10TH RESIDENTIAL COURSE ON CLINICAL PHARMACOLOGY OF ANTIRETROVIRALS

Clinical Pharmacology of Toxicity

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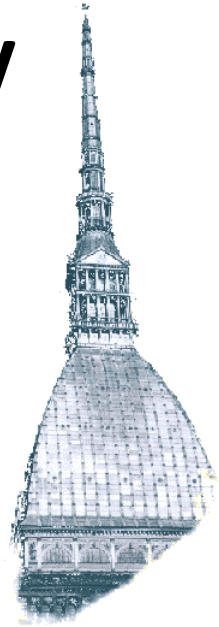
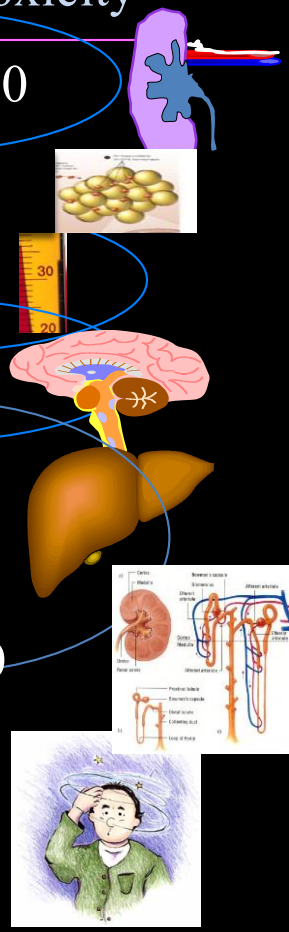
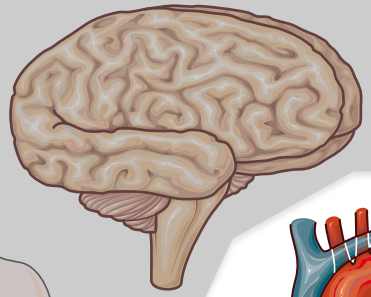


Reference Concentrations (C_{min}) for Efficacy & Toxicity

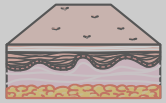
Drug	C_{min} (ng/mL) Efficacy	C_{min} (ng/mL) Toxicity
Indinavir	100	8000-10000
Ritonavir	2100	2100
Atazanavir	150	850
Efavirenz	1000 – 2200 - 3000*	** 4000
Nevirapine	1000 - 4300**	6000
Tipranavir	15000 – 20000 #	35000
Tenofovir	-	100 – 140
Maraviroc	50	300 -600



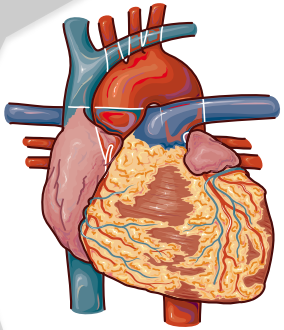
* after NVP failure **prior failures of NRTIs # in case of triple drug failure



CNS



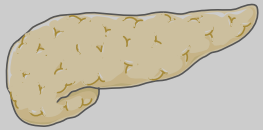
SKIN



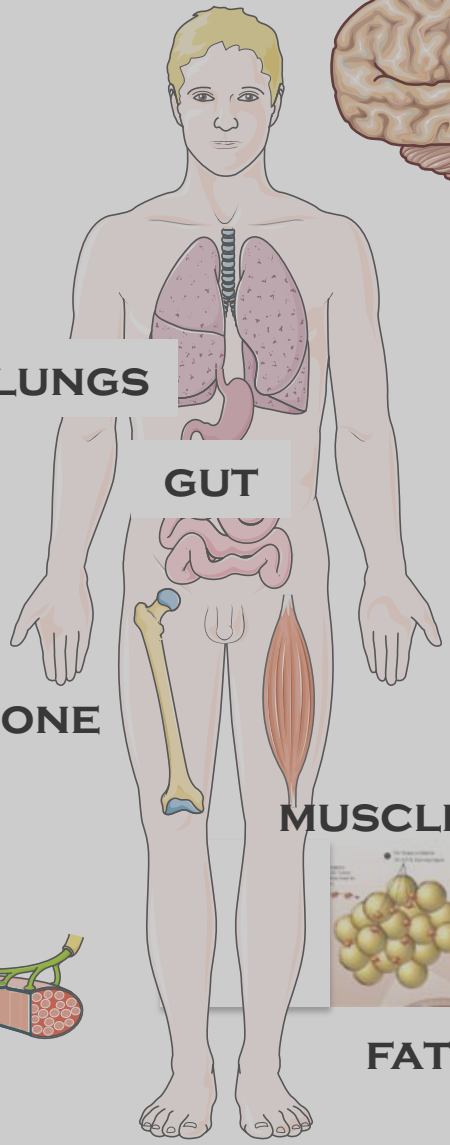
CARDIOVASCULAR

LUNGS

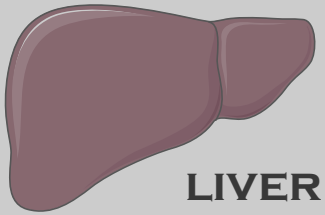
GUT



PANCREAS



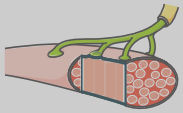
BONE



LIVER

MUSCLES

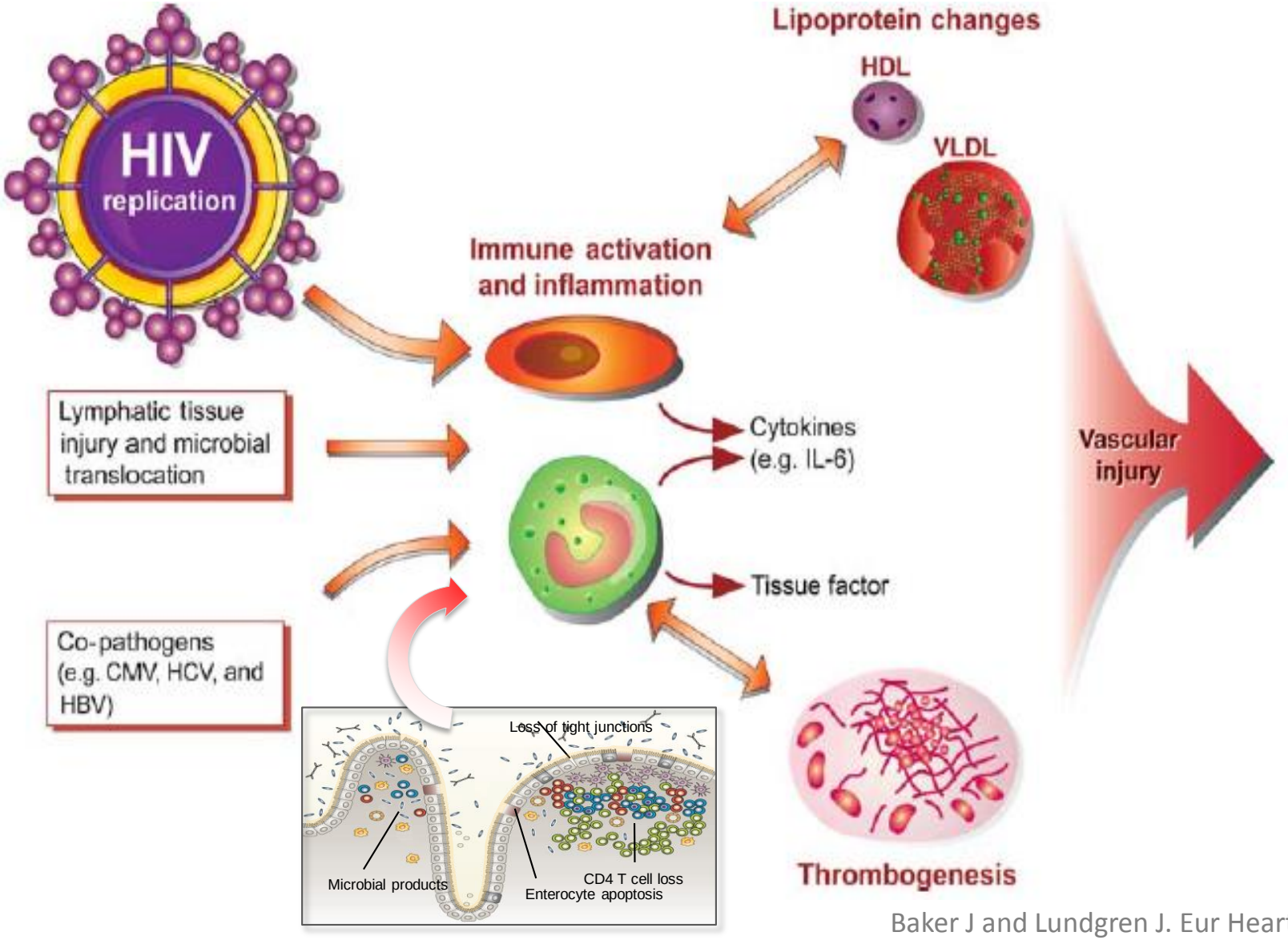
KIDNEY



FAT

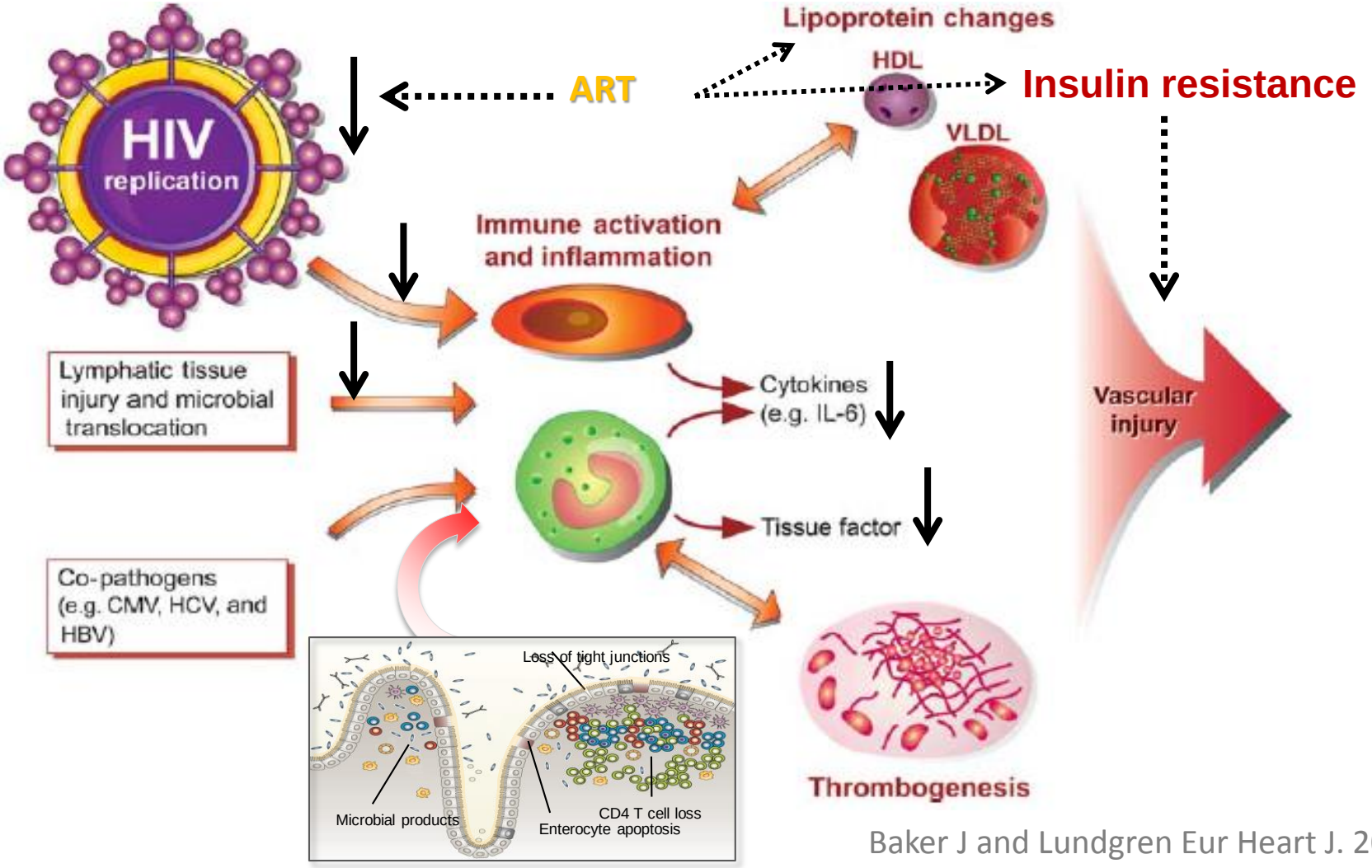
PERIPHERAL NERVES

Untreated HIV infection and CVD pathogenesis: a proposed model



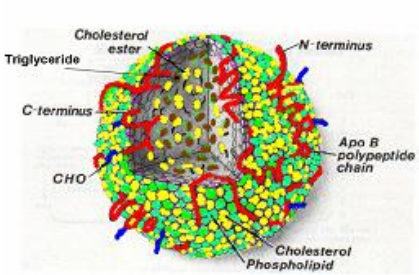
Baker J and Lundgren J. Eur Heart J 2011

Treated HIV infection and CVD pathogenesis: a proposed model

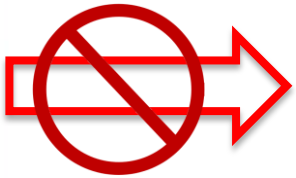


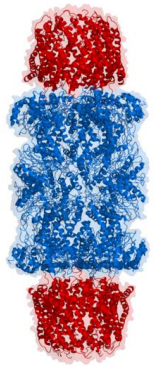
Baker J and Lundgren Eur Heart J. 2011

Protease Inhibitors (PIs) inhibit the proteosomal degradation of apolipoproteins



Structure of apoB-100 in LDL





Stockpiling and excessive release in response to FFA

- Increase in FFA turnover
- Increased lipolysis
- Decreased clearance of TG-rich VLDL and chylomicrons

Impaired post-prandial insulin-mediated lipid metabolism

INDINAVIR

Impaired insulin action

Without changes in lipid metabolism

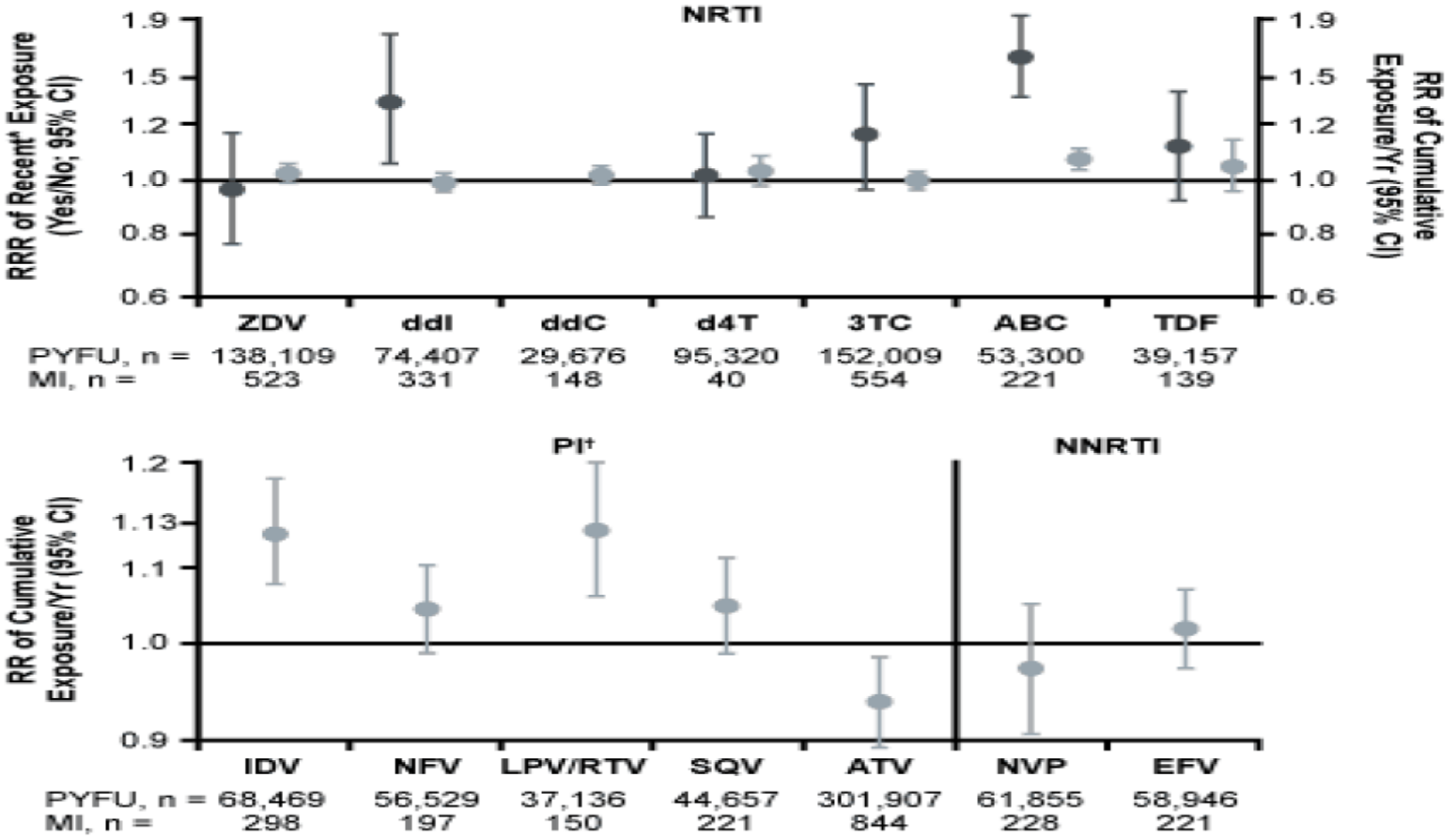
Dyslipidemia

RITONAVIR

Without major changes in glucose metabolism

Cardiovascular complications of HIV

MI risk disease by ARV exposure in D:A:D

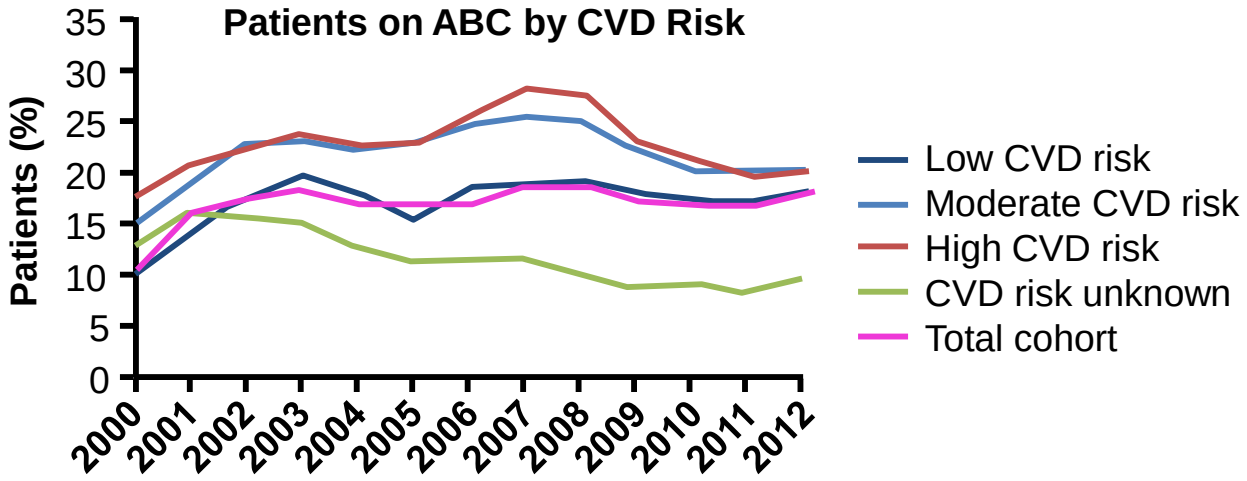


Worm S, et al. D:A:D. JID 2012.

D:A:D: Abacavir Remains Associated With Elevated Risk of MI

- Update of analysis of ABC and risk of acute MI in pts with low, medium, and high CVD risk
- After initial D:A:D report in March 2008, decline in ABC initiations in pts with higher CVD risk

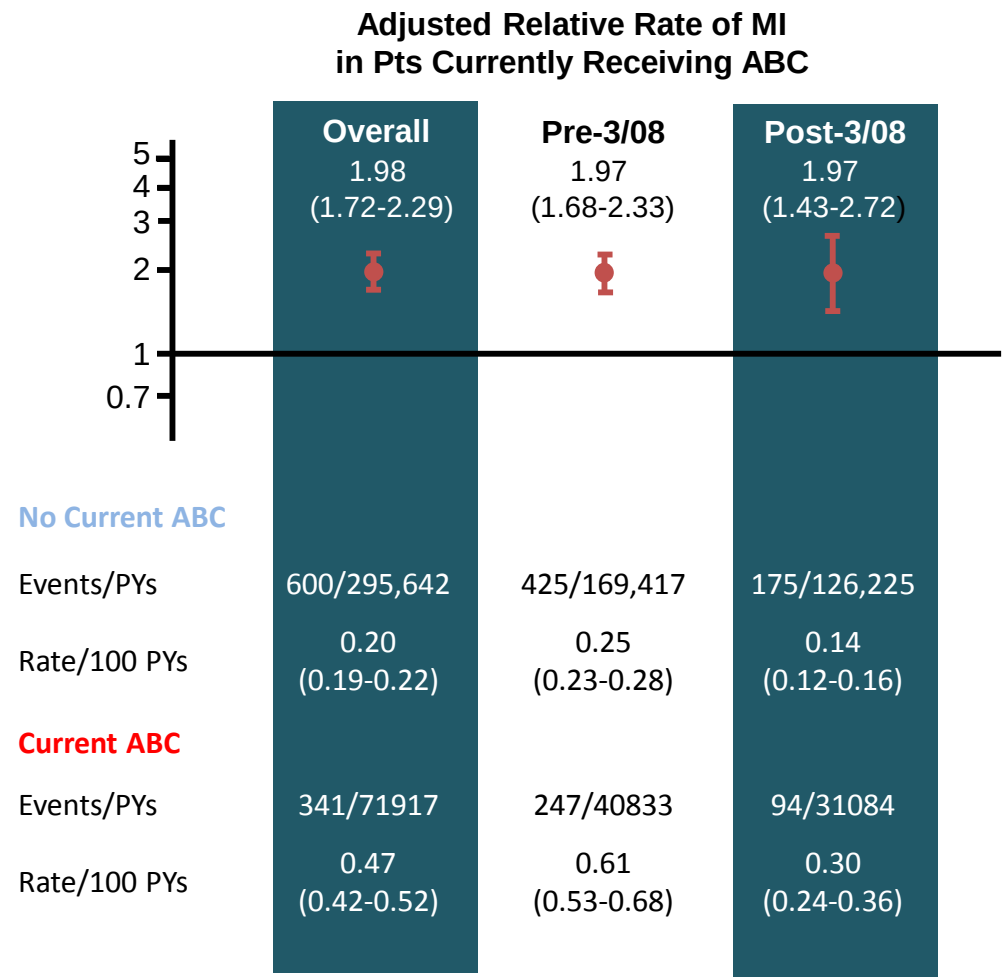
Framingham Risk Group	ABC Use as Proportion of All ART Initiations, %
Before March 2008	
▪ Low/unknown CVD risk	13.6
▪ Moderate/high CVD risk	17.1
After March 2008	
▪ Low/unknown CVD risk	7.6
▪ Moderate/high CVD risk	5.3



Sabin C, et al. CROI 2014. Abstract 747LB. Reproduced with permission.

D:A:D: Current Abacavir Use Associated With 98% Increase in Acute MI Risk

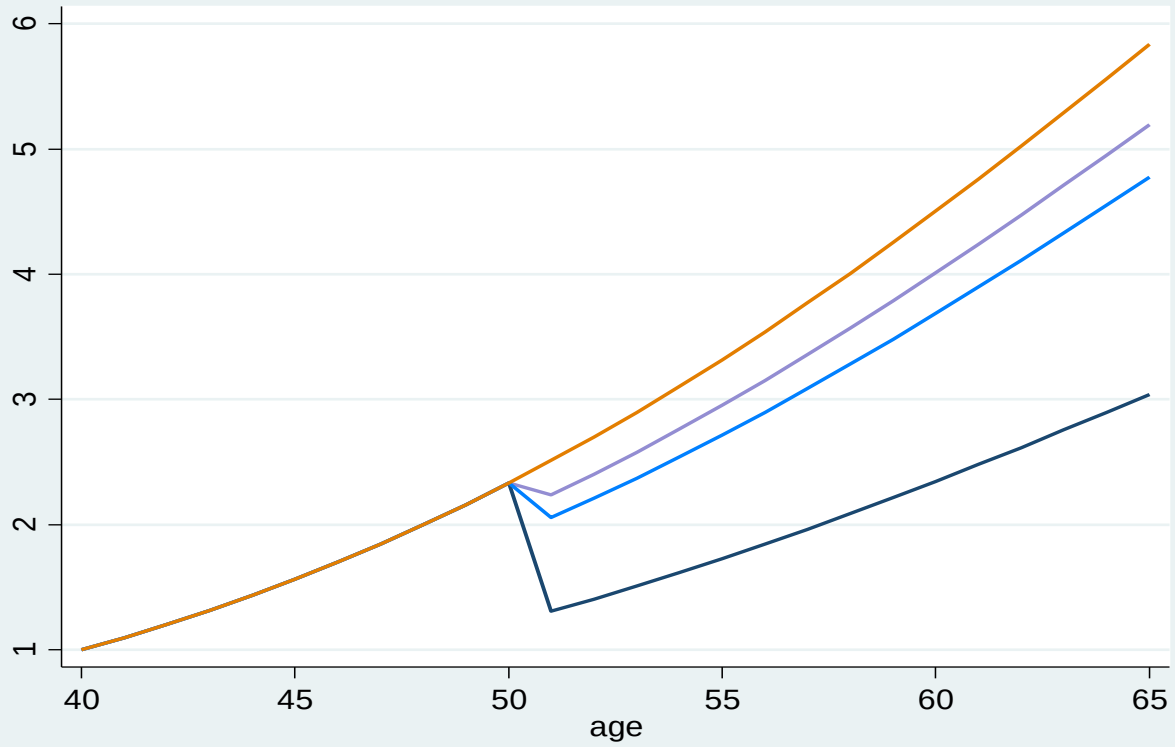
- Current ABC use remained associated with increased risk of acute MI
  - Similar RR in post-3/08 group vs pre-3/08 group, despite decrease in ABC use in pts with high CVD risk
  - Absolute risk in the post 2008 small: 6 cases /2000 PY vs 3 cases/2000 PY or absolute risk ↑ 0.15%
- Overall cohort: 941 MI events during 367,599 PYs
  - 0.47/100 PYs (95% CI: 0.42-0.52) with current ABC
  - 0.21 (95% CI: 0.19-0.22) with no current ABC



Sabin C, et al. CROI 2014. Abstract 747LB.

Cardiovascular disease in HIV

Prevention: monitor and modify risks



CVD hazard in D:A:D*

Reduce sysBP 10 mmHg

Reduce TC 1 mmol/L

Stop smoking

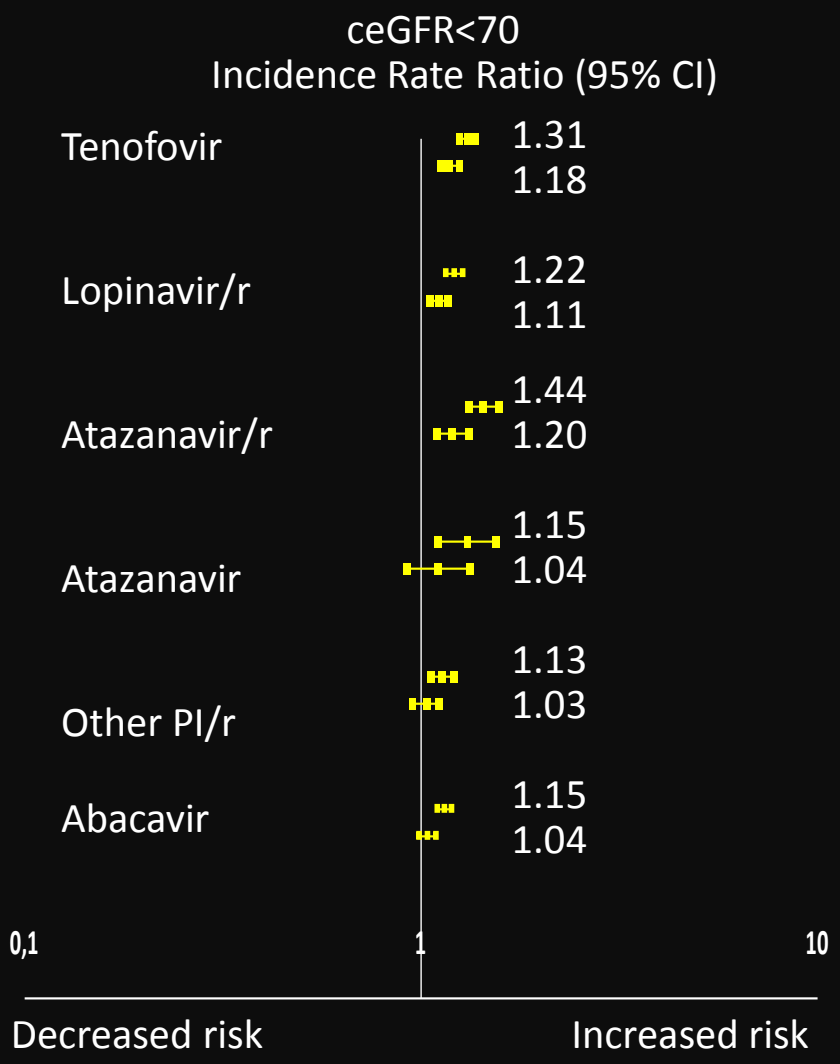
*relative to 40 y.o. HIV+ male

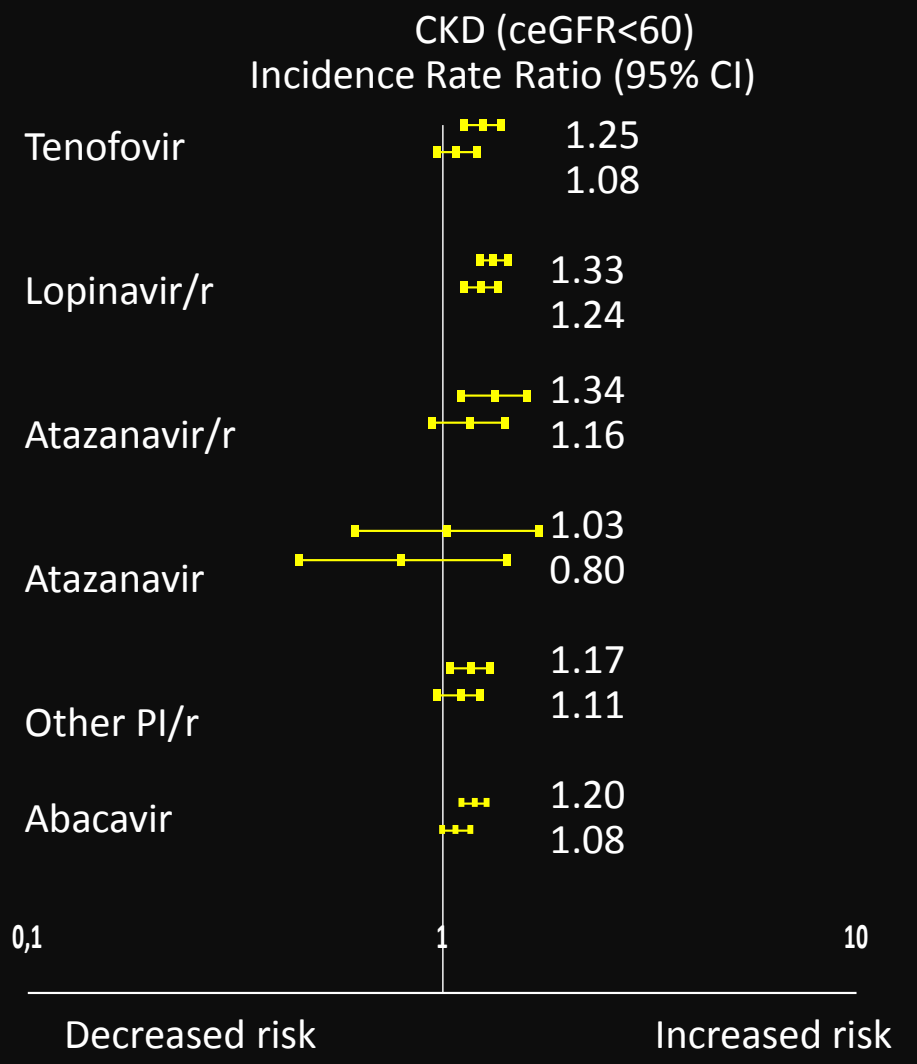
Petoumenos K for D:A:D . 20th CROI 2013.

Figure 3 ARV use (per year) & risk of ceGFR≤70 & CKD from eGFR≥90

Univariate
Multivariate*

Ryom L, et al. CROI 2012, Poster n. 1009





* Adjusted for gender, race, HIV risk group, enrolment cohort, Prior AIDS, HBV/HCV status, smoking status, hypertension, diabetes, prior CV event, baseline eGFR, age (per 10 yrs), CD4 per doubling/nadir, VL and cumulative exposure (per year) tdf, ind, lpv/r, atv, atv/r, abc and other PI/r

ABV and the risk of Myocardial infarction: More CONs than PROs

Hammond E, McKinnon E, Mallal S, Nolan D. Longitudinal evaluation of cardiovascular disease-associated biomarkers in relation to abacavir therapy. AIDS. 2008;22:2540–2543.

Martin A, Amin J, Cooper DA, Carr A, Kelleher AD, Bloch M, et al. Abacavir does not affect circulating levels of inflammatory or coagulopathic biomarkers in suppressed HIV: a randomized clinical trial. AIDS. 2010;24:2657–2663.

Martínez E, Larrousse M, Podzamczer D, Pérez I, Gutiérrez F, Loncá M, et al. Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction. AIDS. 2010;24:F1–F9.

Palella FJ, Gange SJ, Benning L, Jacobson L, Kaplan RC, Landay AL, et al. Inflammatory biomarkers and abacavir use in the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. AIDS. 2010;24:1657–1665.

Kristoffersen US, Kofoed K, Kronborg G, Benfield T, Kjaer A, Lebech AM. Changes in biomarkers of cardiovascular risk after a switch to abacavir in HIV-1-infected individuals receiving combination antiretroviral therapy. HIV Med. 2009;10:627–633.

Hileman CO, Wohl DA, Tisch DJ, Debanne SM, McComsey GA. Abacavir containing regimen leads to less of a decrease in inflammation and endothelial activation in HIV-infected anti-retroviral-naïve adults [abstract 1138]. Infectious Diseases Society of America Annual Meeting; 2010; Vancouver, British Columbia, Canada.

Jong E, Meijers JC, van Gorp EC, Spek CA, Mulder JW. Markers of inflammation and coagulation indicate a prothrombotic state in HIV-infected patients with long-term use of antiretro-viral therapy with or without abacavir. AIDS Res Ther. 2010;16:7–9.

Mitochondrial toxicity

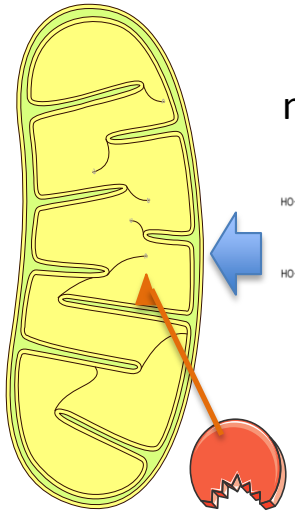
(Poly γ polymerase hypothesis)

NRTIs

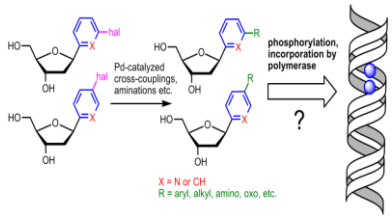
Competition with natural nucleoside substrates:

Incorporation of NRTIs into mt DNA

- Mt DNA depletion
- Impairment of mitochondrial enzymes
- Uncoupling of oxydative phosphorylation
- Induction of apoptosis



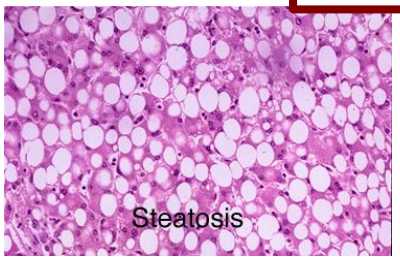
Constant supply of nucleosides required



RNA-dependent DNA polymerase

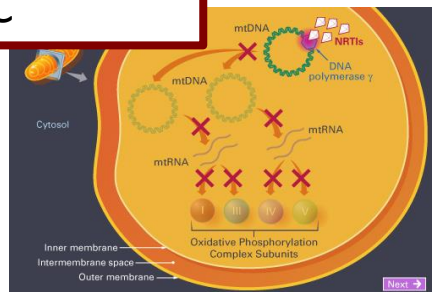
Hierarchy:

ddc > ddI > d4T > AZT > 3TC > ABV> TDF > FTC

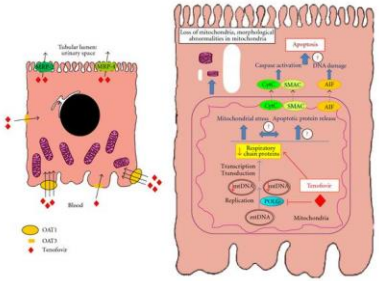


Hepatic steatosis

Severe hyperlactatemia

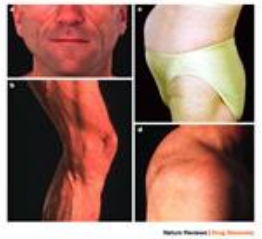


Polyneuropathy



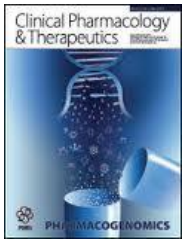
Renal tubular dysfunction

Fat tissue redistribution



Antiretroviral Therapy–Induced Mitochondrial Toxicity: Potential Mechanisms Beyond Polymerase-γ Inhibition

Selvaray S, et al. Clin Pharm Ther 2014; 96: 110-120



Background

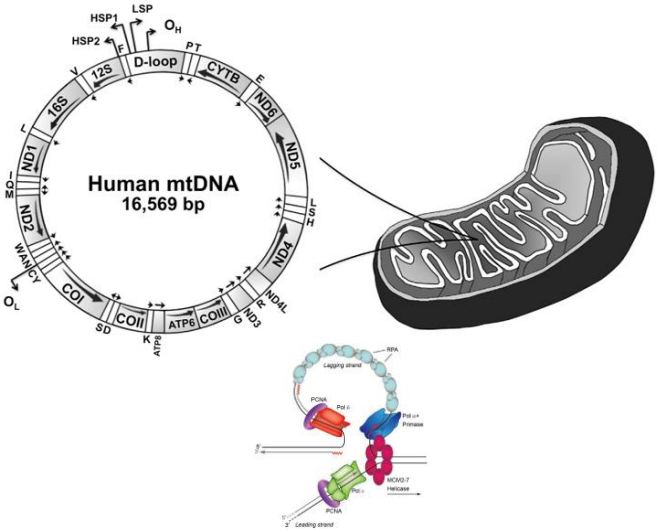
N/NtRTIs (nucleosides/nucleotides reverse transcriptase inhibitors)

Compete, in the PPP form, for incorporation into elongating DNA

dNTPs (endogenous deoxyribonucleotide triphosphates)

Major hypothesis:

Inhibition of pol-γ* by N/NtRTIs leading to mt-DNA** depletion



Alternative hypothesis:

Competition between N/NtRTIs and dNTP may lead to decrease in RN* & dRN** pool size

* DNA polymerase-γ
** Mitochondrial DNA

* Ribonucleotides
** Deoxyribonucleotides

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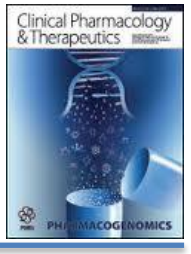
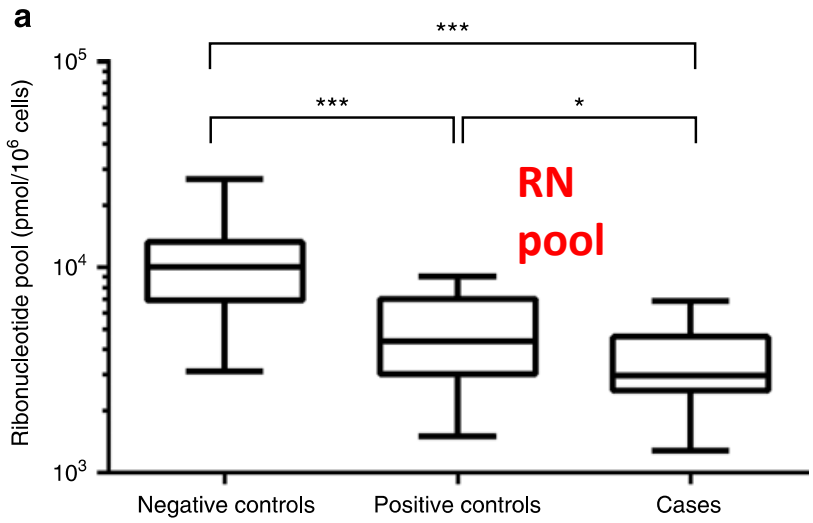
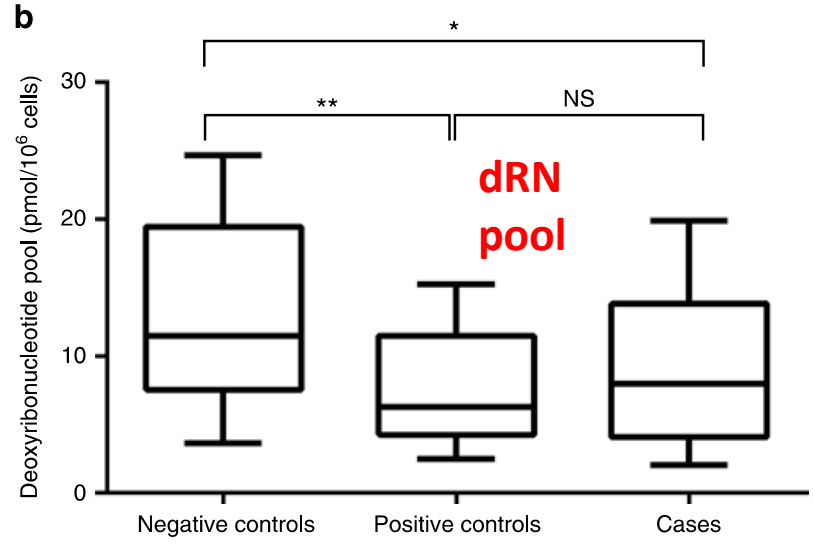
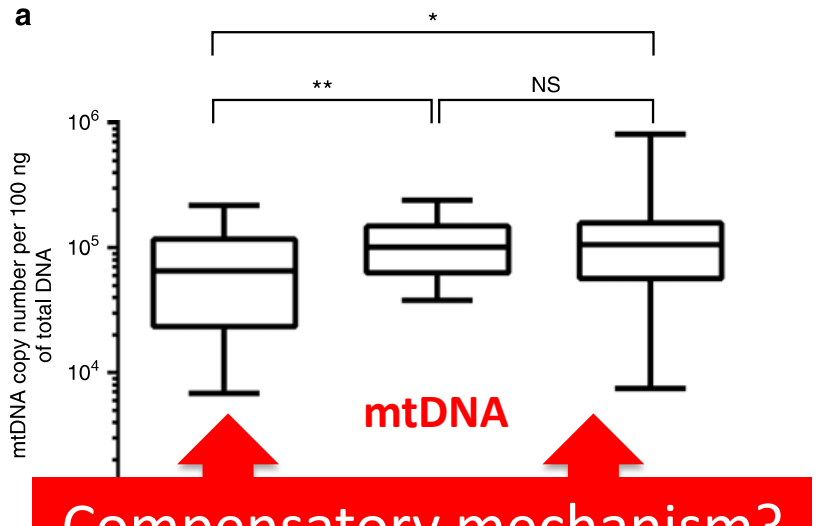


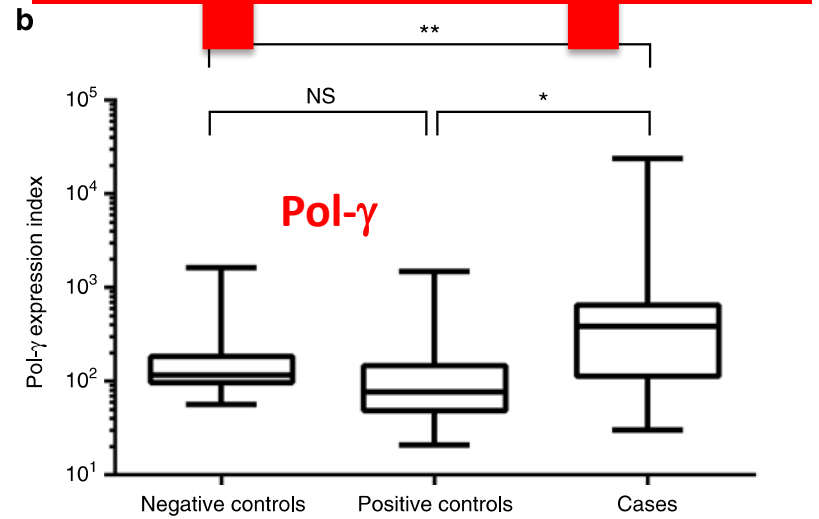
25 cases of N/NtRTIs-associated mitoch.toxicity, 25 HIV+ controls, 25 HIV- controls







Compensatory mechanism?



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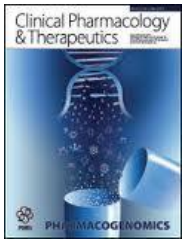

Further to an increased expression of cellular kinases (TK1, thymidine kinase 1; dCK, deoxycitidine kinase), the following transporters were found to be significantly more expressed in **cases**:

ENT1

OAT1

OCT2

MRP1

MRP2

MRP4

MRP5

Which suggests a possible causal relationship between reduced RN & dRN pool sizes in **cases**

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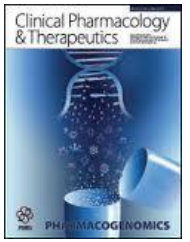
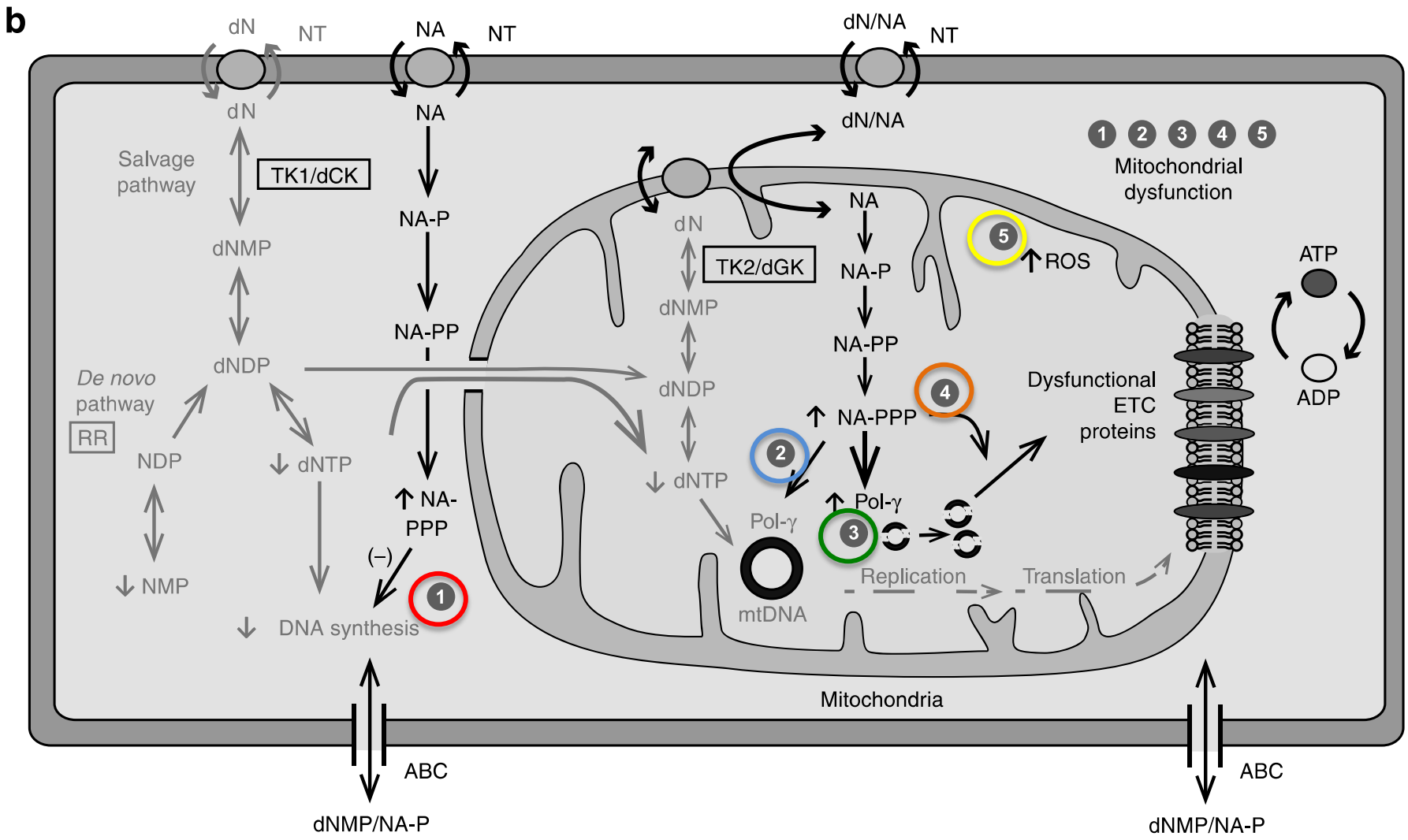


The dNTP pool size will depend on the rate of transport of nucleotide into the cell, rate and efficiency of phosphorylation and rate of efflux of nucleotides.

- Because N/NtRTIs and endogenous nucleotides share the same transport and phosphorylation system, any attempt to increase the efficiency of these systems will enhance N/NtRTIs metabolism and potentiate the associated toxicity.

- Increased expression of nucleotide transporters and cellular kinases might be an attempt to compensate the reduced nucleotide pool sizes, but overexpression of ABC efflux transporters to avoid N/NtRTIs genotoxicity can also cause the efflux of dRN, which further contributes to nucleotide depletion.



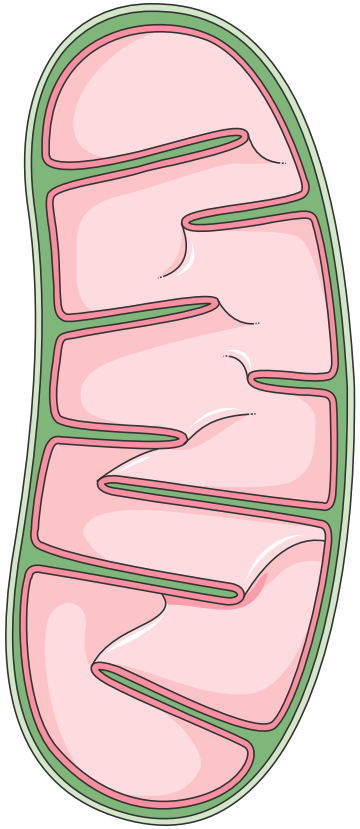
1. Competitive inhibition of nucleotide metabolism resulting in decreasing DNA synthesis
2. Inhibition of Pol-γ by NA-PPP
3. Compensatory proliferation of mtDNA
4. Direct effect of ART on mtDNA replication and translation process
5. Production of reactive oxygen species

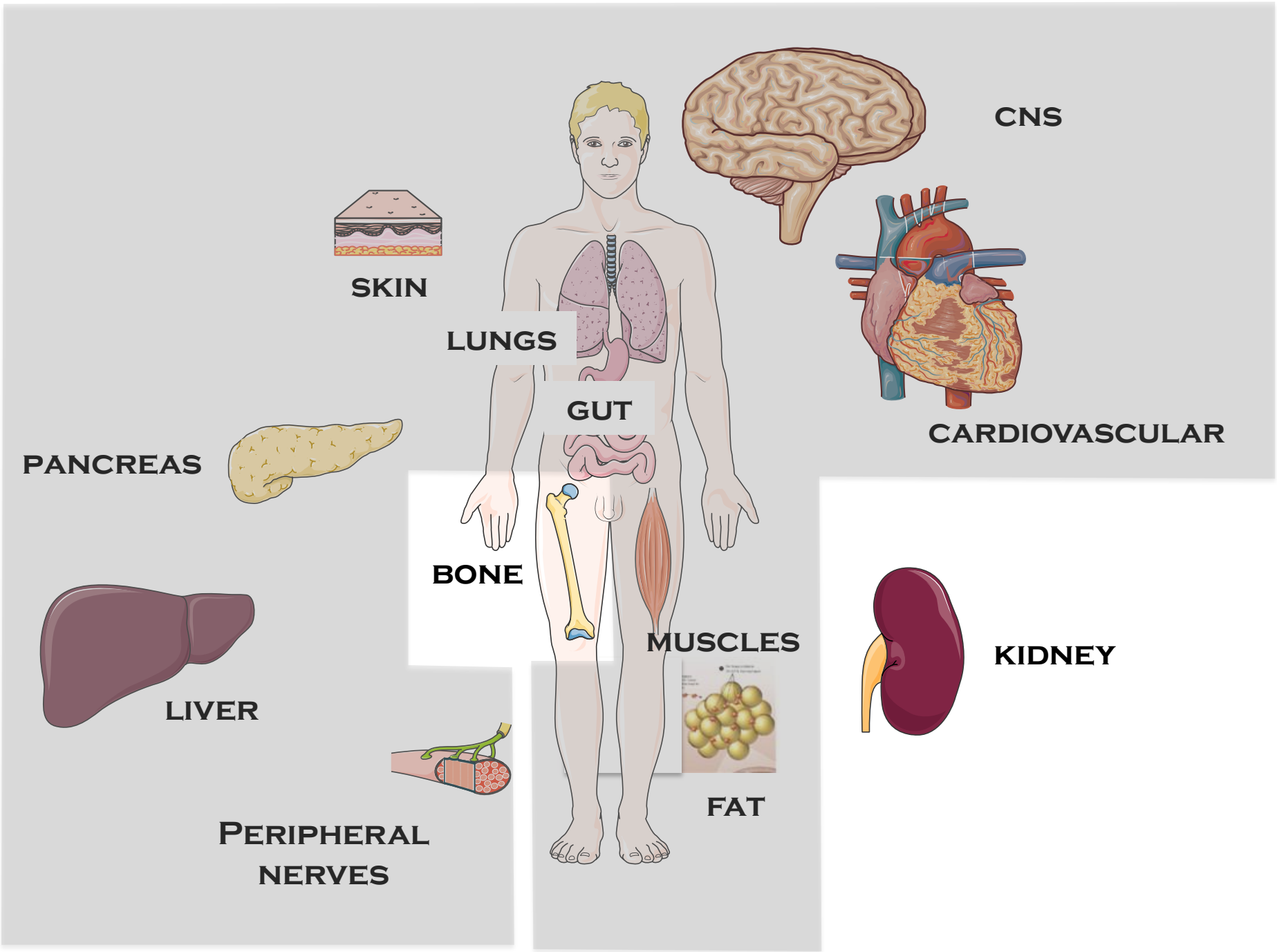
There are significant differences in the relative potencies of N/NtRTIs in their ability to interact with polymerase-gamma:

The hierarchy:

ddC
ddI
d4T
AZT* →
3TC
ABC
TDF
FTC

*** Also inhibitor of mitochondrial thymidine kinase type 2, thus interfering with the synthesis of natural pyrimidine nucleotides**

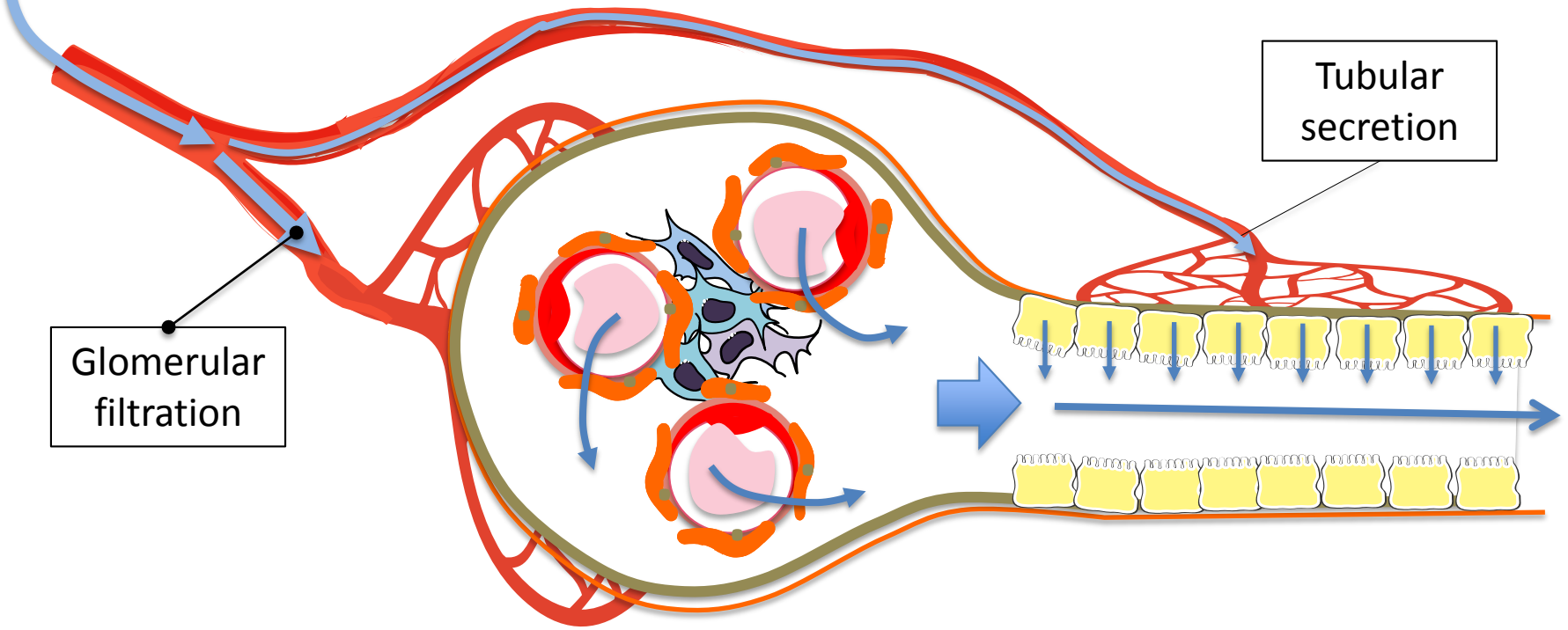



CNS
SKIN
LUNGS
GUT
CARDIOVASCULAR
PANCREAS
BONE
MUSCLES
KIDNEY
LIVER
FAT
Peripheral nerves

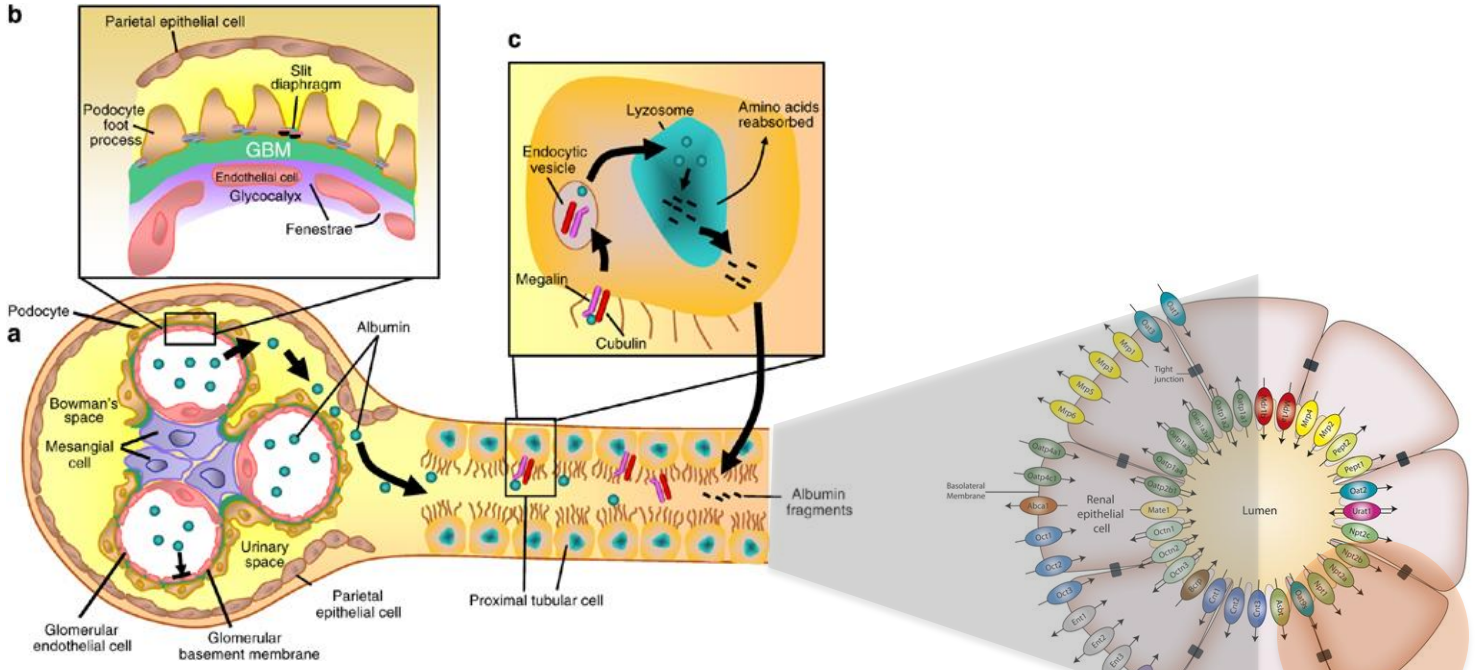
How Tenofovir (TDF) – associated Renal Disease has so far been described

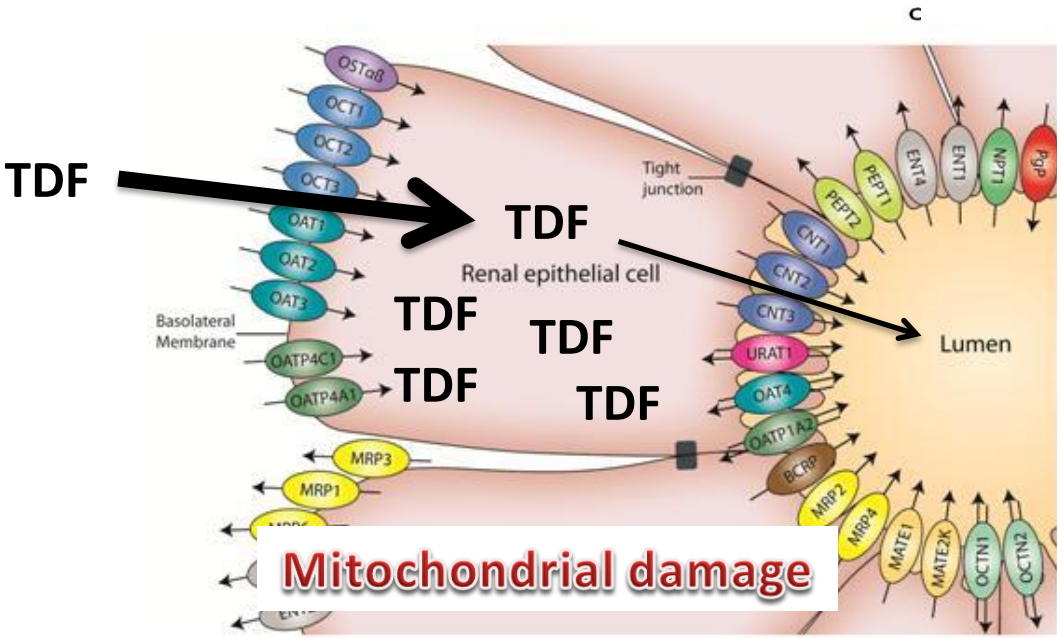
Tenofovir Clearance:

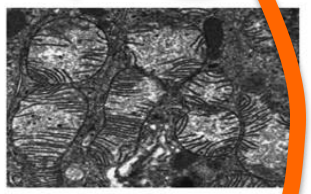
Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. **30% of TDF clearance is thus estimated to occur via tubular secretion**.*



** VIREAD. Summary of Product Characteristics last updated on the eMC: 12/11/2013*

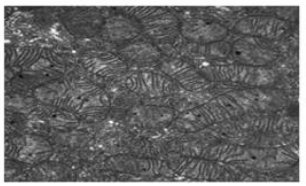


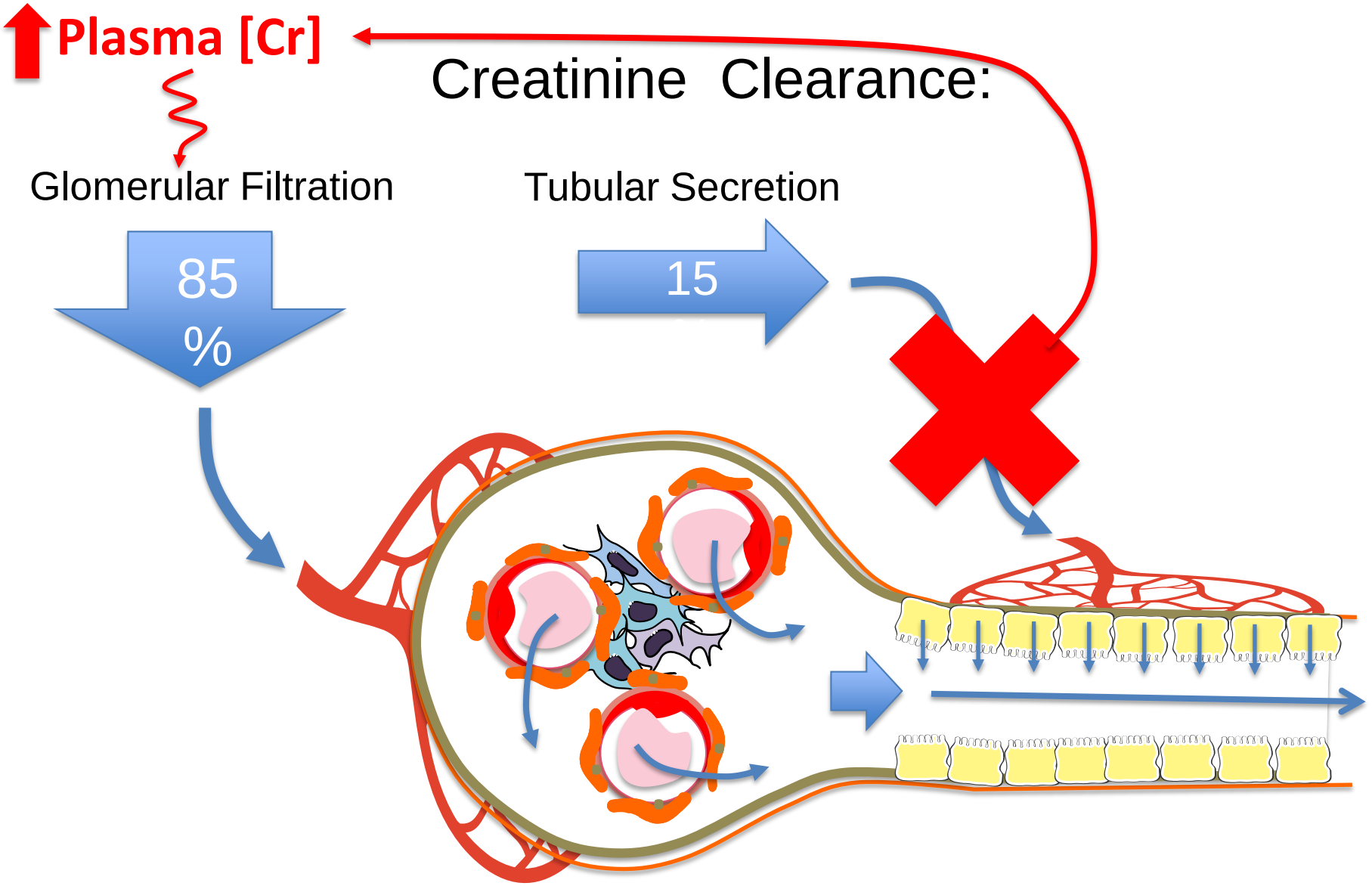




OAT1 KO + TDF

MRP4 KO + TDF





Shemesh O, et al. *Kidney Int.* 1985; **28** (5): 830–8.

TDF-PI/r: A potential for drug interactions

PI/r

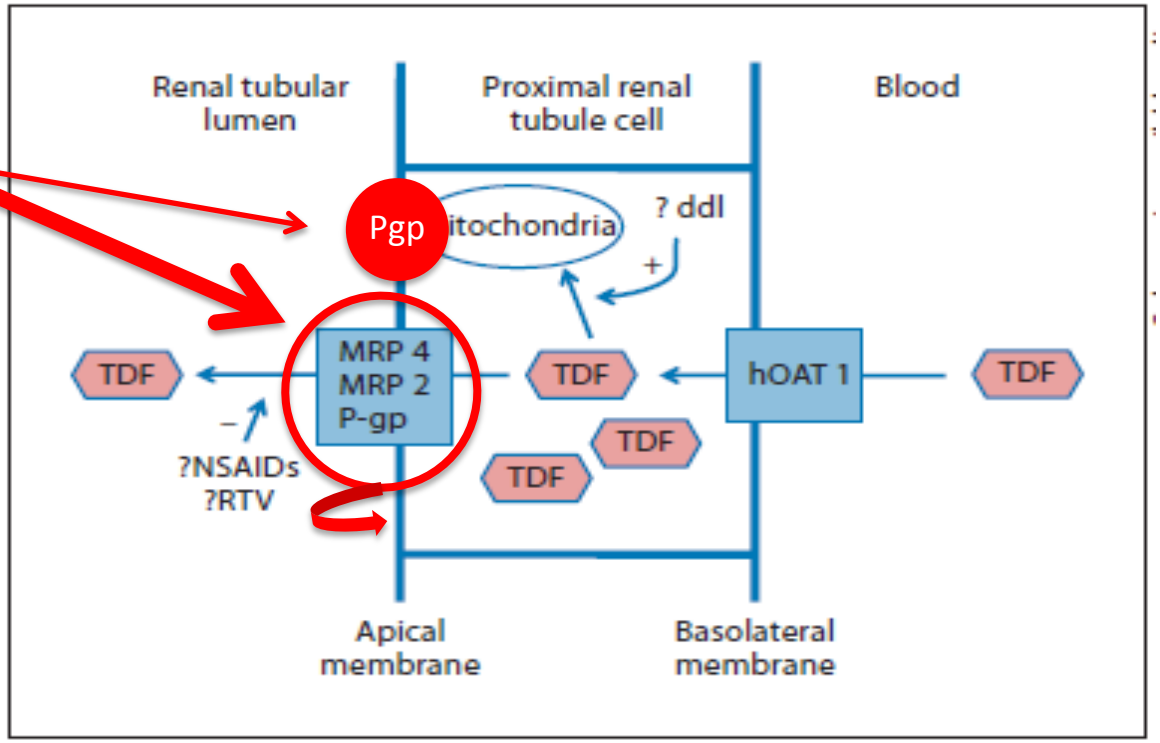
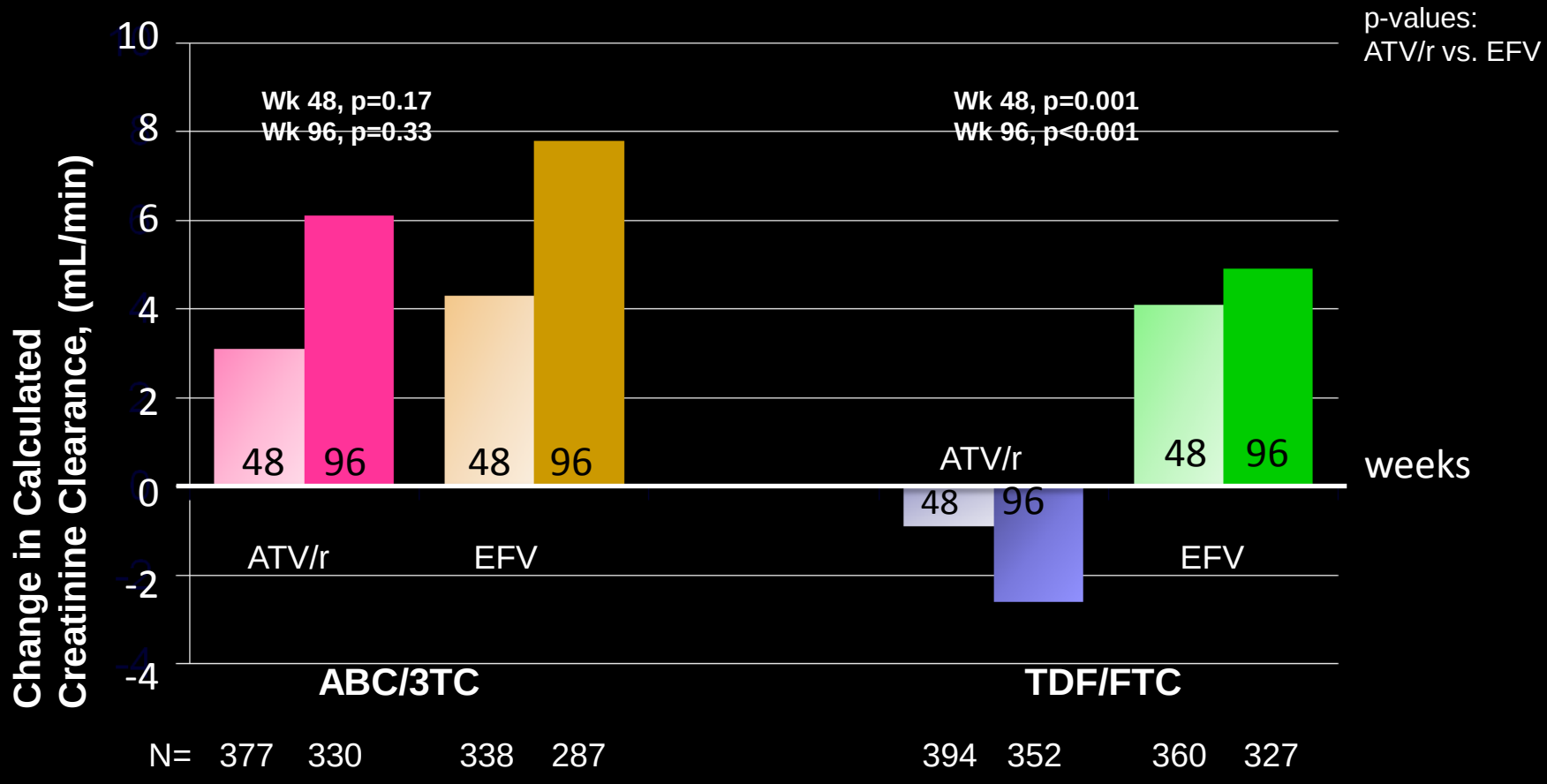


Fig. 1. Schematic diagram of the renal tubular secretion of TDF and potential intracellular accumulation with resultant mitochondrial toxicity in the presence of other pharmaceutical agents. See text for explanation and citations. hOAT = Human organic anion transporter; MRP = multidrug resistance-associated protein; P-gp = renal P-glycoprotein; ddI = didanosine; NSAIDs = nonsteroidal antiinflammatory drugs; RTV = ritonavir.

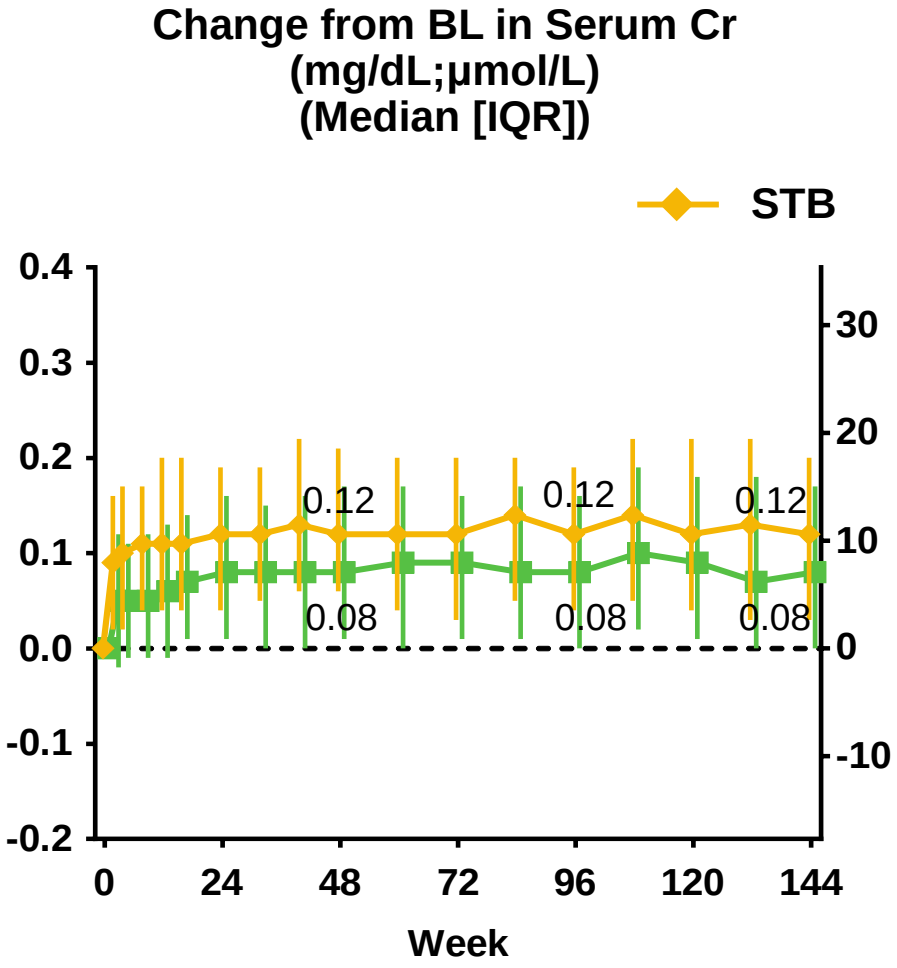
Cooper RD. Nephron Clin Pract 2011;118(3):c262-8. Epub 2011 Jan 4

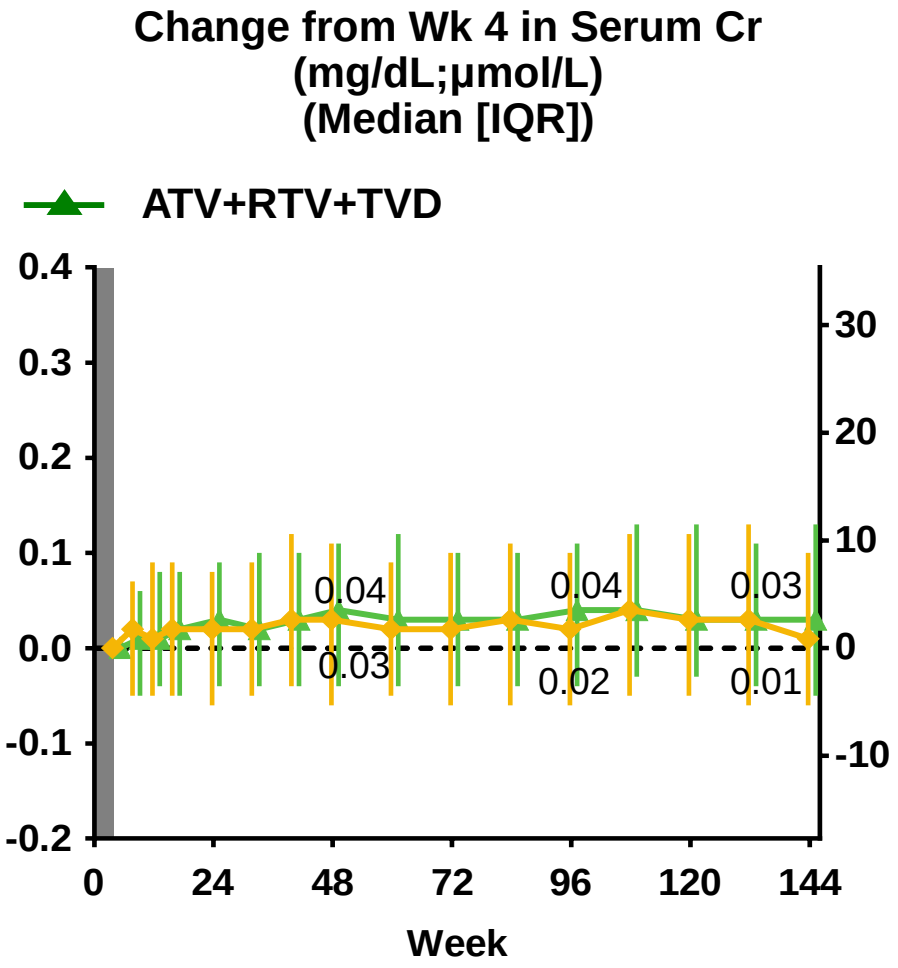
ATV/r vs. EFV
Median Change in Creatinine Clearance



Changes in Serum Cr from Baseline and from Week 4

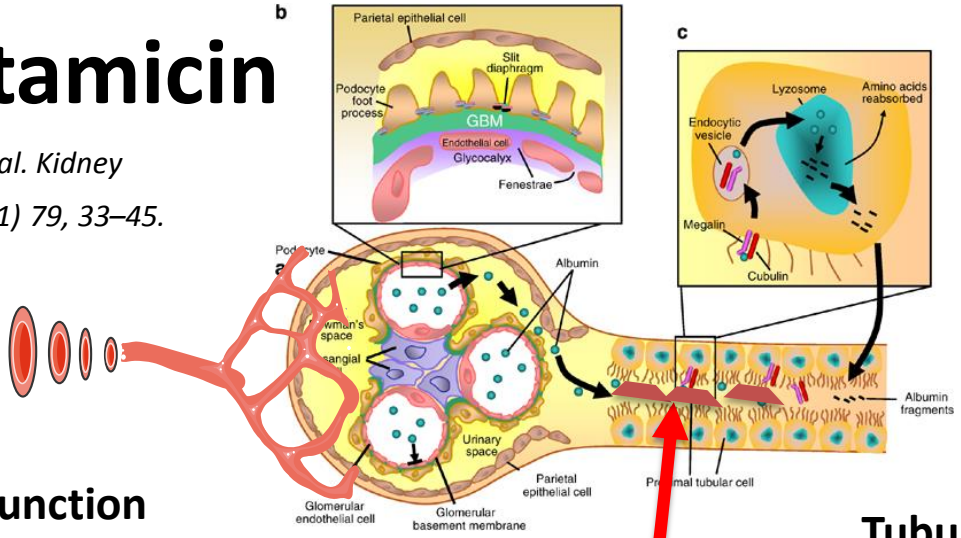
Study 103 – Week 144





Gentamicin

Lopez-Novoa F, et al. Kidney International (2011) 79, 33–45.



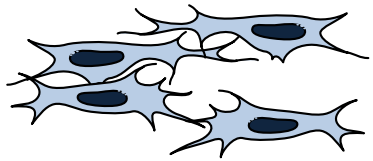
Tubular dysfunction
(decreased reabsorption of low-molecular weight proteins, calcium phosphates, electrolytes)

Tubulo-glomerular feedback (24hrs)

Luminal obstruction by dead tubular cells (apoptosis and necrosis)

Reduced afferent glomerular blood

Mesangial contraction & proliferation



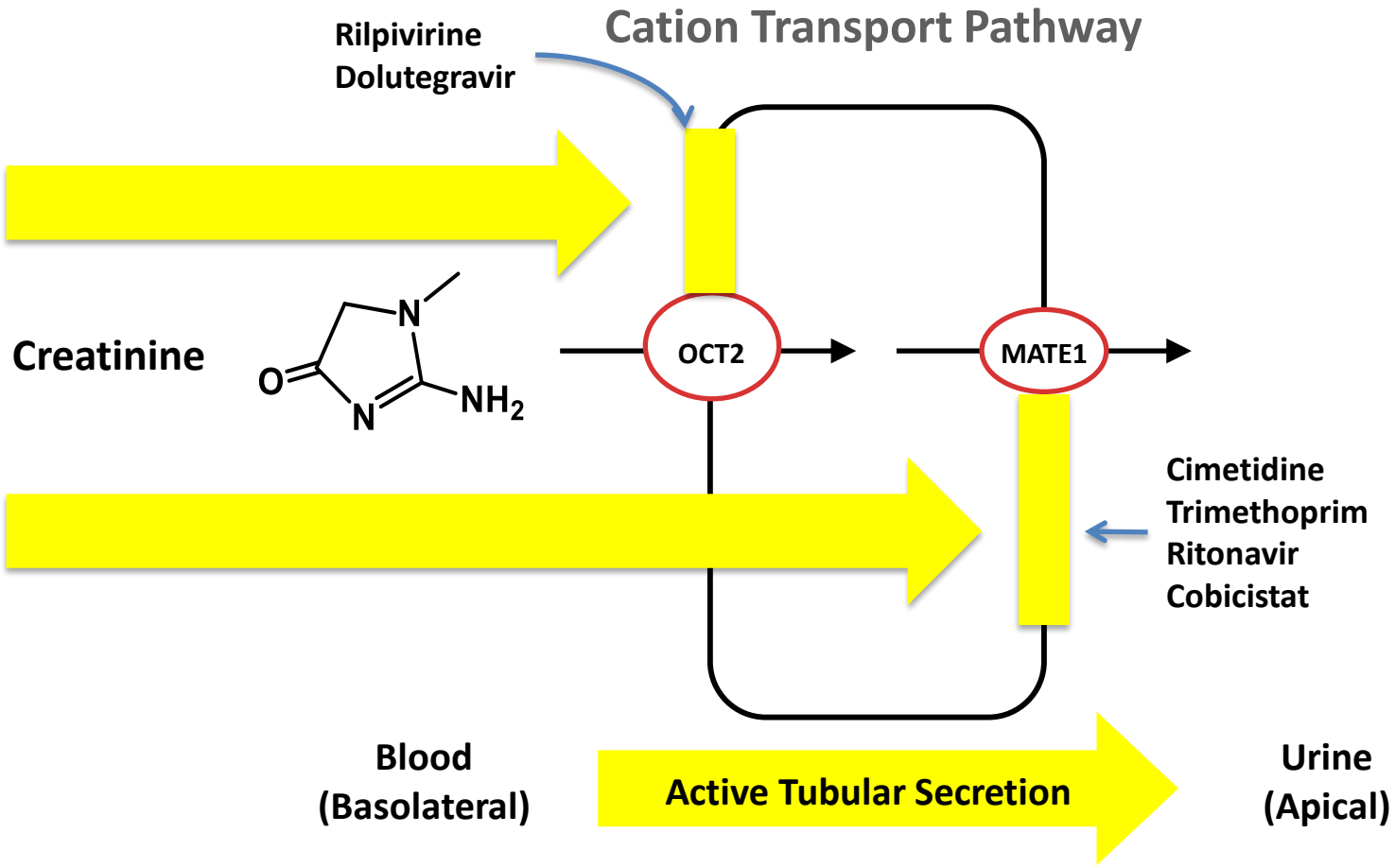
Tenofovir

Tubular dysfunction
(decreased reabsorption of low-molecular weight proteins, calcium phosphates)

Minor, variable degree of secondary hyperparathyroidism

Minimal tendency to apoptosis or necrosis

DRUGS INTERFERING ON CREATININE TUBULAR TRANSPORTER



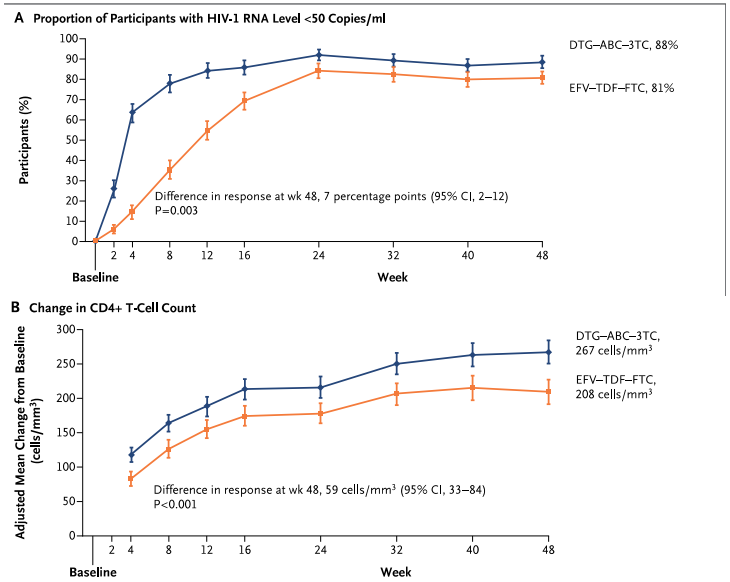
OCT2 = organic cation transporter 2
MATE1 = multidrug and toxin extrusion transporter 1

Lepist EI, et al. 51st ICAAC 2011.

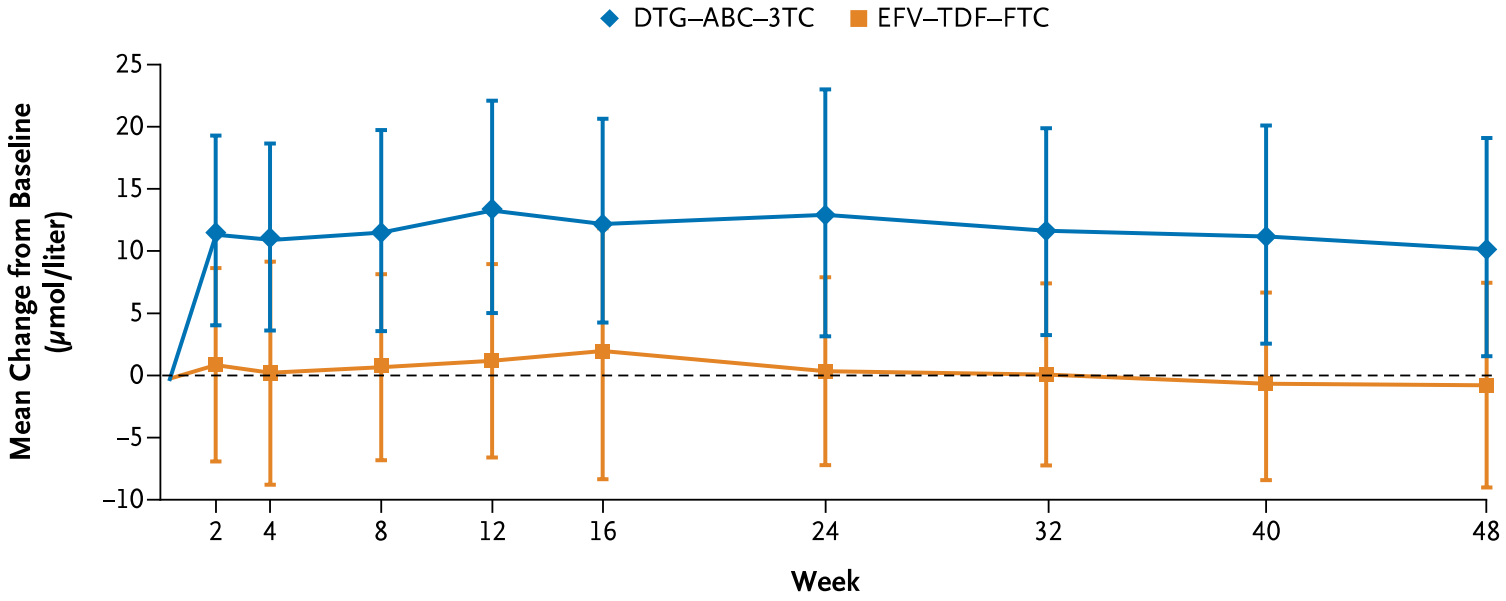
ORIGINAL ARTICLE

Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D., Dan Duiculescu, M.D., Andrea Eberhard, M.D., Felix Gutiérrez, M.D., Laurent Hocqueloux, M.D., Franco Maggiolo, M.D., Uriel Sandkovsky, M.D., Catherine Granier, D.E.S.S., Keith Pappa, Pharm.D., Brian Wynne, M.D., Sherene Min, M.D., and Garrett Nichols, M.D., for the SINGLE Investigators*



B **Change in Creatinine Level**



N Engl J Med 2013;369:1807-18.

Definition / Pathophysiology of Tenofovir (TDF) – associated Renal Disease

Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir

Pablo Labarga[a], Pablo Barreiro[a], Luz Martin-Carbonero[a], Sonia Rodriguez-Novoa[b], Carmen Solera[a], Jose Medrano[a], Pablo Rivas[a], Marta Albalater[c], Francisco Blanco[a], Victoria Moreno[a], Eugenia Vispo[a] and Vincent Soriano[a]

AIDS 2009, **23**:689–696

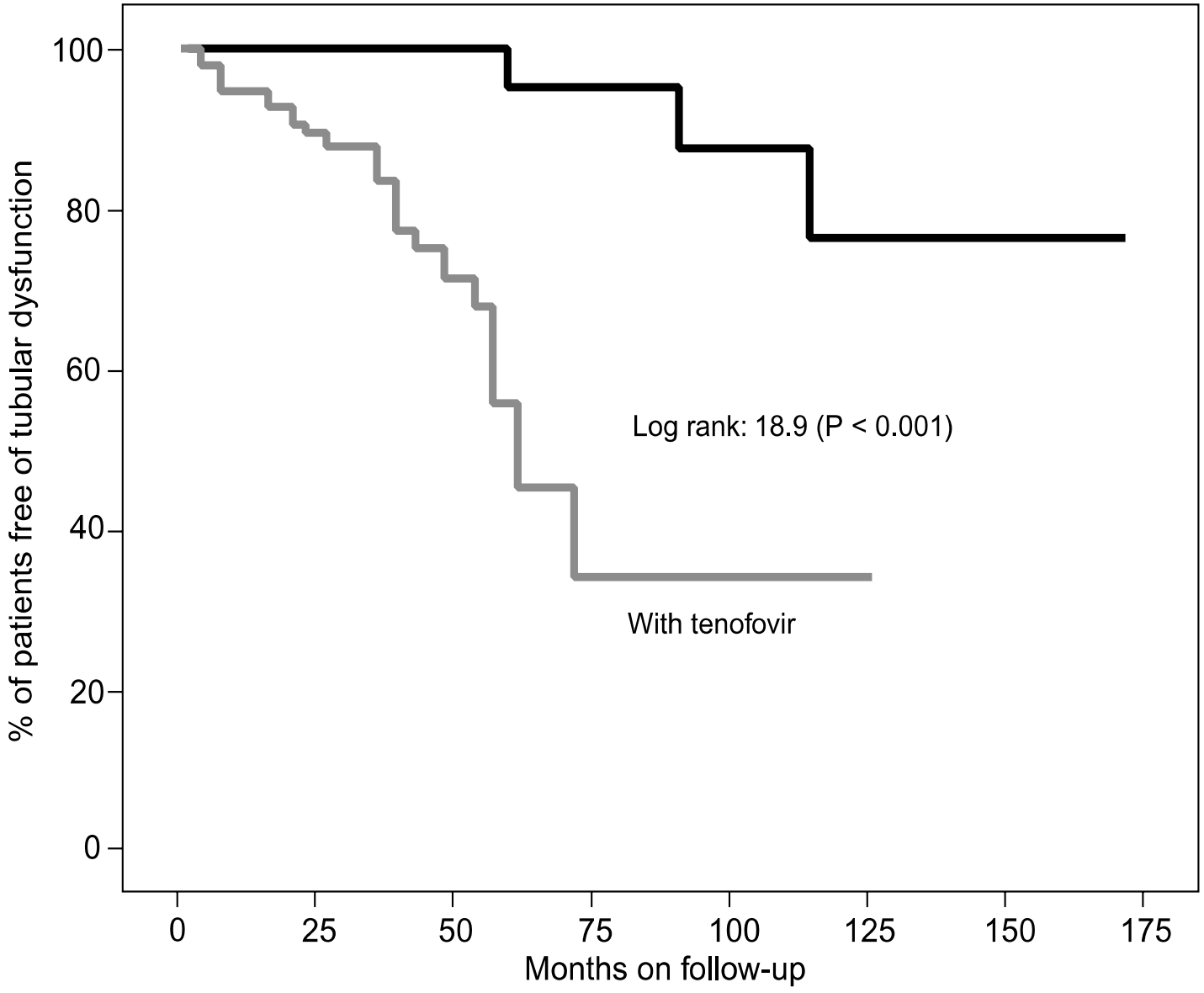
Methods: Cross-sectional study of plasma and 24 h urine markers of kidney tubulopathy (glycosuria, hyperaminoaciduria, hyperphosphaturia, hyperuricosuria and β2-microglobulinuria) could be allocated in three groups: **patients under a TDF-containing HAART**; **patients on HAART never exposed to TDF**; and **antiretroviral- naive individuals**. Significant tubular damage was defined when at least two of these parameters were repeatedly present, being at least one part of the Fanconi syndrome criteria (glucosuria, hyperaminoaciduria and hyperphosphaturia).

Glomerular function was assessed using creatinine clearance.

	HAART with TDF (Group 1)	HAART, never TDF (Group 2)	Drug-naive (Group 3)	Differences among groups
No. of patients (%)	153 (54)	49 (17)	81 (29)	
Plasma creatinine (mg/dl)	0.9 (0.8–1.0)	0.9 (0.9–1.1)	0.9 (0.8–1.0)	ANOVA, $P=0.8$
Creatinine clearance (ml/min)	109 (90–138)	119 (98–142)	123 (86–154)	ANOVA, $P=0.1$
Plasma phosphorus (mg/dl)	3.4 (2.9–3.7)	3.3 (3.0–3.7)	3.4 (3.1–3.9)	ANOVA, $P=0.2$
Plasma phosphorus <2.5 mg/dl (%)	13 (9.8)	3 (6.7)	2 (2.6)	$P=0.1$
Fractional tubular resorption of phosphorus (units)	0.82 (0.75–0.86)	0.85 (0.81–0.88)	0.87 (0.83–0.90)	1 versus 2, $P=0.002$ 2 versus 3, $P=0.11$ 3 versus 1, $P<0.001$
Plasma uric acid (mg/dl)	5.0 (4.3–5.8)	5.6 (4.9–6.0)	5.6 (4.9–6.5)	1 versus 2, $P=0.005$ 2 versus 3, $P=0.5$ 3 versus 1, $P<0.001$
Fractional excretion of uric acid (%)	9 (7–12)	7 (6–8)	7 (6–9)	1 versus 2, $P<0.001$ 2 versus 3, $P=0.81$ 3 versus 1, $P<0.001$
Nondiabetic glucosuria (%)	2 (2)	0 (0)	1 (2)	ANOVA, $P=0.7$
β_2-microglobulinuria (μg/l)	250 (210–664)	210 (204–219)	235 (208–434)	1 versus 2, $P<0.001$ 2 versus 3, $P=0.01$ 3 versus 1, $P=0.3$
Aminoaciduria (%)	24 (19)	8 (17)	11(16)	$P=0.9$
Alkaline phosphatase (IU/l)	242 (200–292)	224 (202–309)	192 (163–226)	1 versus 2, $P=0.4$ 2 versus 3, $P<0.001$ 3 versus 1, $P<0.001$
Tubular damage* (%)	30 (22)	3 (6)	9 (12)	1 versus 2, $P=0.01$ 2 versus 3, $P=0.3$ 3 versus 1, $P=0.06$

Continuous variables are expressed as median (interquartile range). *Definition: At least two parameters of tubular function were altered, being one of them nondiabetic glucosuria, reduced tubular resorption of phosphorus or pathologic aminoaciduria. ANOVA, analysis of variance; TDF, tenofovir.

Labarga P, et al. *AIDS* 2009, **23**:689–696



No. of patients

Without tenofovir	54	54	54	17	9	5	0	0
With tenofovir	164	83	30	2	1	1	0	0

Labarga P, et al. *AIDS* 2009, **23**:689–696

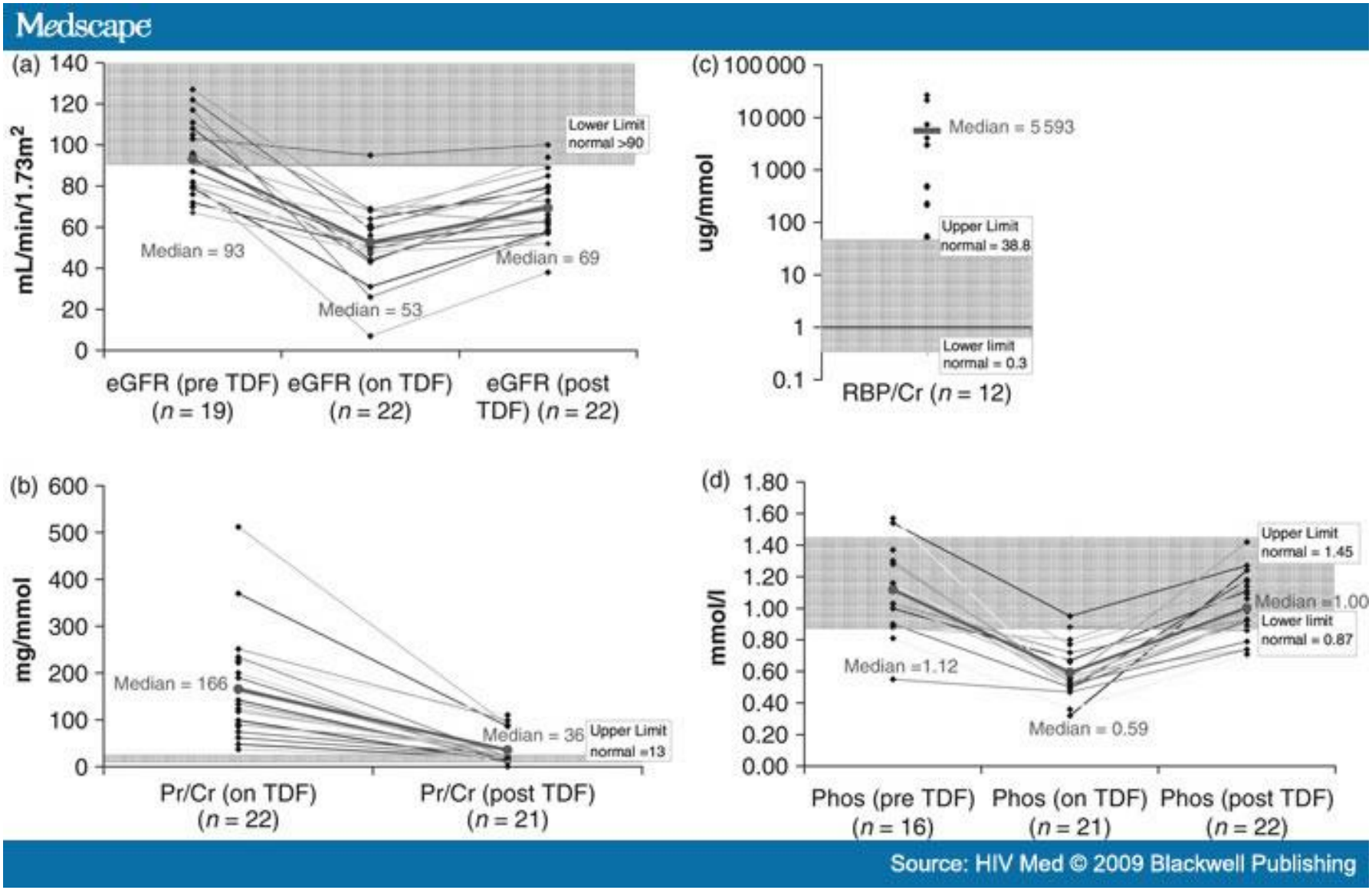
Table 3. Predictors of renal tubular damage in HIV patients.

	Tubular damage		Univariate analysis		Multivariate analysis	
	Yes*	No	OR (95% CI)	*P*	OR (95% CI)	*P*
No. of patients	33	150				
Age (years)	47 (43–52)	44 (39–48)	1.0 (0.9–1.0)	0.26	1.06 (1.0–1.1)	0.01
Male sex (%)	75	85	0.5 (0.2–1.2)	0.18		
Body weight (kg)	65 (57–73)	70 (62–79)	0.9 (0.9–1.0)	0.20		
History of hypertension (%)	26	29	1.0 (0.4–2.3)	0.93		
History of diabetes (%)	50	24	1.8 (0.9–3.6)	0.09		
Plasma HIV-RNA (log copies/ml)	1.7 (1.7–1.7)	1.7 (1.7–1.7)	0.1 (0–11.4)	0.34		
CD4 cell count (cells/μl)	494 (306–784)	506 (351–712)	0.9 (0.9–1.1)	0.07		
Length of ART (months)	76 (39–118)	54 (30–98)	0.9 (0.9–1.1)	0.24		
HAART with TDF (%)	91	71	10.6 (3.0–37.4)	<0.001	21.6 (4.1–113)	<0.001
HAART with PI (%)	64	50	2.3 (1.1–4.8)	0.02		
Concomitant nephrotoxic drugs (%)	21	14	2.2 (0.9–5.1)	0.07		
Serum HCV-RNA positive (%)	35	29	1.4 (0.6–2.9)	0.35		
Serum HBsAg positive (%)	12	6	1.8 (0.6–5.1)	0.28		

Continuous variables are expressed as median (interquartile range).
*Definition: At least two parameters of tubular function were altered, one of them being nondiabetic glucosuria, reduced tubular resorption of phosphorus or pathologic aminoaciduria.
ART, antiretroviral; HCV, hepatitis C virus; OR, odds ratio; PI, protease inhibitor; TDF, tenofovir.

Tenofovir-associated Renal and Bone Toxicity

C.L.N. Woodward; A.M. Hall; I.G. Williams; S. Madge; A. Copas; D. Nair; S.G. Edwards; M.A. Johnson; J.O. Connolly. *HIV Medicine 2009; 10: 482-87.*



Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/Lamivudine Versus Tenofovir/Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study

Frank A. Post, et al. J Acquir Immun Defic Syndr 2010; 55: 49-57.

EFV – ABV/3TC vs EFV/TDF/FTC in HLAB-5701 – negative HIV-infected patients

ABC/3TC FDC QD (n = 192)	TDF/FTC FDC QD (n = 193)	Total (n = 385)

Conclusions: The study showed **no difference in estimated glomerular filtration rate** between the arms, however, **increases in markers of tubular dysfunction were observed in the tenofovir/emtricitabine arm**, the long-term consequence of which is unclear. A significant difference in efficacy favoring tenofovir/emtricitabine was observed.

TABLE 2. Summary of Renal Biomarkers—Week 24 and Week 48

Renal Biomarker	Baseline, Median (IQR)* ABC/3TC FDC QD	Baseline, Median (IQR)* TDF/FTC FDC QD	Visit	Percentage of Baseline† ABC/3TC FDC QD	Percentage of Baseline† TDF/FTC FDC QD	Ratio of Changes From Baseline (95% CI)	*P*
Albumin (mg/mmol)‡	0.798 (0.501–1.540)	0.750 (0.477–1.556)	Week 24	90%	86%	0.96 (0.78 to 1.17)	0.6650
			Week 48	87%	94%	1.08 (0.90 to 1.29)	0.4237
β_2M (mg/mmol)‡	0.013 (0.005–0.024)	0.015 (0.009–0.030)	Week 24	72%	124%	1.72 (1.32 to 2.24)	<0.0001
			Week 48	53%	124%	2.33 (1.71 to 3.19)	<0.0001
RBP (μg/mmol)‡	12.26 (8.86–18.57)	12.57 (8.49–16.73)	Week 24	108%	151%	1.40 (1.21 to 1.63)	<0.0001
			Week 48	100%	150%	1.50 (1.28 to 1.76)	<0.0001
NAG (μmol/h/mmol)‡	34.39 (21.87–60.99)	34.87 (21.63–47.57)	Week 24	85%	92%	1.09 (0.95 to 1.24)	0.2344
			Week 48	87%	92%	1.05 (0.91 to 1.22)	0.5084

AJKD
Narrative Review

Am J Kidney Dis. 57(5):773-780. © *2011*

Index:

Tenofovir-Associated Kidney Toxicity in HIV-Infected Patients: A Review of the Evidence

Andrew M. Hall, MD, PhD,[1] Bruce M. Hendry, MD, PhD,[2] Dorothea Nitsch, MD, MSc,[3] and John O. Connolly, MD, PhD[1]

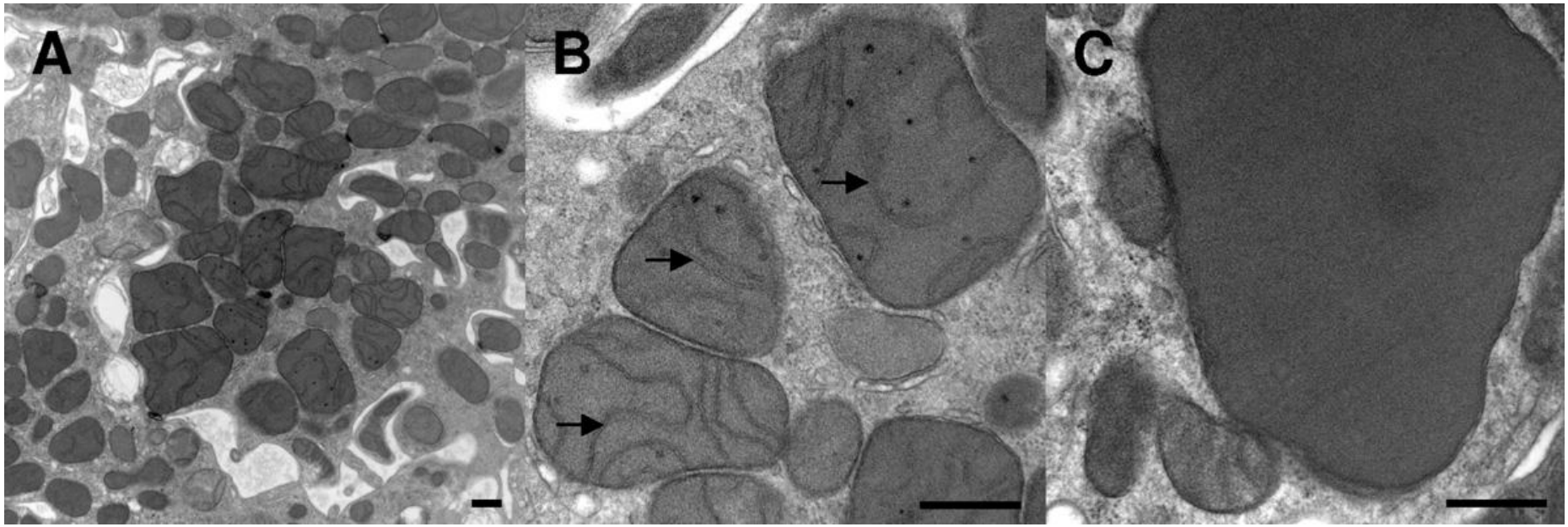
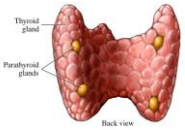
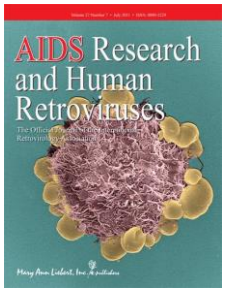


Figure 1. Electron micrographs of proximal tubule cells in a kidney biopsy specimen from a patient with Fanconi syndrome secondary to tenofovir toxicity. (A) Mitochondrial size and morphologic characteristics are highly irregular, with (B) disruption of the normal cristae (arrows) and (C) occasional giant mitochondria. (Scale bars = 500 nm.)

Early Changes in Parathyroid Hormone Concentrations in HIV-Infected Patients Initiating Antiretroviral Therapy with Tenofovir

Mar Masiá, et al. AIDS Research and Human Retroviruses. 2012, 28(3): 242-246





31 initiating **tenofovir**/emtricitabine and 26 initiating abacavir/lamivudine.

Median PTH levels turned out to be significantly higher among **tenofovir**/emtricitabine users at week 4 (p=0.01), week 24 (p=0.008), and week 36 (p=0.02), and were above the upper limits of normal values (ULN) at weeks 24, 36, and 48 only in patients receiving **tenofovir**/emtricitabine.

iPrEX: PrEP in HIV-Negative Individuals: Mean Change in BMD Through Week 72

	FTC/TDF (n=247)	Placebo (n=256)	Difference (95% CI)	P-value
Total hip				
Wk 24	-0.33 (0.13)	+0.36 (0.13)	-0.69 (-1.06 to -0.33)	< 0.001
Wk 48	-0.02 (0.21)	+0.91 (0.21)	-0.94 (-1.53 to -0.35)	0.002
Wk 72	+0.25 (0.27)	+0.59 (0.27)	-0.34 (-1.10 to 0.42)	0.38
Spine				
Wk 24	-0.65 (0.20)	+0.30 (0.20)	-0.94 (-1.50 to -0.39)	0.001
Wk 48	-0.38 (0.24)	+0.20 (0.24)	-0.58 (-1.24 to 0.07)	0.081
Wk 72	-0.96 (0.31)	+0.07 (0.30)	-1.03 (-1.88 to -0.19)	0.017

Mulligan K, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 94LB.

Determinants of Parathyroid Hormone Levels in HIV-positive Tenofovir-treated Patients with Normal Renal Function Marinaro L*, et al.

to be presented at CROI 2015

294 adult HIV-positive patients on **TDF-containing HAARTs** since at least six months, presenting estimated creatinine clearance (eCRCL) above 60 ml/min, with no significant comorbidity (hypertension, diabetes, urinary tract abnormalities), signing an informed consent were included.

RESULTS

72.3%, **15%** and 16.8% of patients presenting vitamin D deficiency (<30 ng/mL), secondary **hyperparathyroidism (>79.6 pg/mL)** and hypophosphoremia (<2.6 mg/dL).

At multivariate linear regression (including also age, gender, BMI and time on TDF) **vitamin D levels** (p>0.001), **cirrhosis** (p=0.04) and the **vitamin D receptor uncommon variants Cdx2** (rs11568820, p=0.025) were independent predictors of [PTH].

At multivariate linear regression **PTH levels** (p=0.023), **HAART class** (NNRTIs associated with the lowest levels, p=0.005), **SLC28A2 124** (rs11854484, p=0.037) SNP and **TDF urinary output** (urinary TDF/plasma TDF, p=0.038) were independent predictors of phosphorus levels.

Changes in Bone Mineral Density (BMD) over 96 Weeks on Darunavir/Ritonavir (DRV/r) + Raltegravir (RAL) or Darunavir/Ritonavir + Tenofovir/Emtricitabine (TDF/FTC)

NEAT 001/ANRS 143. BMD sub-study

Bernardino JI, Mocroft A, Mallon PW, Wallet C, Reiss P, Katkama C, de Wit S, Antinori A, Gerstoft J, González-Garcia J, Palmisano L, George EC, Saillard J, Raffi F, Arribas JR, NEAT 001/ANRS143 Study Group

54th ICAAC. Washington DC. September 5-9, 2014. H-1198

NEAT 001/ANRS 143 Study Design

Phase III, randomised, open-label, multicenter, parallel-group, non-inferiority trial
78 sites, 15 European countries

HIV-1 ART-näive
≥ 18 years
HIV-1 RNA > 1000 c/ml
CD4+ ≤ 500/mm³
Hbs Ag negative
No major IAS-USA RAM

→ DRV+r 800+100 mg QD + RAL 400 mg BID

→ DRV+r 800+100 mg QD + TDF/FTC FDC QD

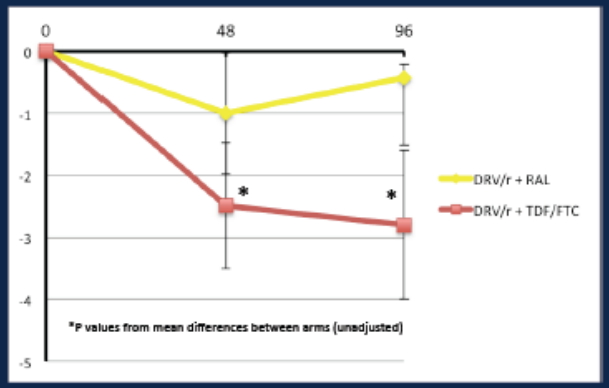
Randomisation 1:1
Stratified by country and participation in virology/immunology substudy

Week 96

- Bone substudy: patients randomised at same time main study
- Whole body dual-energy x-ray absorptiometry (DXA) scans assessed BMD (total hip, lumbar spine, femoral neck)
- Hologic and Lunar devices used. No central reading

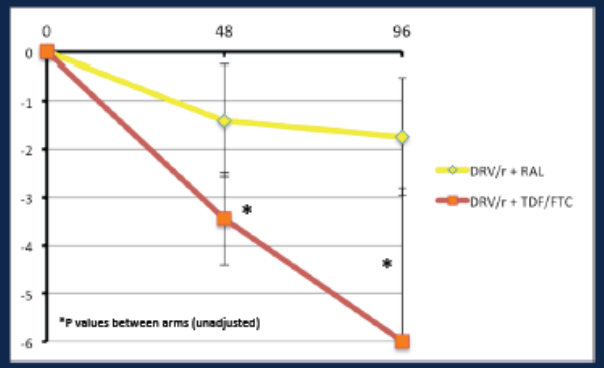
Raffi et al. Lancet 2014 Published online 5th Aug

Mean % Change in lumbar spine BMD



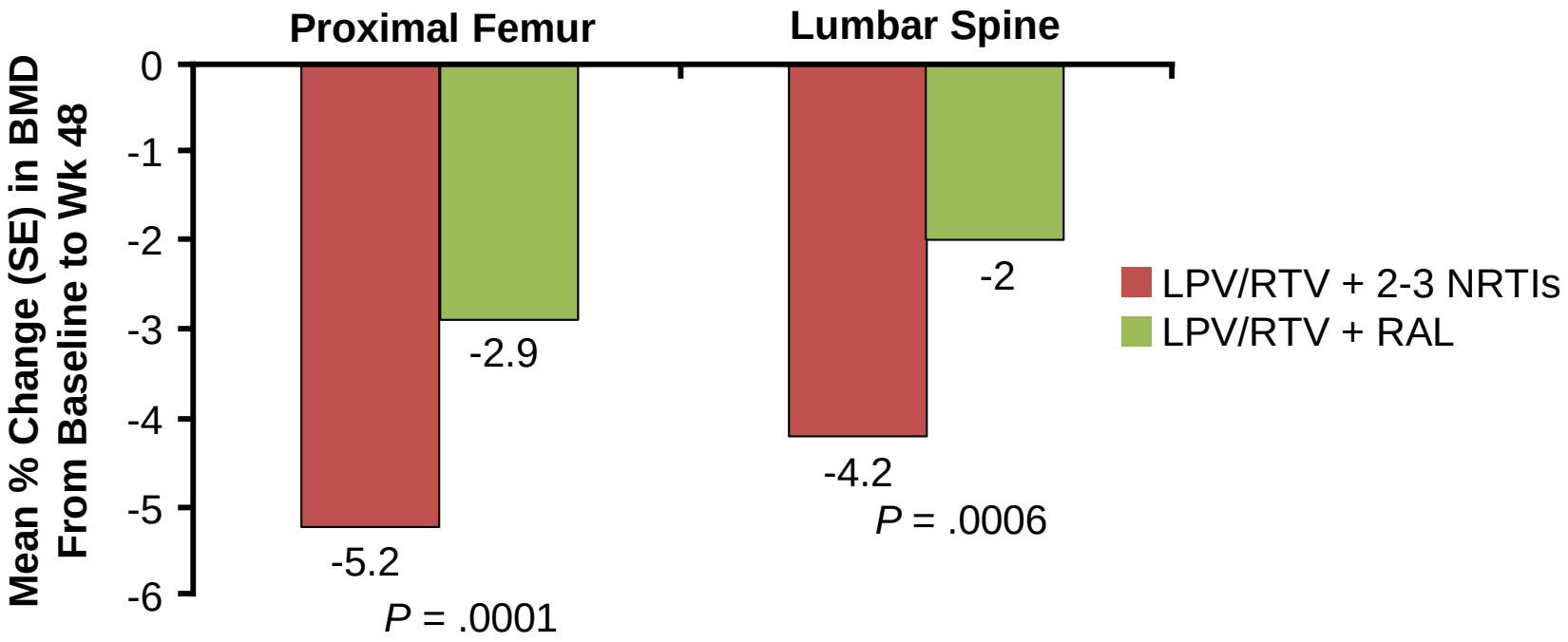
	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =70	51	-1.0 (-1.98, -0.02)	48	-0.43 (-1.51, 0.65)
DRV/r + TDF/FTC n = 76	63	-2.49 (-3.51, -1.47)	57	-2.8 (-4.0, -1.6)
Mean difference (95% CI); p	- 1.49 (-2.94, -0.04); p = 0.046*		-2.37 (-4.0, -0.74); p = 0.0054*	

Mean % Change in femoral neck BMD



	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =70	55	-1.41 (-2.57, -0.25)	49	-1.74 (-2.96, -0.52)
DRV/r + TDF/FTC n = 76	67	-3.45 (-4.41, -2.49)	59	-5.99 (-9.18, -2.80)
Mean difference (95% CI); p	- 2.04 (-3.53, -0.55); p = 0.0084*		-4.25 (-7.92, -0.58); p = 0.025*	

SECOND-LINE: Greater Mean BMD Loss With NRTI-Based Regimen at Wk 48



- No significant difference in frequency of new osteopenia, osteoporosis
- Greater decline in lumbar spine BMD associated with lower BMI, no TDF before study, and TDF initiation on study

Hoy J, et al. IAS 2013. Abstract WELBB05. Graphic used with permission.

ASSOCIATION BETWEEN TDF PLASMA CONCENTRATION AND RENAL PROXIMAL TUBULAR TOXICITY

Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations

Rodríguez-Nóvoa, Sonia et al. AIDS 2010; 24: 1064–1066

Renal Impairment in Patients receiving a TDF-based cART Regimen: Impact of TDF Concentration?

Poizot-Martin I, et al. J Acquir Immune Defic Syndr. 2013; 62:375-80.

Kidney Tubular Dysfunction Is Related to Tenofovir Plasma Concentration

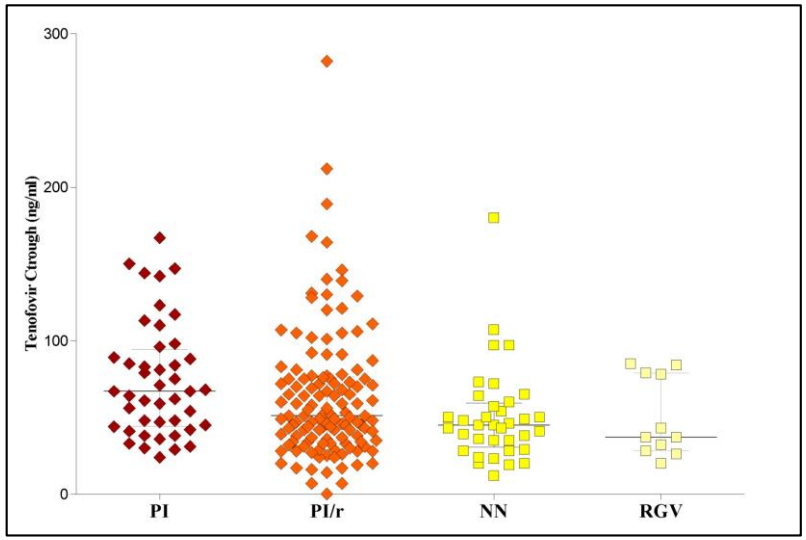
M Ezinga, et al. **CROI 2012, Paper #603**

Determinants of Tenofovir Plasma Trough Concentrations: a Cross-sectional Analysis in the Clinical Setting. Calcagno A, et al. Antimicrob Agents Chemother. 2013 Apr;57(4):1840-3.

No significant differences were found in BMI, eGFR and time on TDF among these groups.

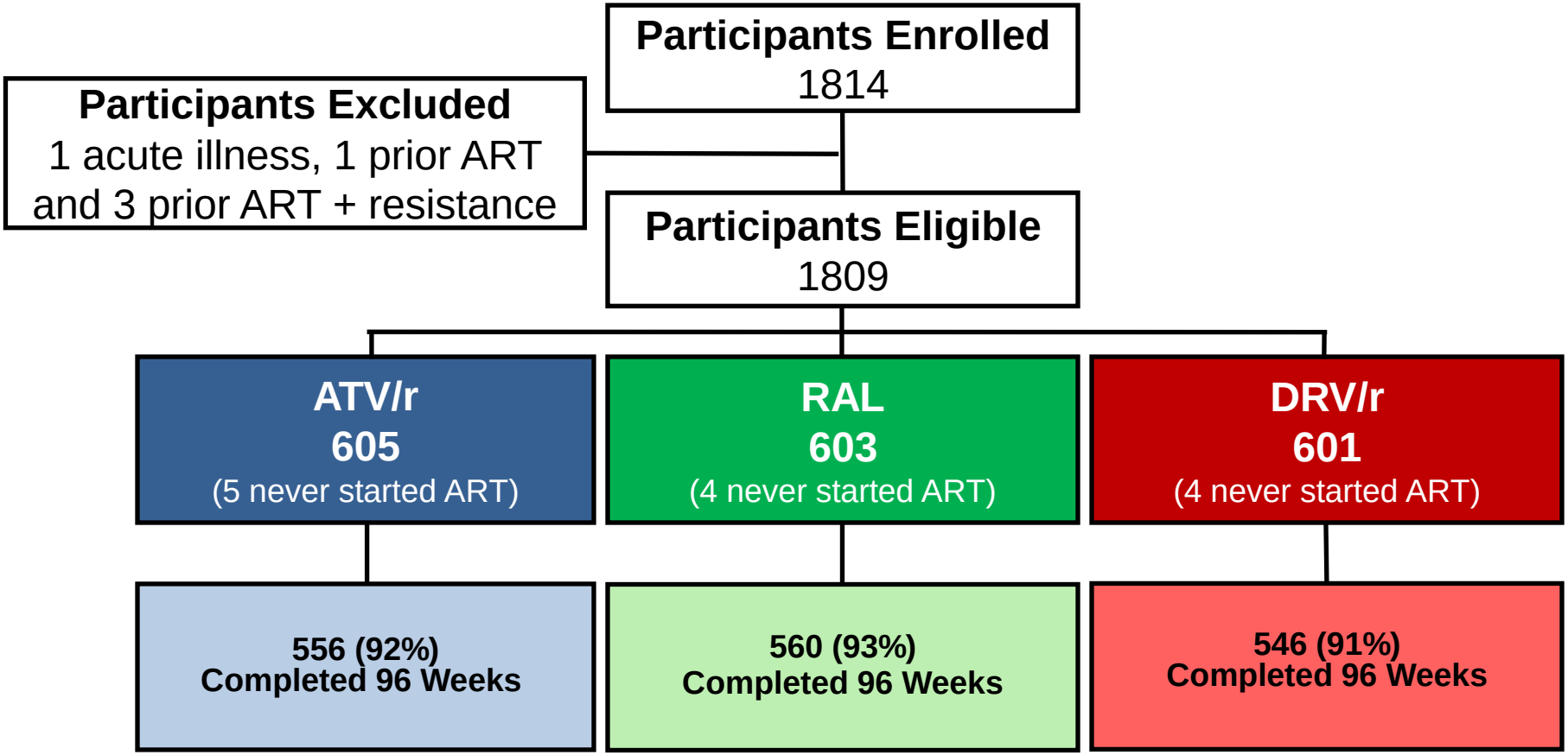
	ATV n=44	PI/r n=126	NN n=36	RGV n=11
Med	**67**	**51**	**45**	**37**
IQR	44-94	35-76	30-59	28-79

Tenofovir Ctroughs (ng/ml; median and IQR) with different companion drugs

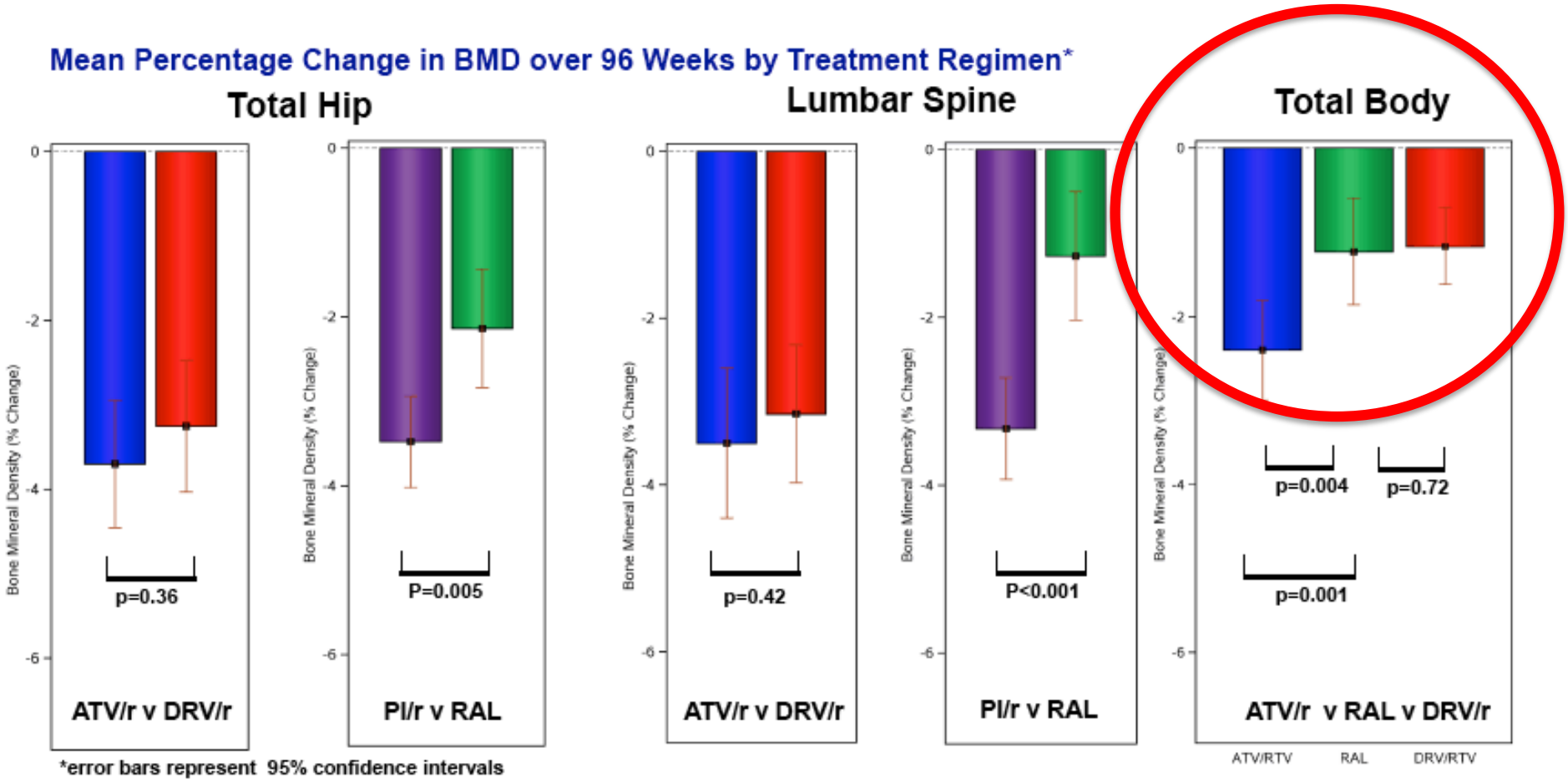


Patient Disposition – ARDENT

Landovitz RJ et al. "Efficacy and Tolerability of Atazanavir, Raltegravir, or Darunavir with FTC/TDF: ACTG A5257." Abstract 85. Presented at 21st CROI 2014.



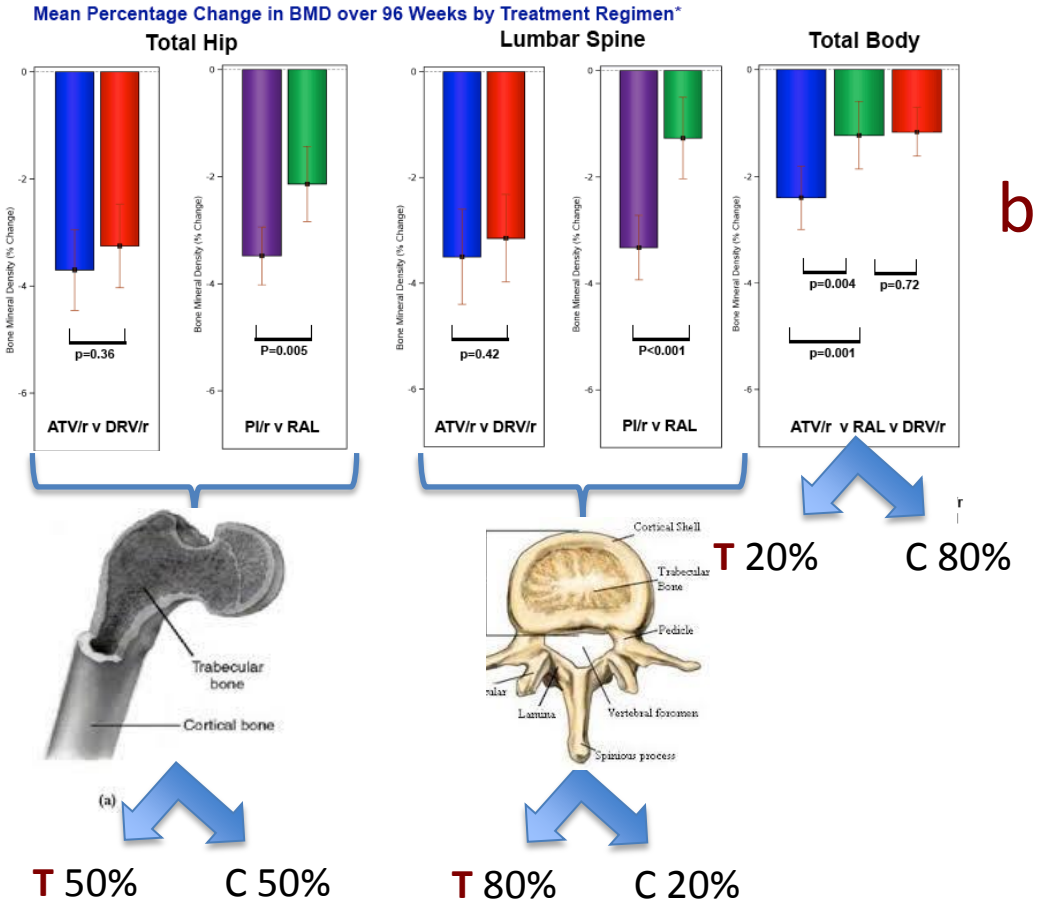
Brown T, Moser C, Currier J, et al. Bone density changes after antiretroviral initiation with protease inhibitors or raltegravir. In: Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston. Abstract 779LB.



*error bars represent 95% confidence intervals

- All of the treatment arms showed a statistically significant loss of BMD over 96 weeks at all of the sites (p<0.001)
- At the hip and the spine, the mean percentage BMD changes over 96 weeks were not different in the PI arms
  - Hip: ATV/r -3.9% v DRV/r -3.4%, p=0.36; Spine: ATV/r -4.0% v DRV/r -3.6%, p=0.42
- At the hip and the spine, the loss of BMD was greater in the combined PI arms than the RAL arm
  - Hip -3.7% v -2.4%, p=0.005;Spine: -3.8% v -1.8%, p<0.001

- Total body BMD loss was greater with ATV/r than DRV/r (-2.9% v -1.6%, p=0.001) and greater with ATV/r than RAL (-2.9% v -1.7%, p=0.004)



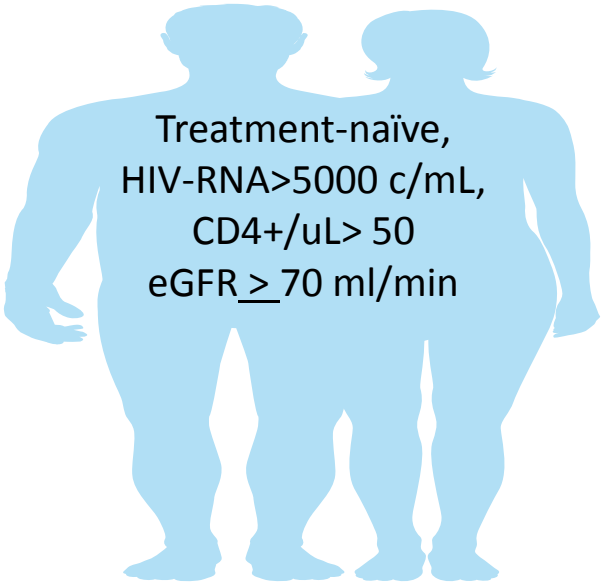
Why such a difference between total body and hip and spine findings?

The total body is about 80% cortical bone and **20% trabecular bone**, whereas the spine is 20% cortical bone/**80% trabecular bone** and the ratio at the total hip is about **50/50**. It is possible that DRV/r has less of an effect on cortical bone compared to ATV/r

Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study

Sax PE, et al. (*J Acquir Immune Defic Syndr* 2014;67:52–58)

Phase 2, randomized, double-blind, double-dummy, multicenter, active-controlled study



Randomized 2:1

ELV/COBI/FTC/TAF

n = 112

ELV/COBI/FTC/TDF

n = 58

Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study

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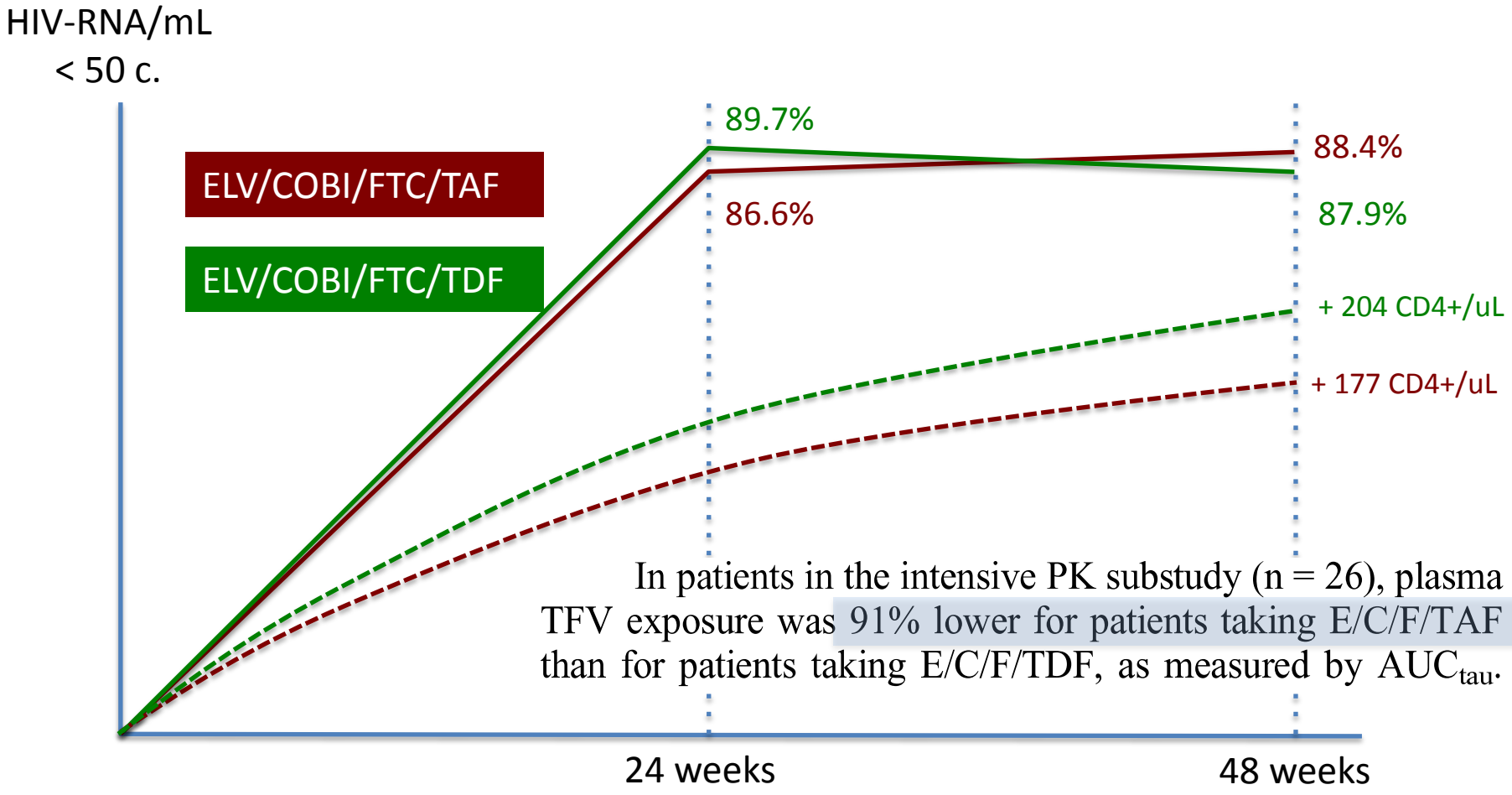

In patients in the intensive PK substudy (n = 26), plasma TFV exposure was 91% lower for patients taking E/C/F/TAF than for patients taking E/C/F/TDF, as measured by AUC_{tau}.

Conversely, intracellular TFV-DP levels in PBMCs were 5.3-fold higher for patients in the E/C/F/TAF arm.

Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study

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Week 48

Total cholesterol:

ELV/COBI/FTC/TAF + 30 mg vs ELV/COBI/FTC/TDF + 17 mg (p = 0.11)

HDL:

ELV/COBI/FTC/TAF + 7 mg vs ELV/COBI/FTC/TDF + 3 mg (p = 0.023)

LDL:

ELV/COBI/FTC/TAF + 9% (17mg) vs ELV/COBI/FTC/TDF + 3% (11mg)

Serum creatinine:

ELV/COBI/FTC/TAF + 0.07 mg/dL vs ELV/COBI/FTC/TDF + 0.10 mg/dL (p = 0.077)

eGFR (CG):

ELV/COBI/FTC/TAF – 5.5 mL/min vs ELV/COBI/FTC/TDF + 10.1 mL/min (p = 0.041)

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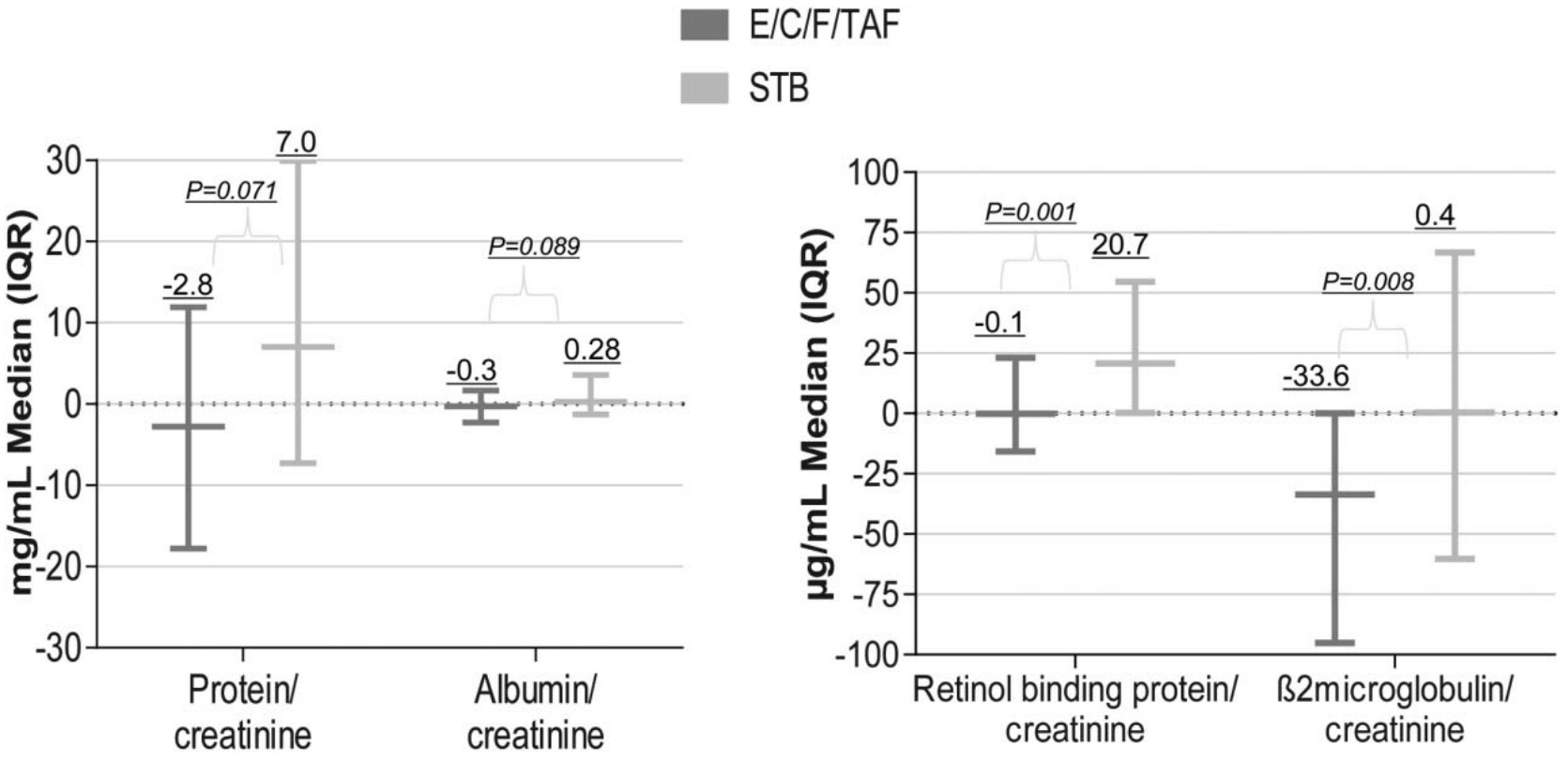
Sax PE, et al. (*J Acquir Immune Defic Syndr* 2014;67:52–58)

Urine Tubular Proteins: Median Change from Baseline Values



Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study

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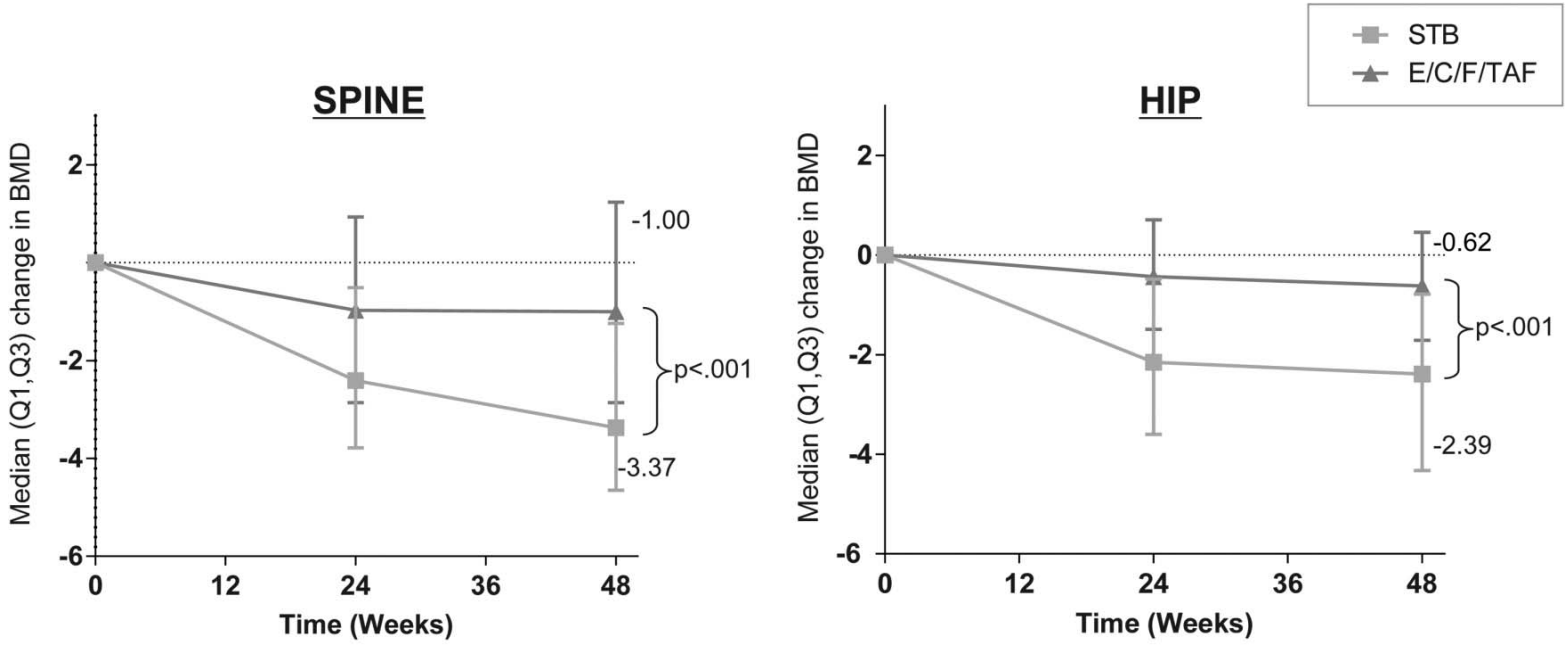
Percent Change in Spine and Hip BMD as determined using DEXA



No decrease in hip BMD: 32% E/C/F/TAF vs 7% STB (p<.001)

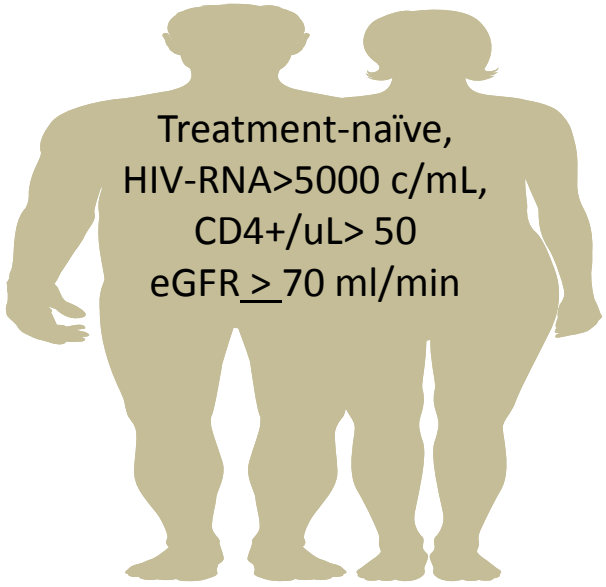
W48 Median Value of Bone Biomarkers as % of Baseline: E/C/F/TAF vs. STB

Procollagen Type 1 N-terminal propeptide (P1NP):	109% vs 169% (p<0.001)
C-terminal telopeptide (CTx):	119% vs. 178% (p<0.001)

H-647c - 48 Week Study of the First PI-based Single Tablet-Regimen (STR) Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) vs. Cobicistat (COBI)-boosted Darunavir (DRV) and Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) in Treatment-naïve (TN) Adults

Mills A, et al. 54th ICAAC, 2014. Washington, DC, September 5-9, 2014

Phase 2, randomized, double-blind, double-dummy, multicenter, active-controlled study



Randomized 2:1

DRV/COBI/FTC/TAF

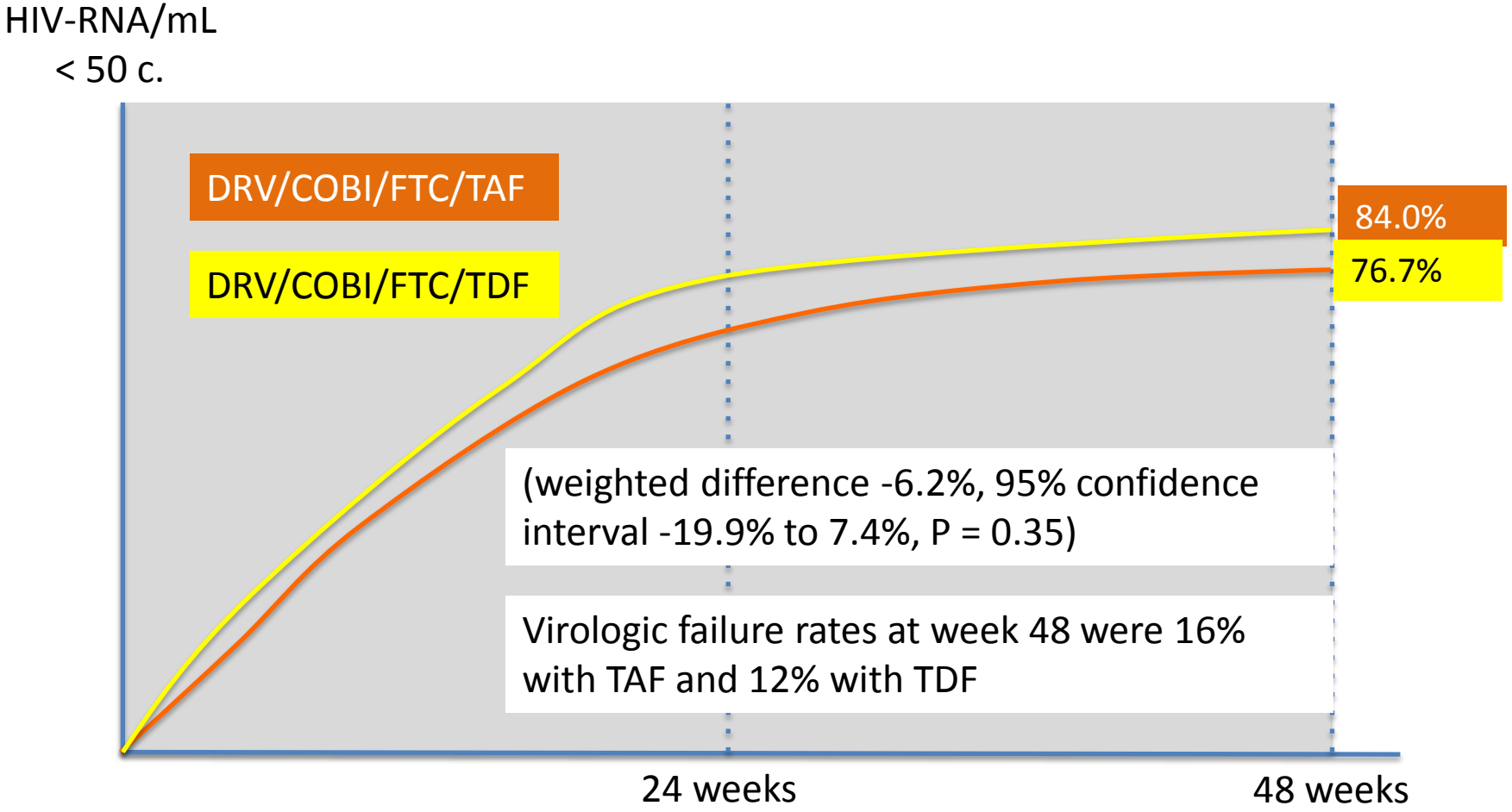
n = 103

DRV/COBI/FTC/TDF

n = 50

H-647c - 48 Week Study of the First PI-based Single Tablet-Regimen (STR) Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) vs. Cobicistat (COBI)-boosted Darunavir (DRV) and Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) in Treatment-naïve (TN) Adults

Mills A, et al. 54th ICAAC, 2014. Washington, DC, September 5-9, 2014



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Mills A, et al. 54th ICAAC, 2014. Washington, DC, September 5-9, 2014

- The median decrease in **eGFR** (mL/min) was **-2.9 (TAF)** vs. -**10.6** (TDF), p=0.017.
- Median change in **proximal tubular proteinuria** **rose significantly less with TAF** than with TDF (+9% versus +54%, P = 0.003).
- Through 48 weeks, **average spine bone mineral density** **decreased significantly less with TAF** than with TDF (-1.57% versus -3.62%, P = 0.003), **as did hip bone mineral density** (-0.84% versus -3.82, P < 0.001). The researchers noted that these TAF-related drops in bone mineral density are among the lowest in antiretroviral trials. No one in either arm had a fracture through 48 weeks of treatment.
- **Levels of tenofovir diphosphate**, the active form of TAF and TDF, were **6.5 times higher in peripheral blood mononuclear cells with TAF** than with TDF. Plasma tenofovir exposure measured as area under the concentration-time curve was **91% lower with TAF** than with TDF.

Tenofovir Urinary Output is Associated With Renal Tubular Dysfunction in HIV-positive Patients

Calcagno(A*,(Marinaro(L,(Simiele(M,(Mussa(M,(Te6 oni(MC,(Tren7 ni(L,(Alcantarini(C,(D'Avolio(A,(Di(Perri(G(and(Bonora(S.((

Cross-sectional study of TDF pharmacokinetics in plasma and urine in TDF intakers undergoing urinary assessment of renal tubular dysfunction

AIDS 2014 STEPPING UP THE PACE

Inclusion criteria:!

- Adult HIV-positive patients;!
- on tenofovir-containing HAARTs since at least six months;!
- estimated creatinine clearance (eCRCL) above 60 ml/min;!
- no significant comorbidity (hypertension, diabetes, urinary tract abnormalities);!
- self-reported adherence above 90%;!
- signing an informed consent.!

!

Twelve-hour tenofovir plasma (pC12) and spot 12-hour urinary concentration (uC12) were measured through HPLC/MS-MS methods.!

!

Urinary retinol binding protein (uRBP) and creatinine (uCR) were assessed through validated methods: tubular damage was defined as uRBP>0.1 mg/dL or uRBP/uCR>159 ug/g. !

Retinol-binding protein is a 21-kDa protein that is synthesized in the liver and is responsible for transporting vitamin A from the liver to other tissues. Similar to other low-molecular- weight proteins, it is relatively **freely filtered by the glomerulus** and **reabsorbed by the proximal tubule** to be catabolized to its amino acid constituents. Increased plasma levels and urinary excretion of RBP correlated with renal injury associated with aminoglycoside and cephalosporin.

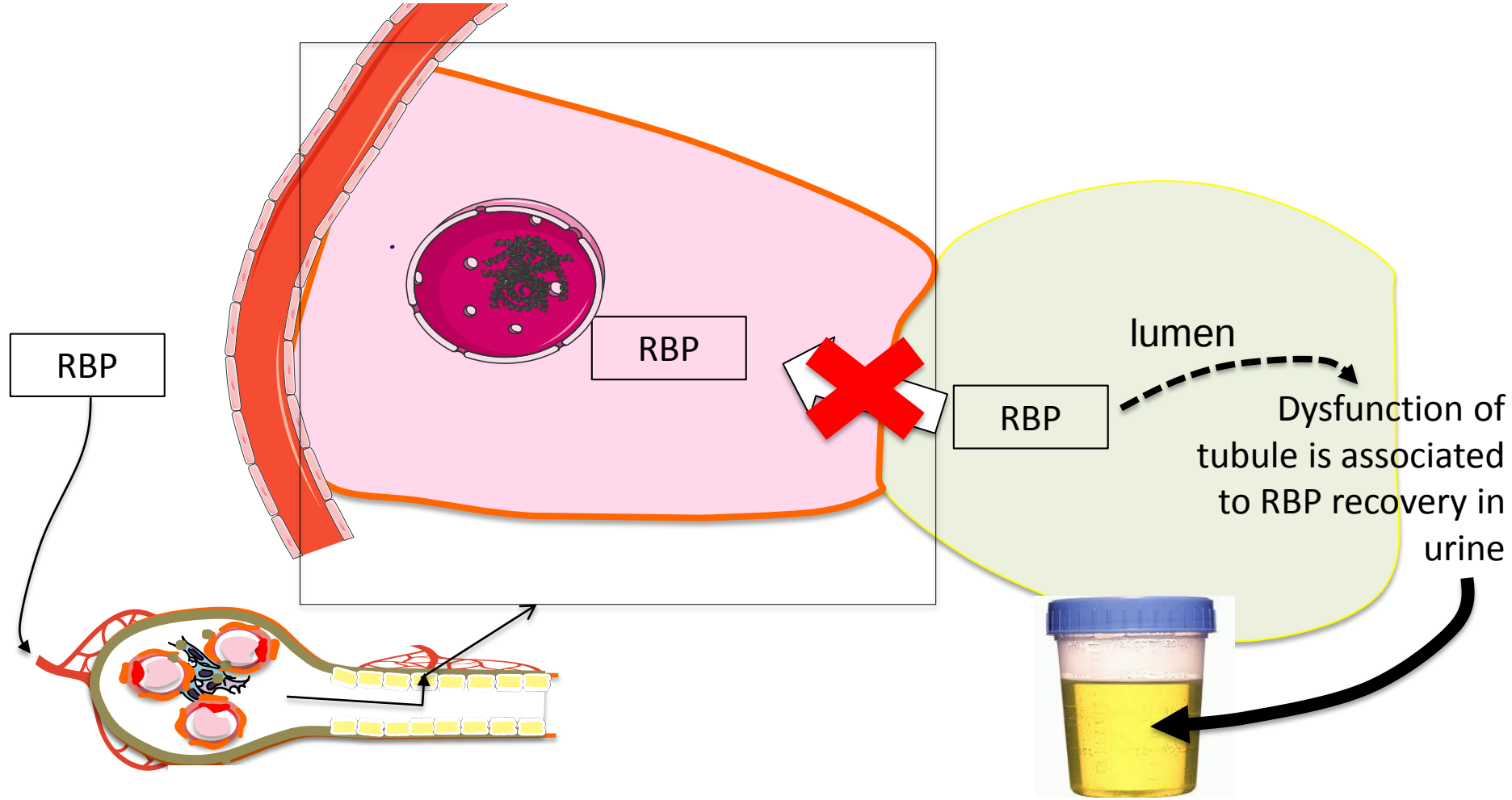

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Table 1 Baseline characteristics (n=170)!		
Gender (male)!		120 (71%)!
Ethnicity (Caucasian)!		140 (82.8%)!
Age (years)!		44.9 (38.5-49.6)!
BMI (Kg/m^2)!		23.5 (21.6-25.6)!
eCRCL (ml/min)!		91.3 (79.9-105-6)!
CD4 (n/uL)!		552 (435-695)!
HIV RNA<50 copies/mL!		154 (91.1%)!
HCV+!		40 (23.5%)!
Exposed to IDV!		13 (7.6%)!
Duration of TDF (months)!		50 (25.5-81.7)!
Third drugs! !	NN!	93 (55%)!
	PI!	66 (39.1%)!
	RAL!	8 (4.7%)!

12-hour TFV concentrations (ng/mL)!	
plasma (pTFV)!	**66** (48-96)!
urinary (uTFV)!	**27086** (15657-38516)!
urinary-to-plasma ratio (u/pTFV)!	**412** (251-616)!

Tenofovir Urinary Output is Associated With Renal Tubular Dysfunction in HIV-positive Patients

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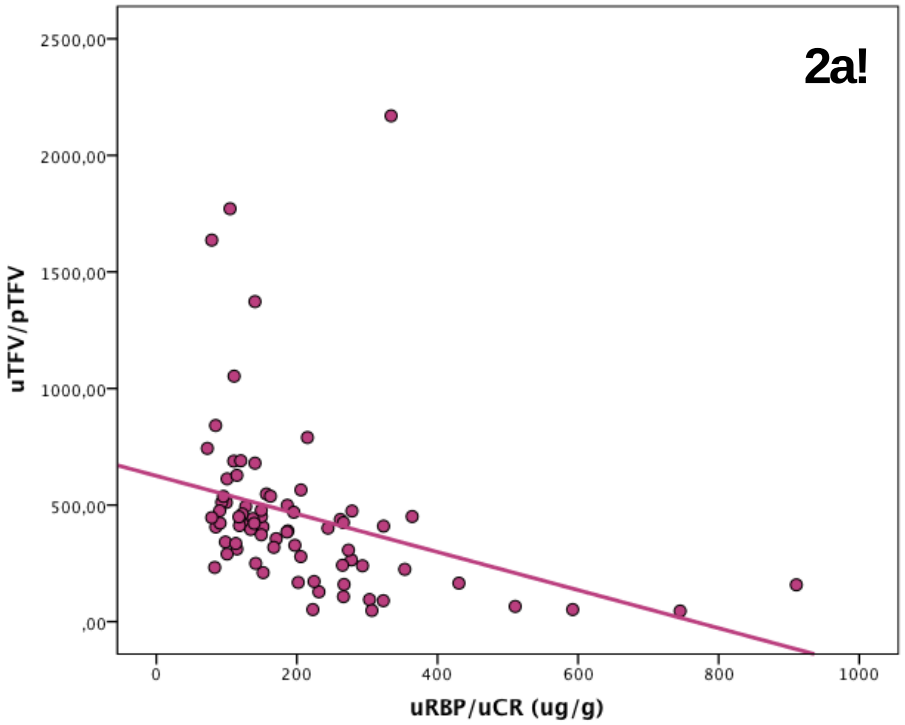
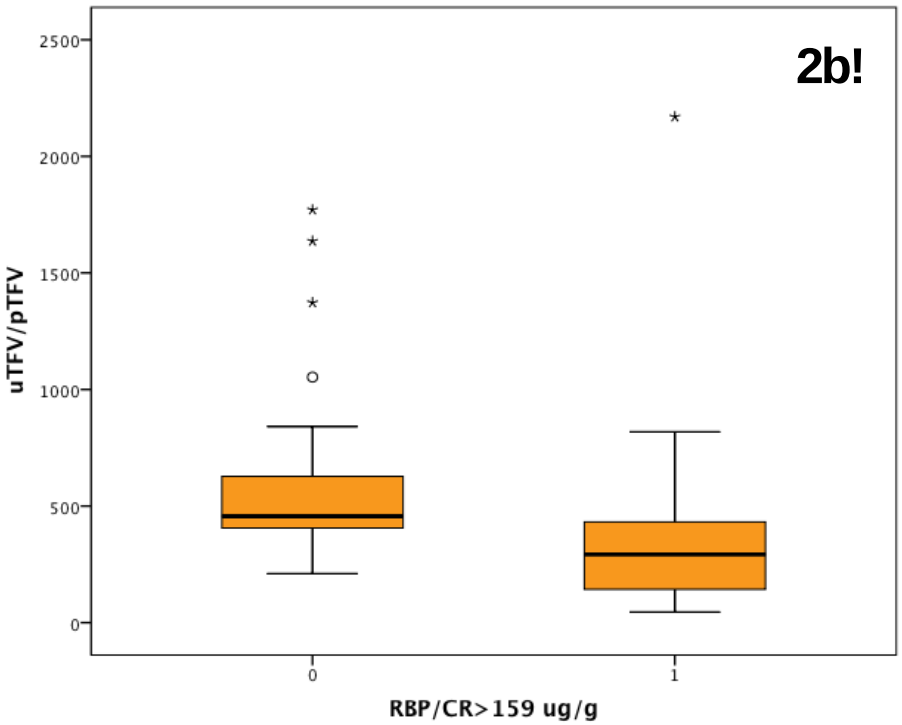
12-hour urinary levels!

uRBP (mg/dL)!	**0.18** (0.13-0.20)!	**uRBP >0.10!**	134 **(78.8%)!**
uRBP/uCr (ug/g)!	**170** (114-266)!	**uRBP/uCr >159!**	90 **(52.9%)!**

An inverse correlation was found between u/p TDF [c] and uRBP/uCr (rho = 0.513, p<0.001)

!





Tenofovir Urinary Output is Associated With Renal Tubular Dysfunction in HIV-positive Patients

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By ROC analysis a TFV urinary to plasma ratio below 300 was significantly associated with tubular impairment (Fig 3)!

!

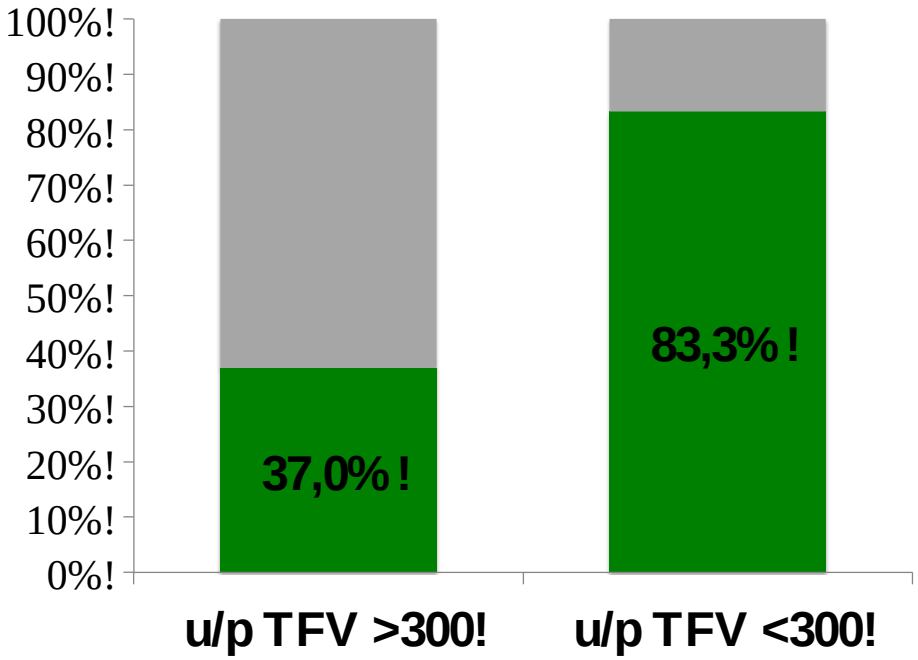

Figure 3: Prevalence of tubular impairment according to TFV urinary output (u/p ratio above or below 300)!

Tenofovir Urinary Output is Associated With Renal Tubular Dysfunction in HIV-positive Patients

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Variables associated with uRBP/uCr > 159 ug/g (tubular dysfunction)

	Univariate		Multivariate (adjusted for*)		
	p	**OR**	**p**	**aOR**	**95% CI**
Age (10 years)	0.136	-	-	-	-
Gender (female)*	**0.002**	**4.84**	**0.025**	**4.19**	**1.19 – 14.66**
BMI (per 5 Kg/m^2 increase)*	0.587	-	-	-	-
Ethnicity (Caucasian)*	0.312	-	-	-	-
HCV	0.509	-	-	-	-
Time on TDF (per year increase)*	0.207	-	-	-	-
PI use	0.110	-	-	-	-
P[TDF] (per 20 ng/mL increase)*	0.565	-	-	-	-
u[TDF] (per 1000 ng/mL increase)*					
u[TDF] / p[TDF] < 300	**<0.001**	**11.04**	**<0.001**	**11.87**	**3.43-41.12**

Tenofovir Urinary Output is Associated With Renal Tubular Dysfunction in HIV-positive Patients

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- The majority of long-term TDF recipients (all with CrCl ≥60 mL/min) were found to have abnormal uRBP/uCr ratios, a marker of tubular dysfunction.

- The concentration of urinary TDF was found to be inversely correlated with uRBP/uCr values , thus suggesting that TDF tends to impair the functional capacity of proximal renal tubule, which accounts for a third of TDF cumulative renal clearance

- An ongoing prospective study in treatment-naïve patients will try to assess the parallel chronology of reduction in TDF urinary clearance and decreasing tubular function ("which is the horse and which is the cart")

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