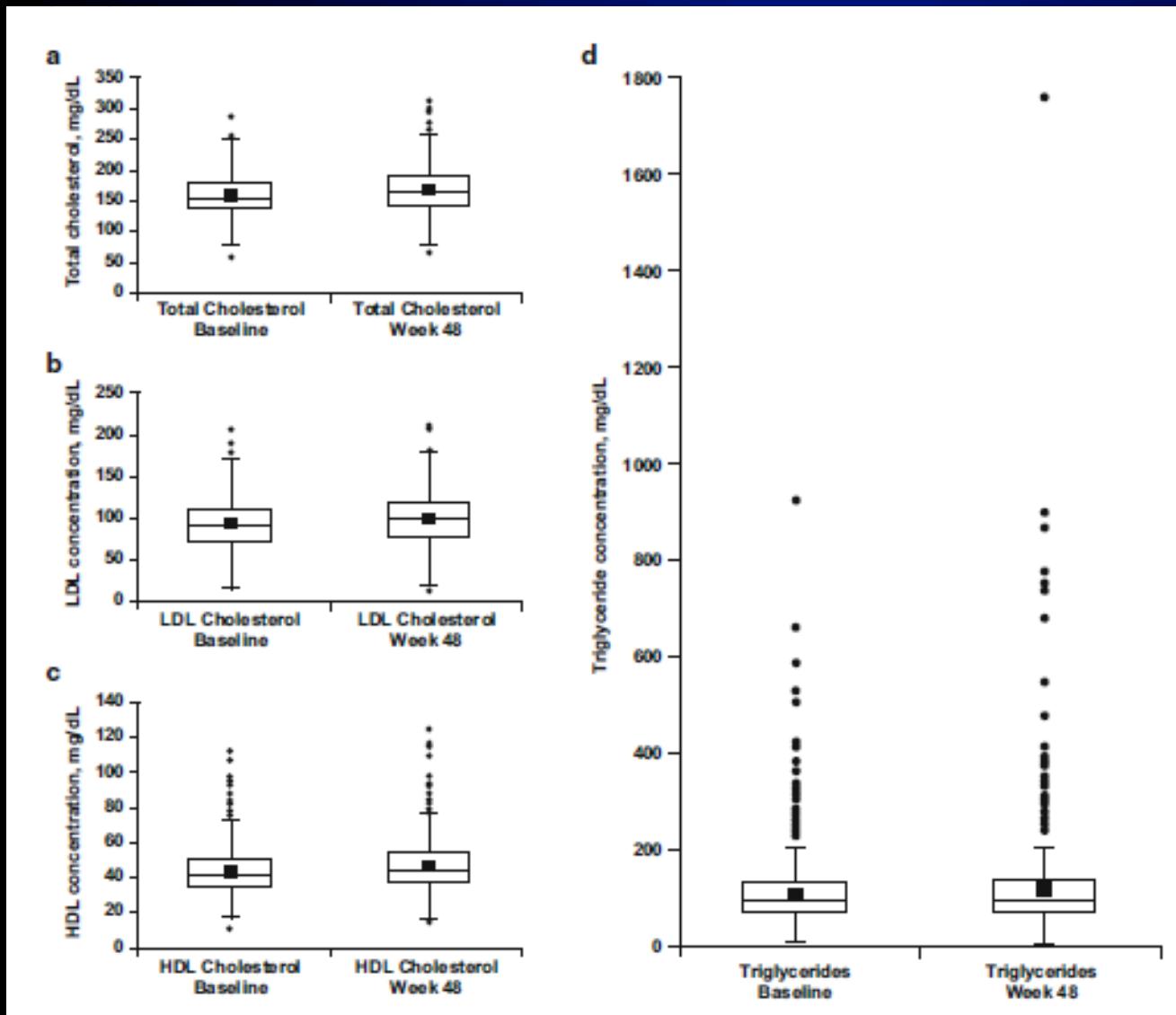


# Pooled DTG at baseline and at week 48



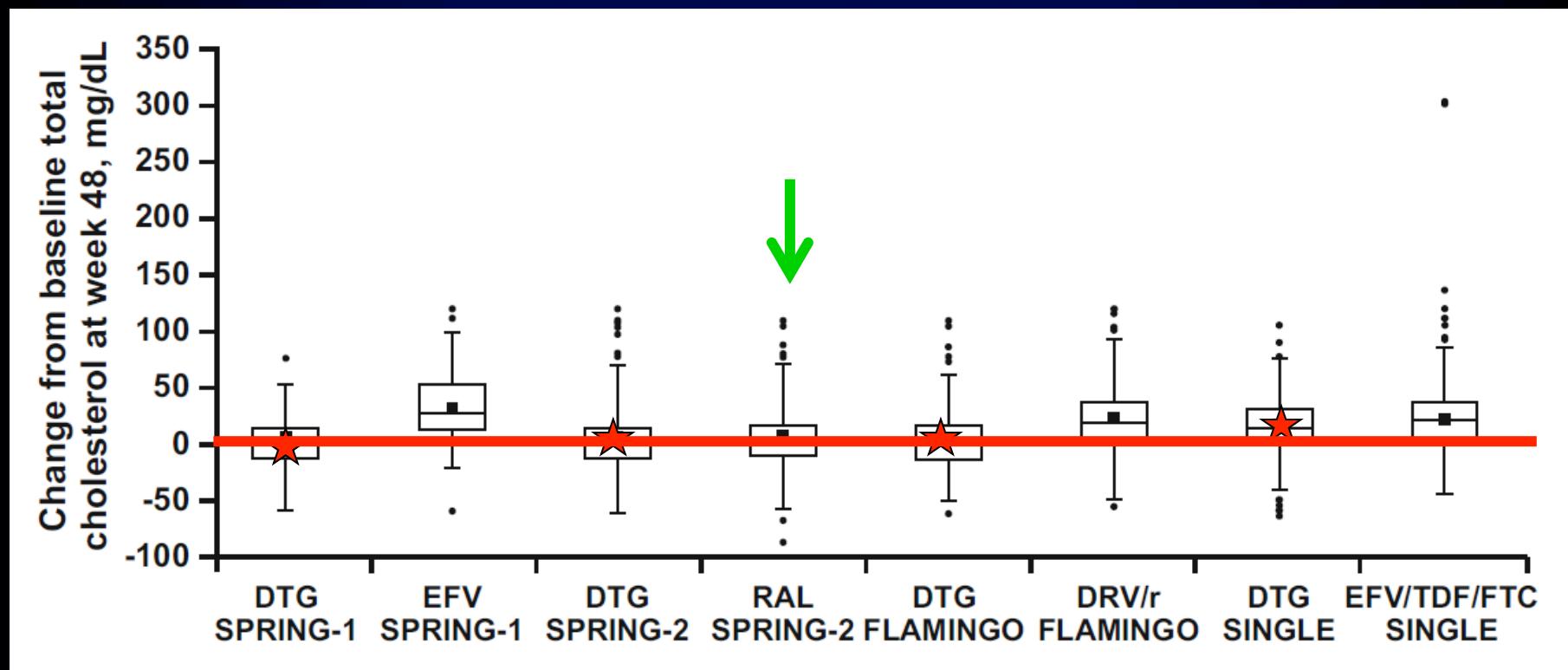
Level of:

- a total cholesterol,
- b LDL cholesterol,
- c HDL cholesterol
- d triglyceride

Boxes represent  
the first to third  
quartile

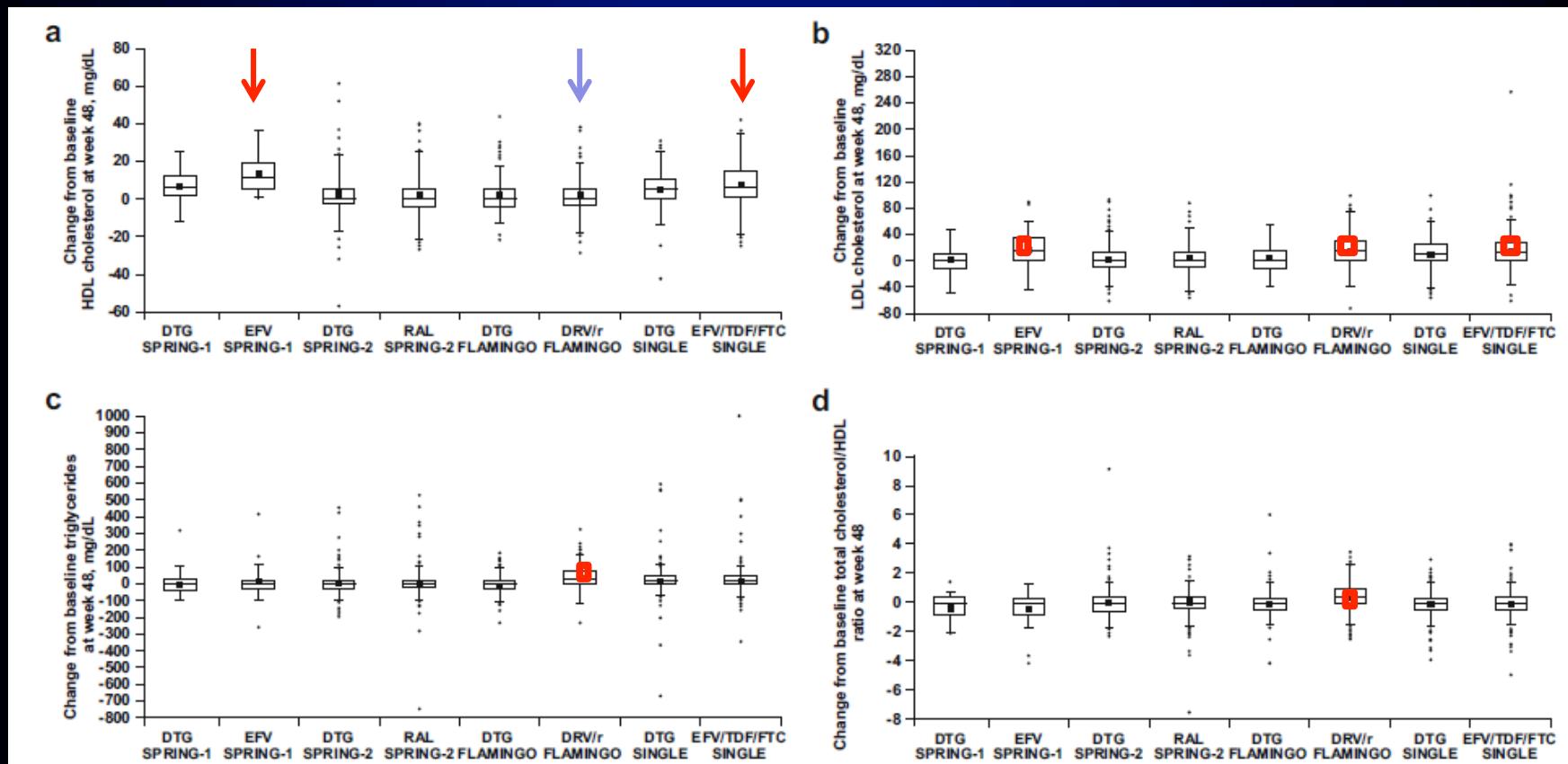
Quercia et al.  
*Clin Drug Investig*  
2015; 35:211-219.

# Changes from baseline total cholesterol at week 48 in Treatment-Naive, HIV-1 Infected Adults Treated with Dolutegravir.



Quercia et al. Clin Drug Investig 2015; 35:211-19

**Changes from baseline in a HDL cholesterol, b LDL cholesterol, c triglycerides, and d total cholesterol/HDL ratio at 48 weeks.**



*Quercia et al. Clin Drug Investig 2015; 35:211-19*

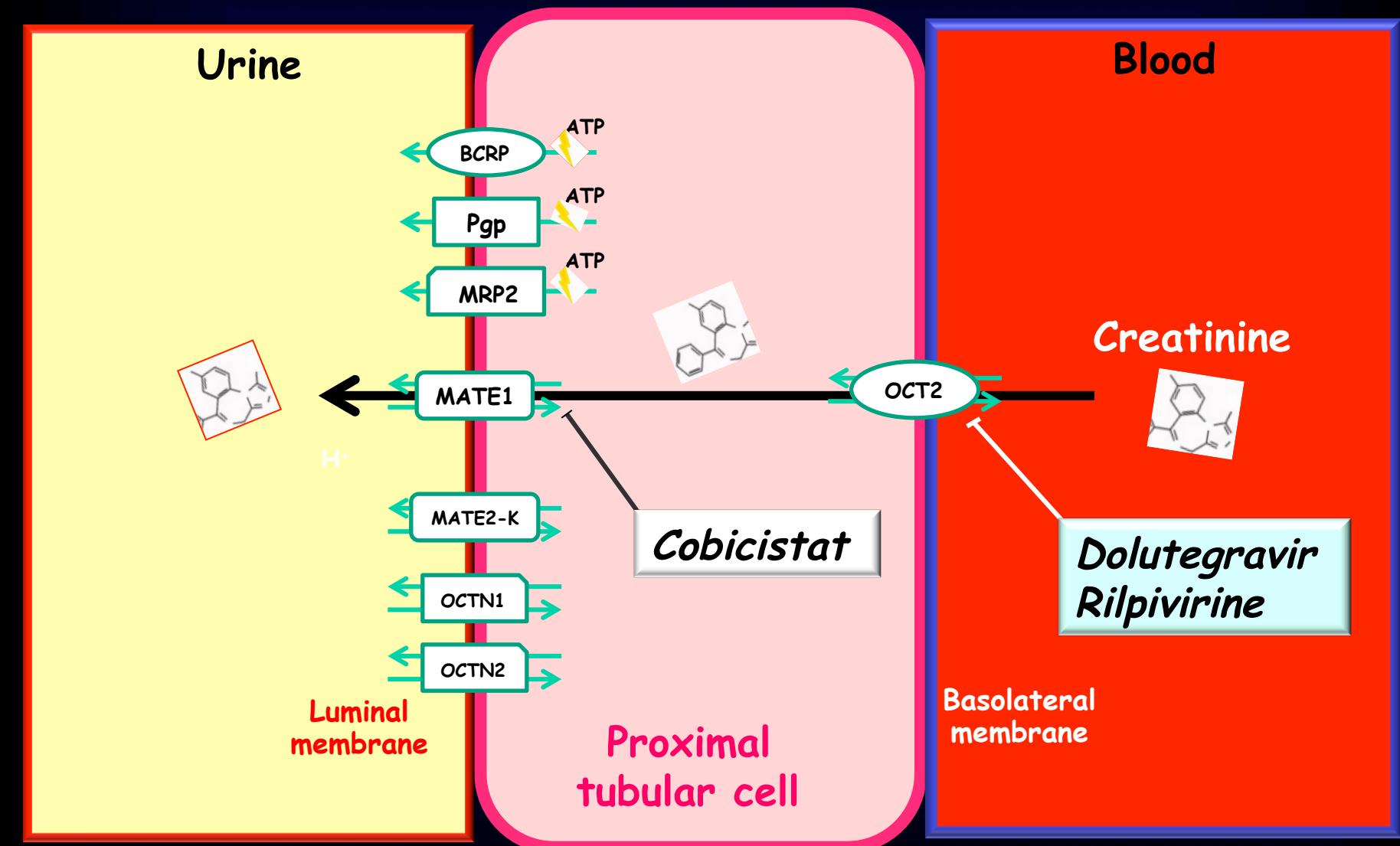
# Current antiretrovirals and their effects on the kidney.

Antiretroviral drug(s)	Alteration of renal function [(generally) not treatment-limiting]	Treatment-limiting renal disease
Tenofovir disoproxil fumarate	Renal tubular dysfunction [18]; eGFR decline >3 ml/min per 1.73 m <sup>2</sup> per year [13]; Proteinuria (nonglomerular origin) [13,27]; Chronic kidney disease [11,13]	Acute kidney injury (rare) <sup>a</sup> [28]; Tubulo-interstitial nephritis (rare) <sup>a</sup> [30]; Renal tubular disease/ Fanconi syndrome (uncommon) [19,25]; CKD with progressive eGFR decline [17]
Ritonavir/atazanavir	Inhibition of tubular creatinine secretion [23,36]; Renal tubular dysfunction [24,37]; Crytalluria [33]; eGFR decline >3 ml/min per 1.73 m <sup>2</sup> per year [13]; Chronic kidney disease [11]	Acute kidney injury (rare) <sup>a</sup> [30]; Tubulo-interstitial nephritis (rare) <sup>a</sup> [30]; Nephrolithiasis (uncommon) [20,21]
Raltegravir	Chronic kidney disease [11,12]	Nephrolithiasis (rare) <sup>a</sup> [22]
Cobicistat/elvitegravir (along with tenofovir-DF/emtricitabine)	Inhibition of tubular creatinine secretion [22,23]	AKI (uncommon) <sup>a</sup> [22,23]; Renal tubular disease/ Fanconi syndrome (uncommon) [22]
Cobicistat/atazanavir (along with tenofovir-DF/emtricitabine)	Inhibition of tubular creatinine secretion [36]	AKI (uncommon) <sup>a</sup> [36]; Renal tubular disease/ Fanconi syndrome (uncommon) [36]
Dolutegravir	Inhibition of tubular creatinine secretion [34]	None reported
Rilpivirine	Inhibition of tubular creatinine secretion [35]	None reported
Raltegravir	Inhibition of tubular creatinine secretion? [34]	None reported
Ritonavir/darunavir	Cryptalluria [33]	Nephrolithiasis (rare) <sup>a</sup> [22]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

<sup>a</sup>Limited evidence (case series or case reports only).

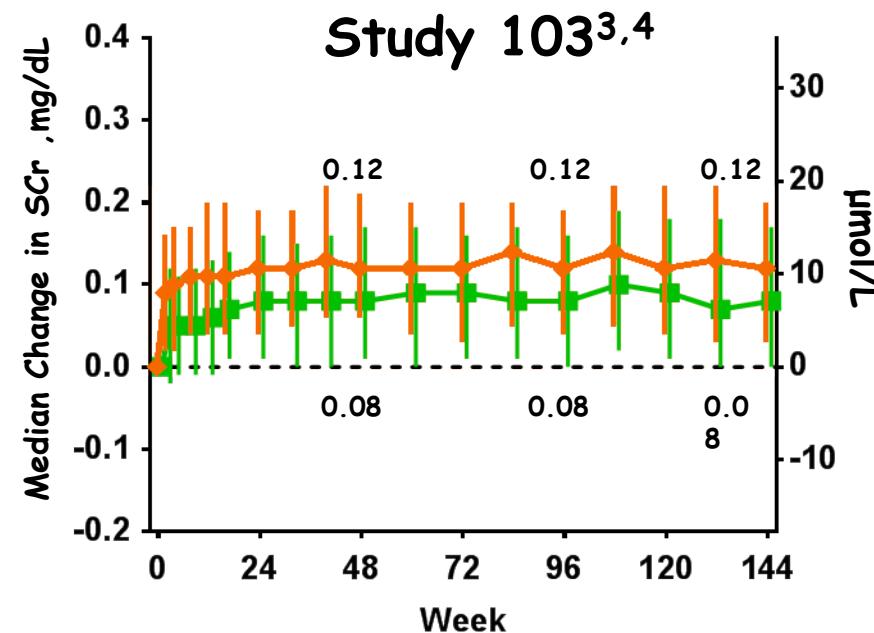
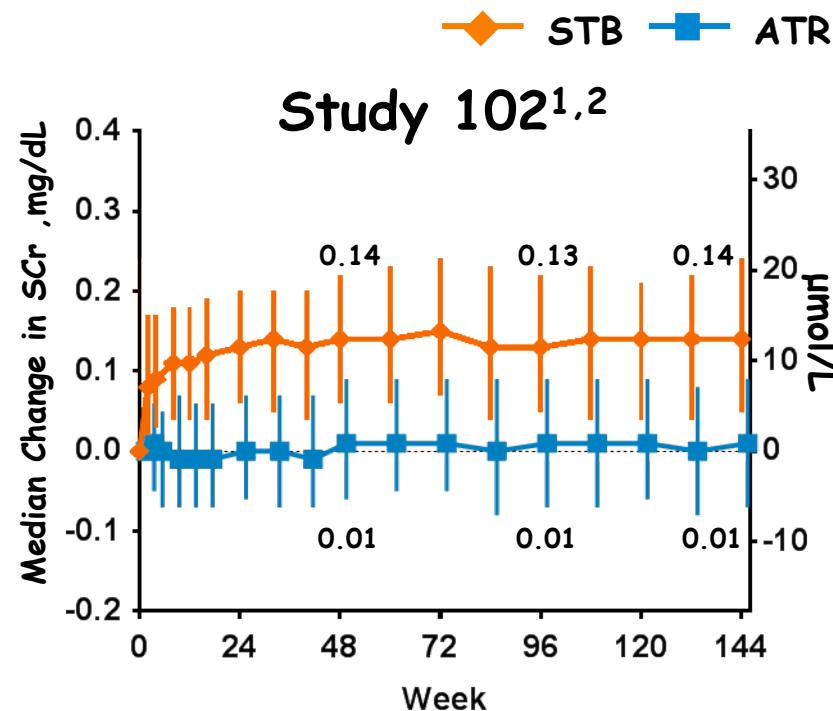
# Creatinine tubular secretion



*Study 102 and 103 (STB vs. ATR and ATV+RTV+TVD) - Week 144*

## Changes in Serum Creatinine

Median [IQR]



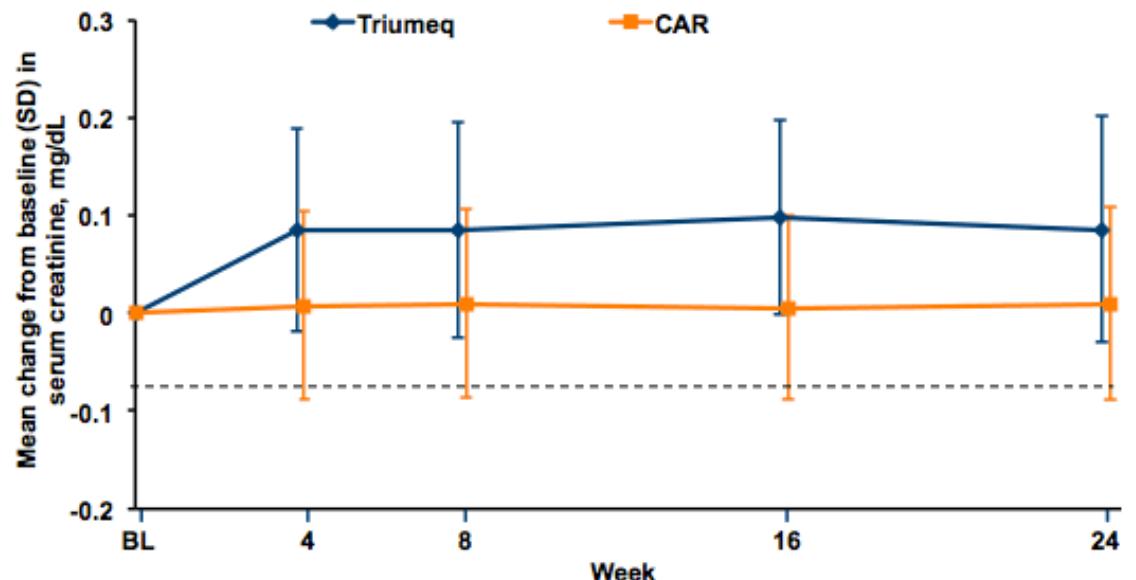
Consistent with inhibition of serum creatinine secretion by cobicistat, small increases in serum creatinine occurred early and then stabilized

1. Wohl D, et al. JAIDS 2014; 65 (3):e119-121  
2. Wohl D, et al. ICAAC 2013. Denver, CO. #H-672a

3. Clumeck N, et al. JAIDS 2014;65 (3):e121-124  
4. Clumeck N, et al. EACS 2013. Brussels, Belgium. #LBPS7/2

# STRIIVING study

## Mean Change From Baseline in Serum Creatinine Through 24 Weeks



Number of patients

Triumeq	275	262	256	237	240
CAR	276	257	257	246	249

- Small, non-progressive changes in serum creatinine were observed in the Triumeq arm due to known inhibition of tubular creatinine secretion by DTG

Trottier et al. ICAAC 2015 Sept 17-21 2015 San Diego, CA

# Creatinine elevation in Dolutegravir treated patients

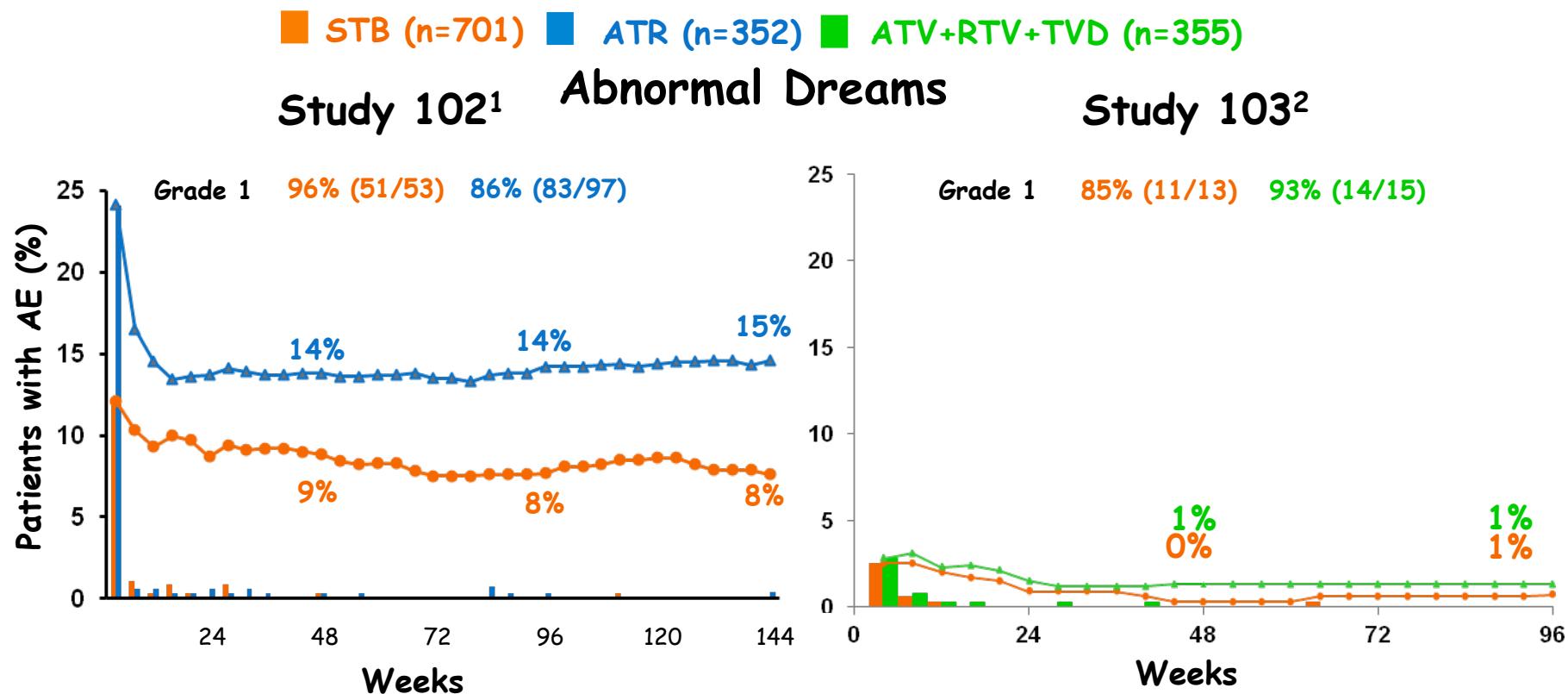
- Creatinine elevation typically occurs within a week of initiation followed by a plateau at an average increase of 11 mmol/L.<sup>1</sup>
- This rise is mediated through inhibition of the renal transporter OCT-2, but the reduced creatinine secretion does not translate into a lower glomerular filtration rate.<sup>2</sup>
- Elevations in transaminases occur in 5%, are generally mild, and occur at a similar rate as with raltegravir, darunavir-ritonavir, and efavirenz.<sup>1</sup>

<sup>1</sup>Curtis L, et al. *HIV Clin Trials.* 2014;15:199-208.

<sup>2</sup>Koteff J, et al. *Br J Clin Pharmacol.* 2013;75:990-996

*Study 102 and 103 (STB vs. ATR and ATV+RTV+TVD) - Week 144 and 96*

## Abnormal Dreams Incidence and Prevalence



Different rates of abnormal dreams for subjects on STB in Study 102 vs. 103 demonstrate potential bias due to blinded EFV comparator in 102

- Incidence (bar): Patients with new onset AEs at each window
- Prevalence (line): Patients with AEs at each window

1. Wohl D, et al. ICAAC 2013. Denver, CO. #H-672a
2. Shalit P, et al. ICAAC 2013. Denver, CO. #H-671

# SINGLE study: Summary of Treatment-Related Adverse Events

Adverse event	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Treatment-related	184 (44%)	282 (67%)
<b>Preferred term ≥10% in either arm</b>		
Dizziness	29 (7%)	139 (33%)
Abnormal dreams	27 (7%)	66 (16%)
Nausea	44 (11%)	49 (12%)
Insomnia	41 (10%)	25 (6%)
<b>Treatment-related Grades 2-4 (≥5% in either arm)</b>	<b>58 (14%)</b>	<b>116 (28%)</b>
Dizziness	2 (<1%)	21 (5%)

- Treatment-related rash was reported significantly more commonly in the EFV/TDF/FTC arm (34/419, 8%) than in the DTG + ABC/3TC arm (4/414, <1%).



Walmsley et al. CROI 2014; Boston, MA. Poster 337.

21st Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, MA

## Tossicità: scenario attuale

- I nuovi farmaci hanno ridotto ed ulteriormente ridurranno in prospettiva i rischi e l'impatto individuale della tossicità a lungo termine
- L'interpretazione del ruolo degli ARV sul rischio cardiovascolare è resa complessa dal rumore di fondo rappresentato dai fattori di rischio 'tradizionali' e comportamentali, dall'avanzare dell'età e dall'infezione *per se*
- È possibile che l'utilizzo di farmacogenetica e farmacocinetica fornisca ulteriori strumenti per orientare le scelte terapeutiche riducendo ulteriormente i rischi da tossicità

# Toxicity in a patient's journey

- A fronte di una letteratura molto vasta sulla tossicità dell'ART, è singolare come la percezione delle persone che assumono antiretrovirali sulla tossicità della terapia e sulle sue possibili implicazioni sia stata poco indagata in studi formali

Grazie per l'attenzione

**Seminario Nadir 2015 - Iniziativa resa possibile grazie al supporto di ViiV Healthcare**

