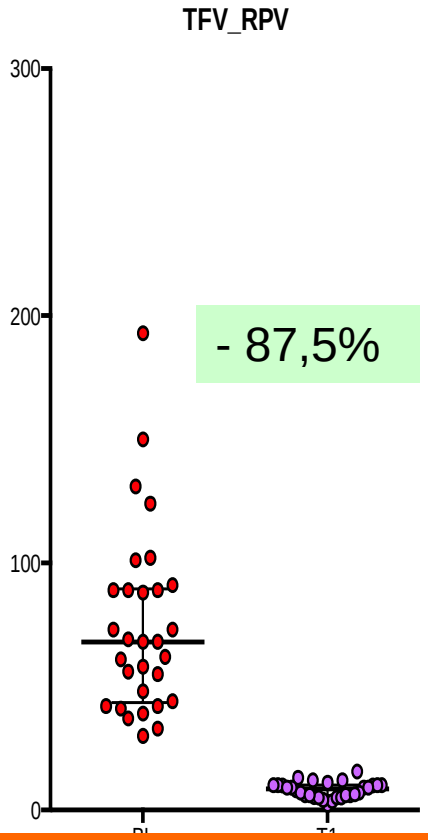
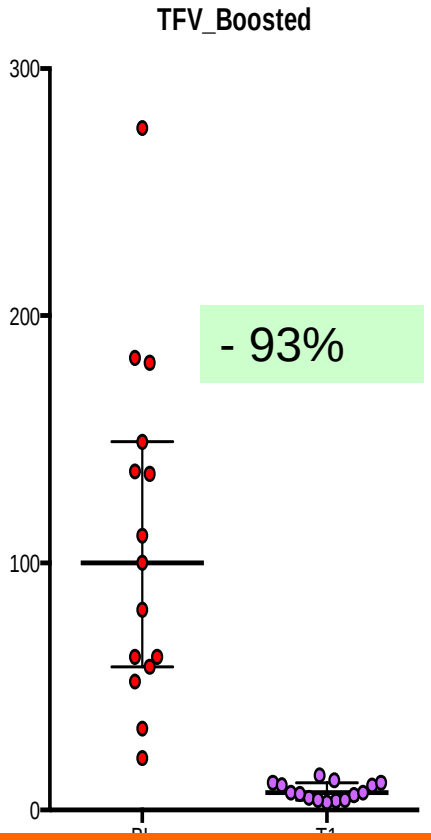
Ramanathan S, *et al.* CROI 2013; Atlanta, GA. #520

Plasma and urinary PK of TFV in the switch from TDF to TAF: preliminary results **at 6 months after switching (**N. Forni, unpublished**)**

Pre switch (% or median)			
N=64	Males 84%	Caucasian 86%	Age 47,5 years
BMI 24,5	Risk MSM 50%	CD4 current 783 cell/ul	CD4 nadir 294 cell/ul
Infected since 15,1 years	Suppressed since 94 monts	On TDF-FTC based therapy since 76 months	HIV_RNA TND 76%: HIV-RNA <20 cp/ml 23%
eGFR 101: >90 ml/min 64%; 89-60 ml/min 31%	PTH 43 U/L	ViT D 29,5 MG/ml	Ca 2.3 P 3.1
TDF/FTC + Boosted (1 uATV; 57ATV/DRV +r/cobi; 7 ELV/c): 15 pts			
TDF/FTC + Unboosted (RPV): 30 pts			
TDF FTC + Real unboosted (6 NVP, 1 EFV, 5 DTG, 7 RAL): 19			





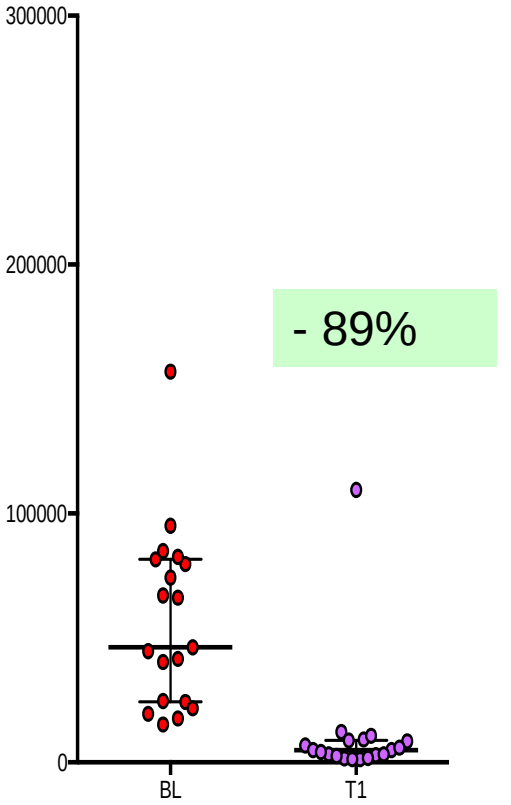


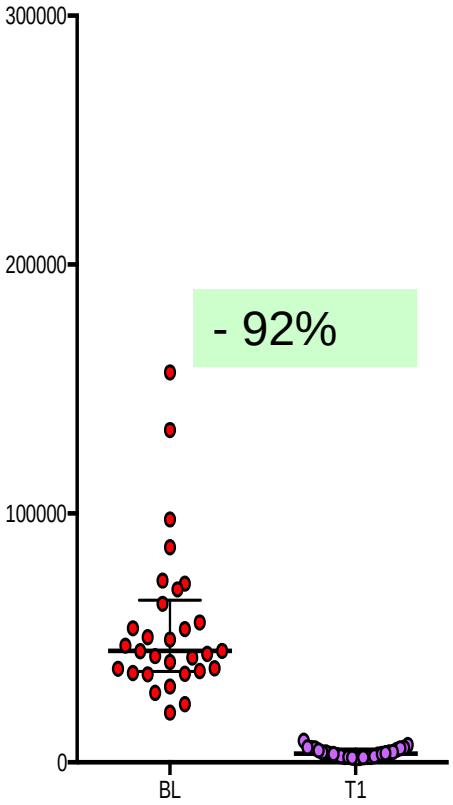
Our data confirmed very low levels of residual plasma TFV and no difference according to companion drug

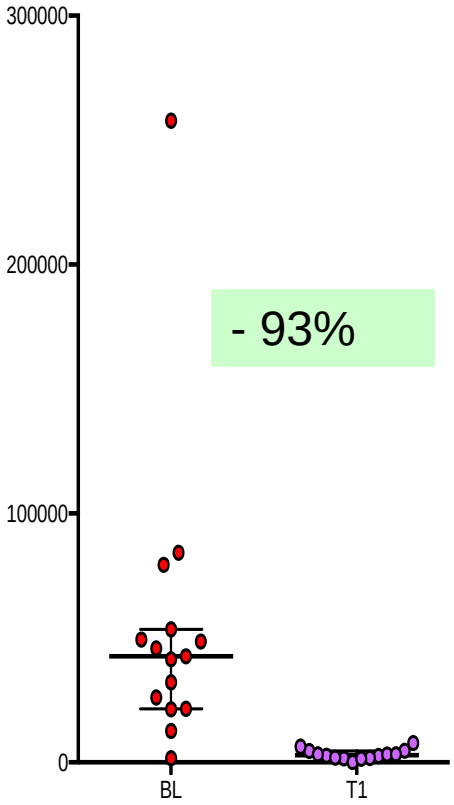
Minimum	18.00	4.000
25% Percentile	58.00	6.000
Median	83.00	8.000
75% Percentile	136.0	9.000
Maximum	254.0	31.00

Minimum	30.00	2.000
25% Percentile	43.50	5.823
Median	68.00	8.500
75% Percentile	89.50	10.00
Maximum	193.0	15.56

Minimum	21.00	3.070
25% Percentile	58.00	4.000
Median	100.0	7.000
75% Percentile	149.0	11.00
Maximum	276.0	14.00



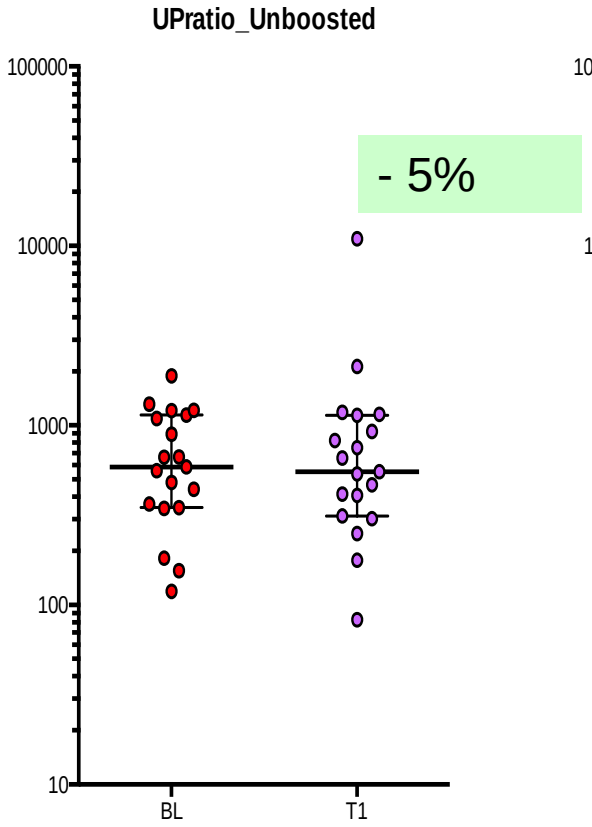


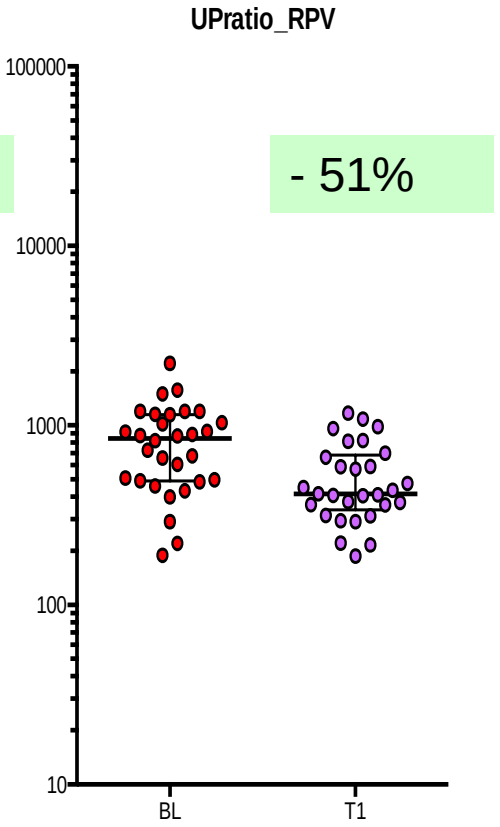


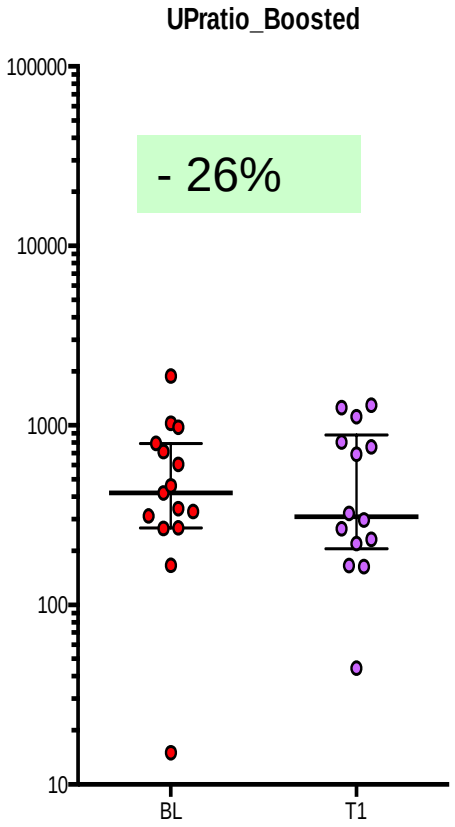
	BL	T1
Number of values	19	19
Minimum	15225	1249
25% Percentile	24277	2561
Median	46189	4875
75% Percentile	81543	8821
Maximum	156958	109441

	BL	T1
Number of values	30	29
Minimum	20040	1622
25% Percentile	36510	2172
Median	44768	3494
75% Percentile	65169	5344
Maximum	156662	8653

	BL	T1
Number of values	15	14
Minimum	1669	140.0
25% Percentile	21564	1770
Median	42577	2978
75% Percentile	53477	4589
Maximum	257708	7818





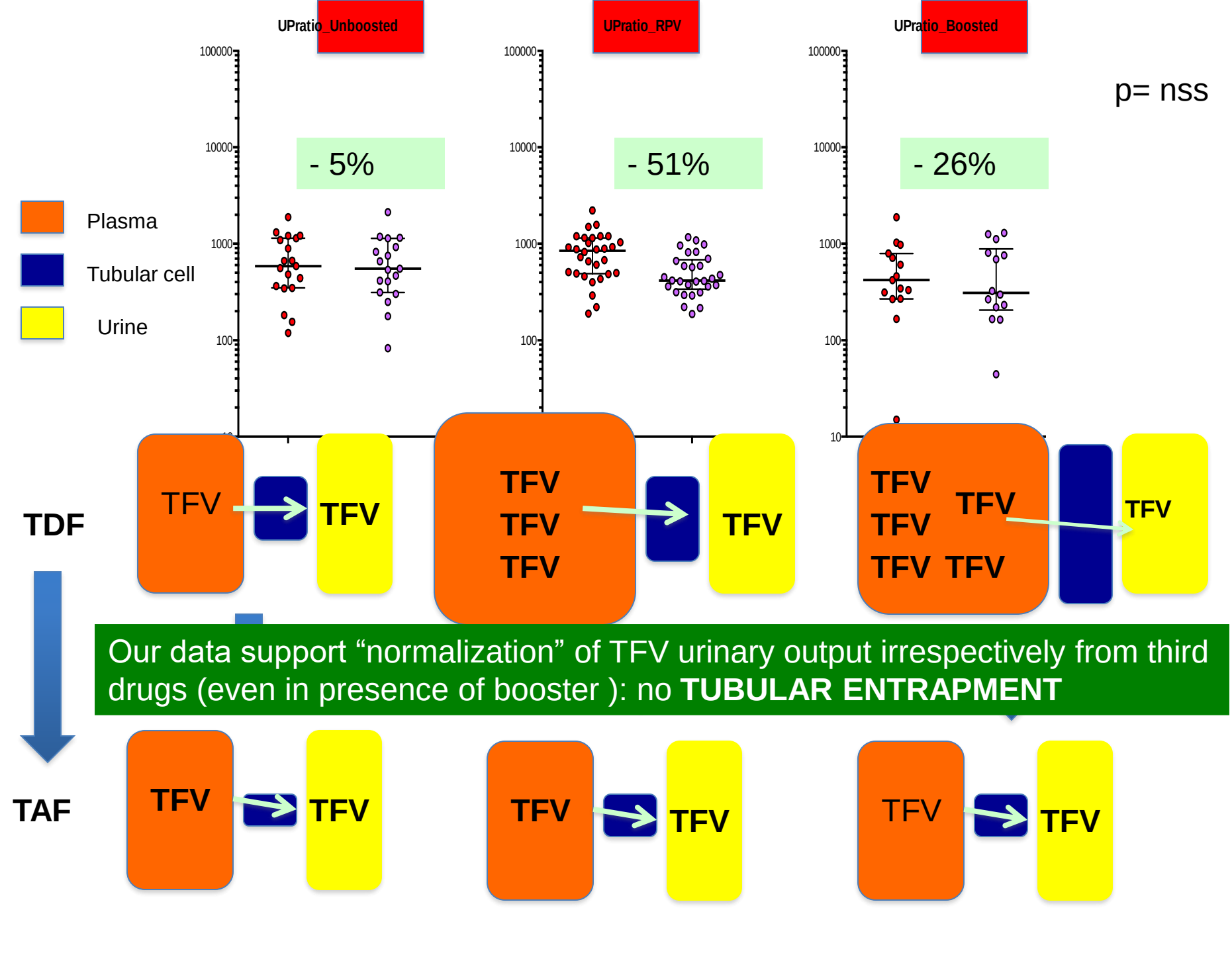


p= nss

	BL	T1
Number of values	19	19
Minimum	119.0	82.61
25% Percentile	348.5	312.8
Median	586.3	552.0
75% Percentile	1142	1139
Maximum	1891	10944

	BL	T1
Number of values	30	29
Minimum	189.1	186.8
25% Percentile	489.5	337.6
Median	847.5	415.3
75% Percentile	1148	682.8
Maximum	2218	1169

	BL	T1
Number of values	15	14
Minimum	15.00	44.44
25% Percentile	268.4	205.9
Median	420.4	310.0
75% Percentile	793.0	884.1
Maximum	1881	1297


UPratio_Unboosted
UPratio_RPV
UPratio_Boosted
p= nss
- 5%
- 51%
- 26%
Plasma
Tubular cell
Urine
TDF
TFV
TFV
TFV
TFV
TFV
TFV
TFV
TFV
TFV
TFV
TFV
Our data support “normalization” of TFV urinary output irrespectively from third drugs (even in presence of booster): no TUBULAR ENTRAPMENT
TAF
TFV
TFV
TFV
TFV
TFV
TFV

Some data gap or criticism still exist……

1. “Absolute renal safety?”

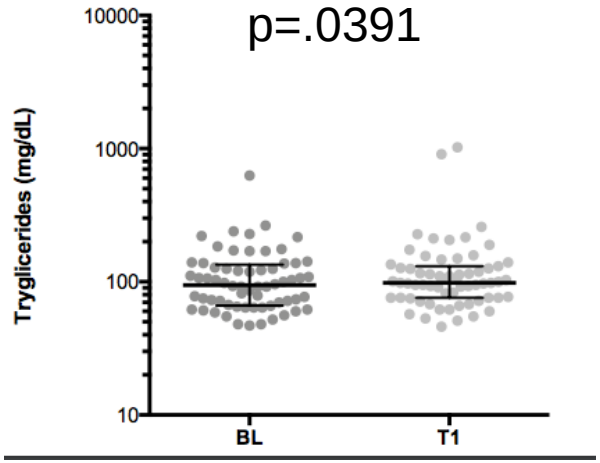
Possibile renal effect, with very slow onset, not still captured in clinical trials.
A renal efftect (tubular) is typical of the family drug (adefovir, cidofovir..) and even with TDF was not reported as a problem only after years of use.

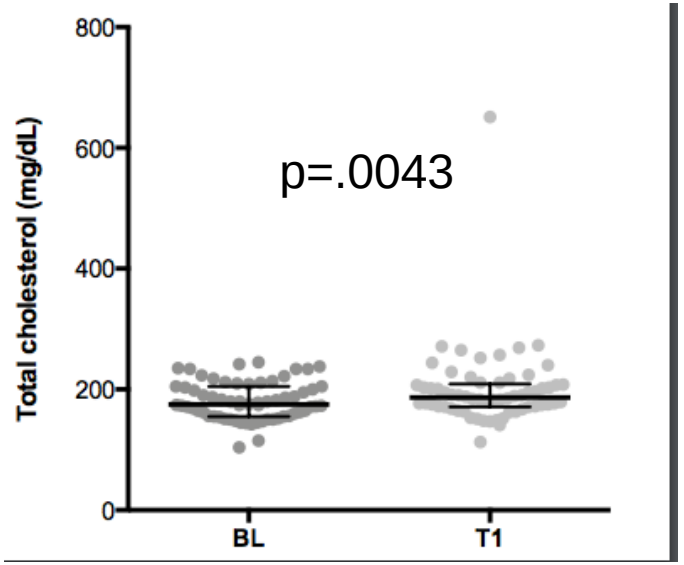
- With TAF it is difficult to envisage TFV tubular entrapment with any companion drugs .

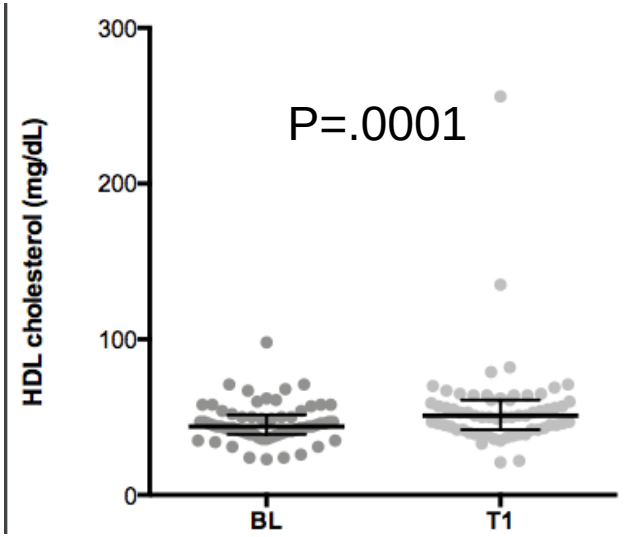
- *This should not led to significant risk of tubular damage even over long time and significant risk of indirect and direct bone loss even over long time,*

Some data gap or criticism still exist……

2. “TAF increases lipids and CV risk”

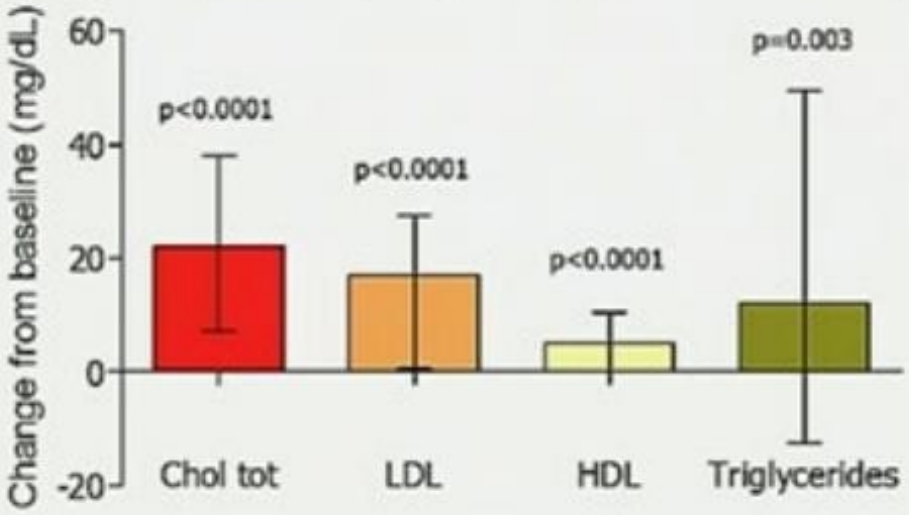






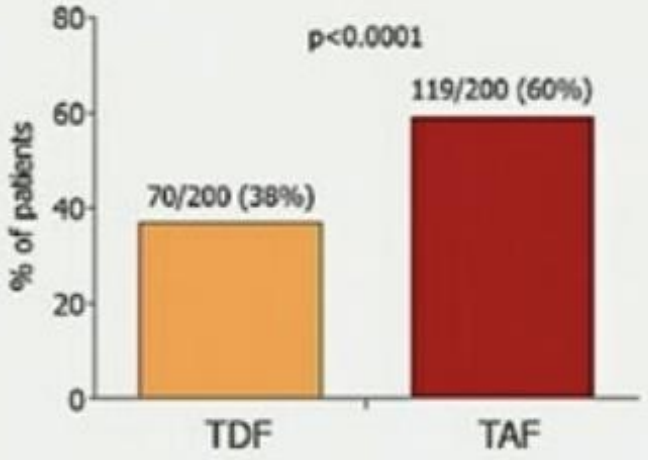
Change in plasma lipid levels after switch to TAF

Median time between palsma lipid point evaluations: 34 weeks (IQR 19-42)



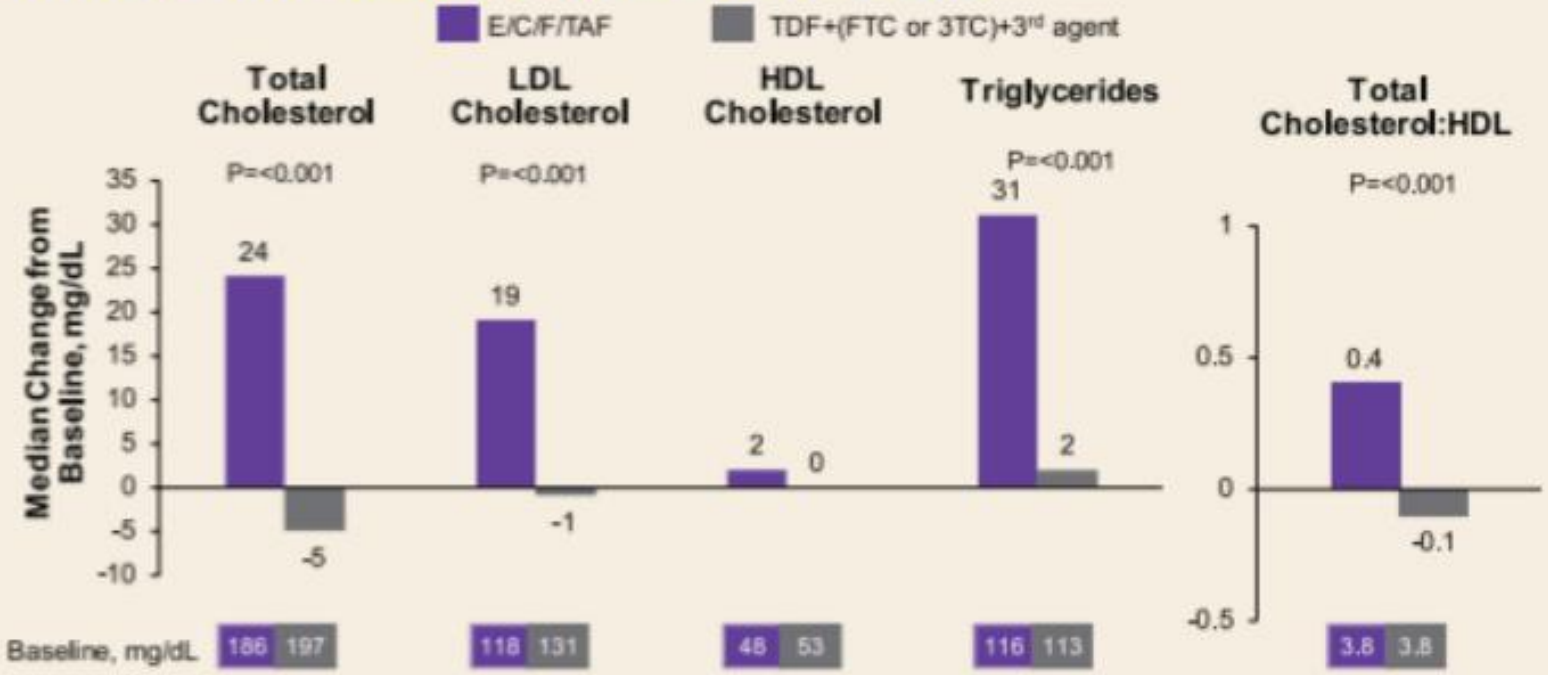
Prevalence of patients with OUT-OF-TARGET LDL

Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline[3] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[3] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).



Gazzola, EACS 2018

Changes in Fasting Lipids at Week 48



- Similar proportions of participants were on lipid-modifying medication
  - At baseline: E/C/F/TAF 37 (34%); TDF+ (FTC or 3TC) +3rd agent 18 (32%)
  - Initiated during study: E/C/F/TAF 3 (3%); TDF+ (FTC or 3TC) +3rd agent 1 (2%)

F. Maggiolo et al. Abstract P145

Some data gap or criticism still exist……

2. “TAF increases lipids and CV risk”

- Debate is ongoing, but switch away from TDF to TAF should simply considered as coming back to “natural” lipids set point.
- *Prevention of CV should rely on validate maesures (life style, statins, etcc)*
- *Up to now , no current evidence of a real increase of CV events in patients managed according to guidelines*

COBI vs RTV, *facts* from the development program

- COBI can be much easier coformulated
- Less DDIs due to selective CYP3A4 activity
- Similar PK robustness to confirm in the clinical setting
- No significant difference of tolerability in a single clinical trial in development phase

Some data gap….

- Does COBI have less impact on lipids in real life as compared to RTV?

Changes in Lipid Parameters

Echeverría P, et al. "Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia." HIV Med 2017.

Lipid parameter	Baseline	Week 24	P-value
Total population (n=299)			
Use of lipid-lowering agents (%)	12%	12%	--
TC (mg/dL) [median (IQR)]	190 (162, 216)	184 (154, 211)	0.085
LDL-c (mg/dL) [median (IQR)]	111 (92, 136)	109 (84, 132)	0.530
HDL-c (mg/dL) [median (IQR)]	44 (38, 54)	45 (38, 54)	0.440
TG (mg/dL) [median (IQR)]	167 (93, 187)	124 (87, 175)	**0.018**
Subjects with TC ≥ 200 mg/dL, LDL-c ≥ 130 mg/dL and/or TG ≥ 200 mg/dL (%)	52%	45%	0.112
Subjects with hypercholesterolaemia at baseline (TC > 200 mg/dL and/or LDL-c > 130 mg/dL) (n = 124)			
TC (mg/dL) [median (IQR)]	231 (209, 243)	212 (189, 239)	**0.001**
LDL-c (mg/dL) [median (IQR)]	144 (131, 161)	131 (113, 152)	**0.047**
HDL-c (mg/dL) [median (IQR)]	45 (40, 54)	52 (44, 59)	**0.002**
TG (mg/dL) [median (IQR)]	157 (109, 209)	131 (101, 202)	**0.025**
Subjects with hypertriglyceridaemia at baseline (TG > 200 mg/dL) (n = 64)			
TC (mg/dL) [median (IQR)]	207 (182, 232)	191 (158, 215)	0.067
LDL-c (mg/dL) [median (IQR)]	109 (84, 121)	105 (83, 127)	0.299
HDL-c (mg/dL) [median (IQR)]	40 (36, 45)	40 (36, 48)	0.381
TG (mg/dL) [median (IQR)]	352 (223, 389)	229 (131, 279)	**< 0.001**

Significant P-values are shown in **bold**.

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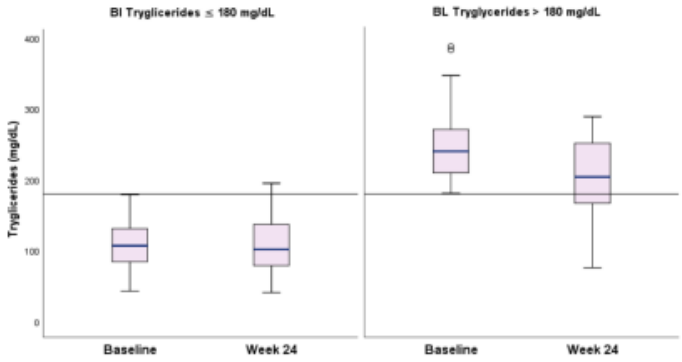
SWITCHING FROM ATAZANAVIR/RITONAVIR (ATV/RTV) TO ATV/COBICISTAT (COBI) IS ASSOCIATED WITH DECREASE OF PLASMA LIPIDS AND LIVER FIBROSIS

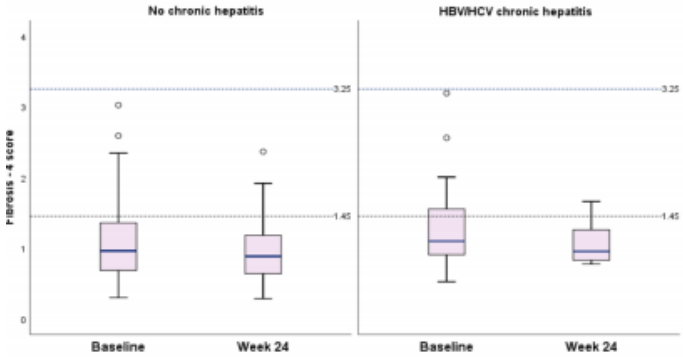
A. Trentalange[1], C. Polifroni[1], C. Carcieri[1], C. Alcantarini[1], C. Montrucchio[1], L. Marinaro[1], N. Forni[1], A. Palazzo[1], A. Barco[1], C. Costa[1], A. Lazzaro[1], M. Tettoni[1], A. De Nicolò[1], A. D'Avolio[1], G. Di Perri[1], A. Calcagno[1], S. Bonora[1]

Table 1.Characteristics of study population (n=121)		
Male gender, n (%)		84 (68,9)
Age*, years		48 (41-55)
CD4+ lymphocytes*, µg/ml		601 (437-820)
HIV RNA plasma < 20 cp/ml, n (%)		105 (88,2)
BMI*, Kg/m2		24,2 (21,1-26,4)
European ancestry, n (%)		100 (81,9)
CD4 lymphocytes*nadir, µg/ml		224 (129-290)
HCV+, n (%)		25 (21,9)
HBV+, n (%)		3 (2,5)
Associated antiretrovirals: NNRTIs	n (%)	1 (0.8)
INSTI	n (%)	26 (21.5)
NRTI	n (%)	96 (79.3)
CCR5i	n (%)	5 (4.1)
Comorbidities: Hypertension:	n (%)	21 (21)
Diabetes:	n (%)	8 (8,1)

- **In patients with BL hypercholesterolemia** (44,6%) total cholesterol decreased from 213 mg/dl (196-228) to 194 mg/dl (175-213) (p<0.001) and LDL-cholesterol from 140 mg/dl (130-155) to 137 mg/dl (120-155) (p=0.05).



- **In patients with baseline hypertriglyceridemia** (27,5%) Triglycerides decreased from 240 mg/dl (207-276) to 204 mg/dl (159-252) (p=0.01).



- **Fib-4** value decreased from 1.04 (0.73-1.41) to 0.93 (0.67-1.21) (p=0.001). This finding was confirmed even in HCV/HBV-negative patients [0.96 (0.68-1.39) to 0.90 (0.63-1.20), p=0.01]

Table 4

Inhibition of Cell Functions in Adipocytes[a]

compound	lipid accumulation EC_{50} (μM)	glucose uptake (% inhibition at 10 μM)
COBI	>30	9.5 ± 6.4
1 (RTV)	16 ± 8	55 ± 10
ATV	>30	0.4 ± 0.9

[a]Data shown represent the mean and s.d. from at least 3 independent experiments.

Xu et al, ACS Med. Chem. Lett. 2010,

J Antimicrob Chemother 2013; **68**: 907–910
doi:10.1093/jac/dks484 Advance Access publication 5 December 2012

Journal of Antimicrobial Chemotherapy

Intracellular accumulation of ritonavir combined with different protease inhibitors and correlations between concentrations in plasma and peripheral blood mononuclear cells

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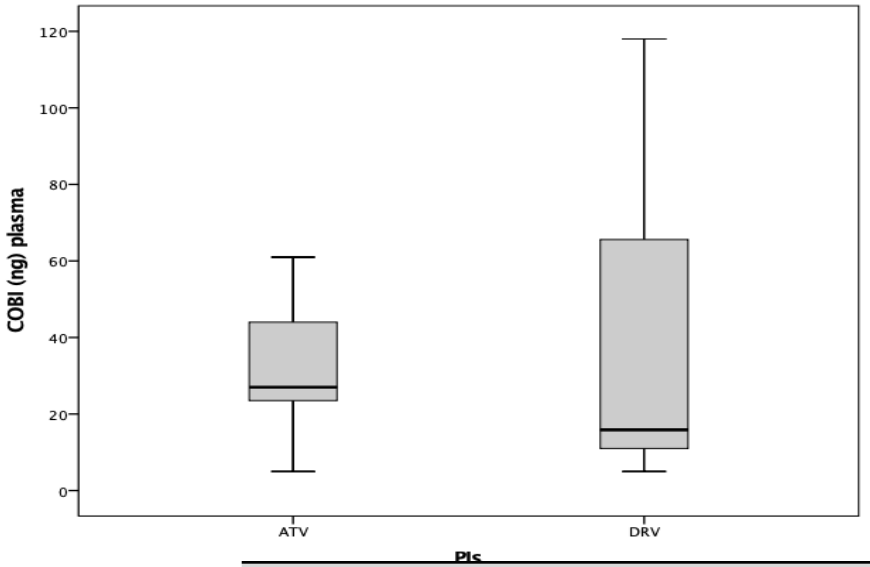
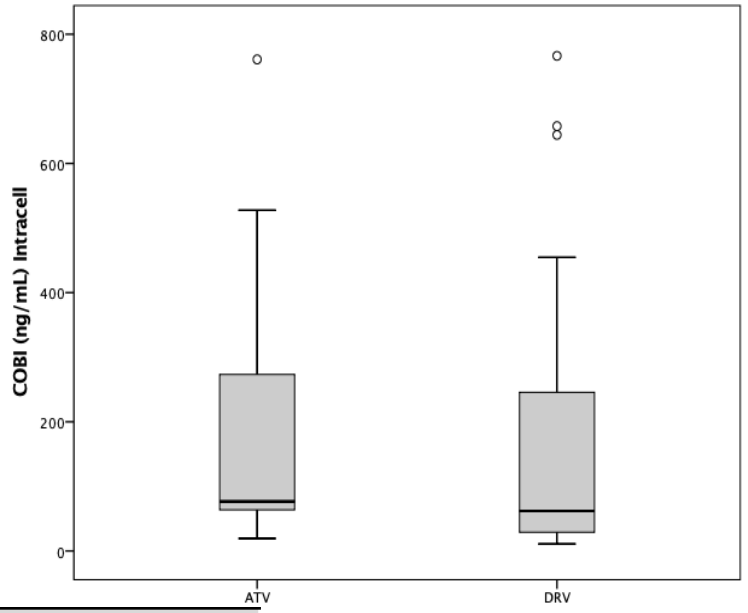
Table 1. Ritonavir, according to concomitant PIs, and PI plasma and intracellular concentrations and cellular accumulation ratios (IQR)

	Plasma (ng/mL)	Intracellular (ng/mL)	Cellular accumulation ratio
Ritonavir			
darunavir 800 mg ($n=8$)	123 (97–182)	1044 (800–2341)	9.6 (7.5–12.1)
darunavir 600 mg ($n=23$)	297 (153–457)	1974 (1279–3220)	7.6 (6.3–8.9)
atazanavir ($n=37$)	75 (45–172)	716 (495–1153)	9.2 (6.0–12.7)
lopinavir ($n=19$)	314 (156–439)	1698 (1397–2620)	6.1 (5.1–9.5)
tipranavir ($n=13$)	244 (130–453)	1152 (618–1605)	5.0 (3.2–6.3)
PI			
darunavir 800 mg ($n=8$)	3121 (1587–8804)	414 (140–2504)	0.22 (0.05–0.3)
darunavir 600 mg ($n=23$)	3077 (2668–4663)	402 (235–654)	0.12 (0.06–0.3)
atazanavir ($n=37$)	645 (454–1029)	1844 (949–3498)	2.44 (1.7–5.1)
lopinavir ($n=19$)	7779 (5615–8658)	2340 (1301–4891)	0.35 (0.16–0.93)
tipranavir ($n=13$)	37862 (17485–48530)	5740 (2014–9839)	0.14 (0.13–0.18)

Plasma ad IC PK di Cobi associated with DRV or ATV in real life





	ATV (n=16)	DRV (n=31)	p**
COBI plasma* (ng/mL)	53,3 (-40,5-147,2)	32,7 (-6,7-72,2)	0,23
COBI IC* (ng/mL)	132,5 (-126,2-391,4)	83,8 (6,8-160,8)	0,209
COBI IC/plasma ratio	2,485 (0,994-3,977)	2,493 (1,232-3,754)	0,836

* Geometric mean (IC95%)

**p calculated with Mann

Ferrara et al, unpublished

Some data gap….

- Does PI-associated COBI have less impact on lipids as compared to RTV in real ife?

- *COBI is associated with lower impact on lipids in patient with hypercholesterolemia and/or hypertriglyceridemia at baseline,*
- *This should be associated with lower lipidogenic profile and/or lower intracellular accumulation as compared to RTV*


Thanks
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