17th Residential Course on Clinical Pharmacology of Antiretrovirals

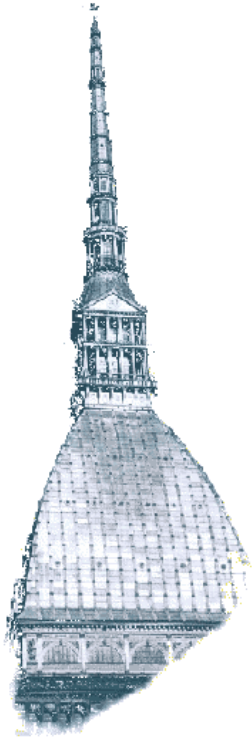
January 19-21, 2022

SESSION II: ART: EVOLUTION OF THE BACKBONE

Is TAF always better ?

Gianni Di Perri

Clinica di Malattie Infettive
Università degli Studi di Torino
Ospedale Amedeo di Savoia



Ospedale Amedeo di Savoia

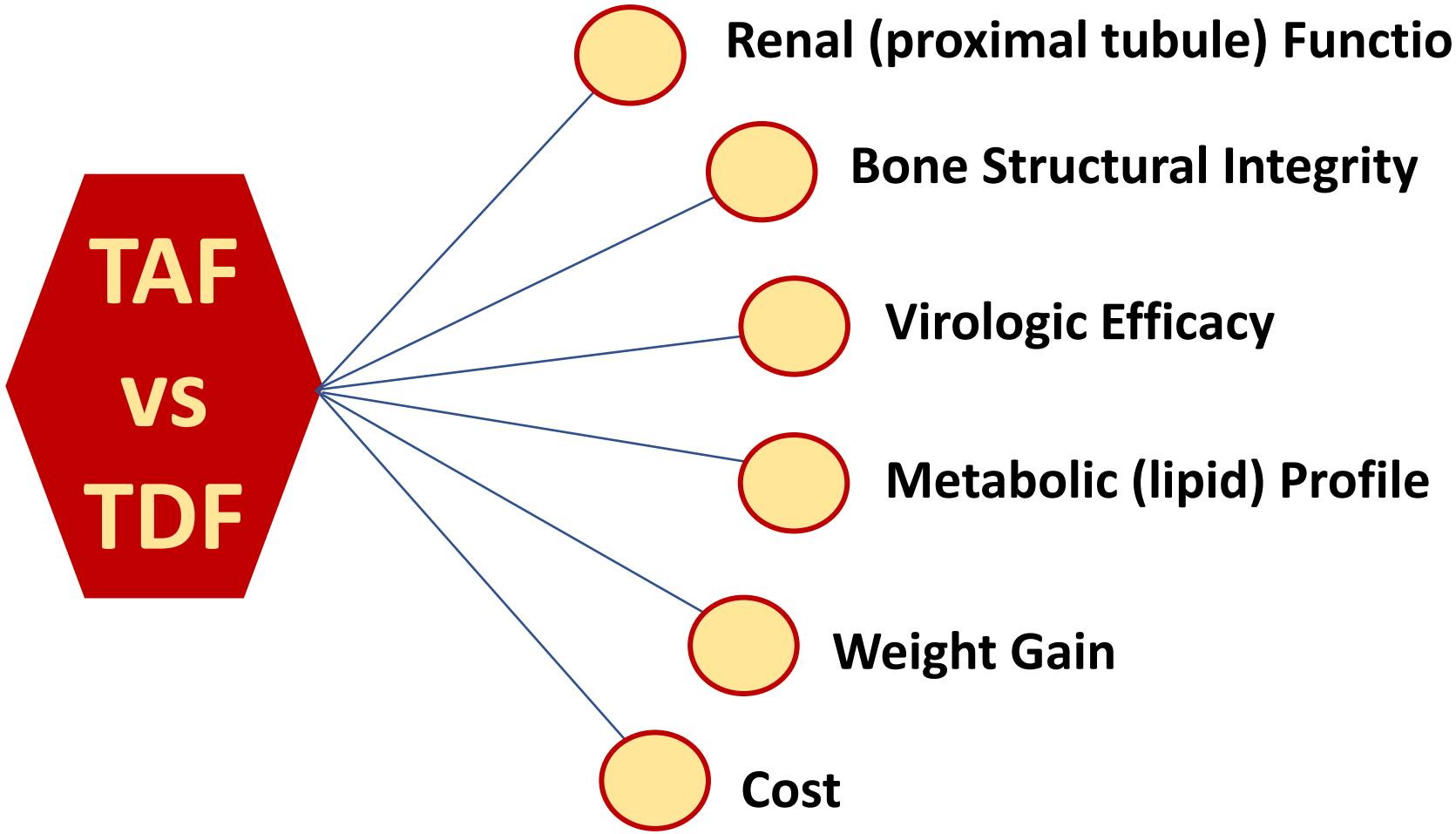
Financial Disclosures

Speaker fees, consultancies, research grants from:

- Abbvie
- BMS
- GS
- MSD
- Janssen
- ViiV
- Pfizer
- Novartis
- Astellas
- Basilea
- Zambon
- Correvio
- Angelini

At present *Tenofovir* (TFV) pro-drugs position is that of the third component of , conventional triple drug regimens, whose main alternatives are dual regimens

Two pro-drugs are available and the main issues concerning the TAF vs TDF comparison are:



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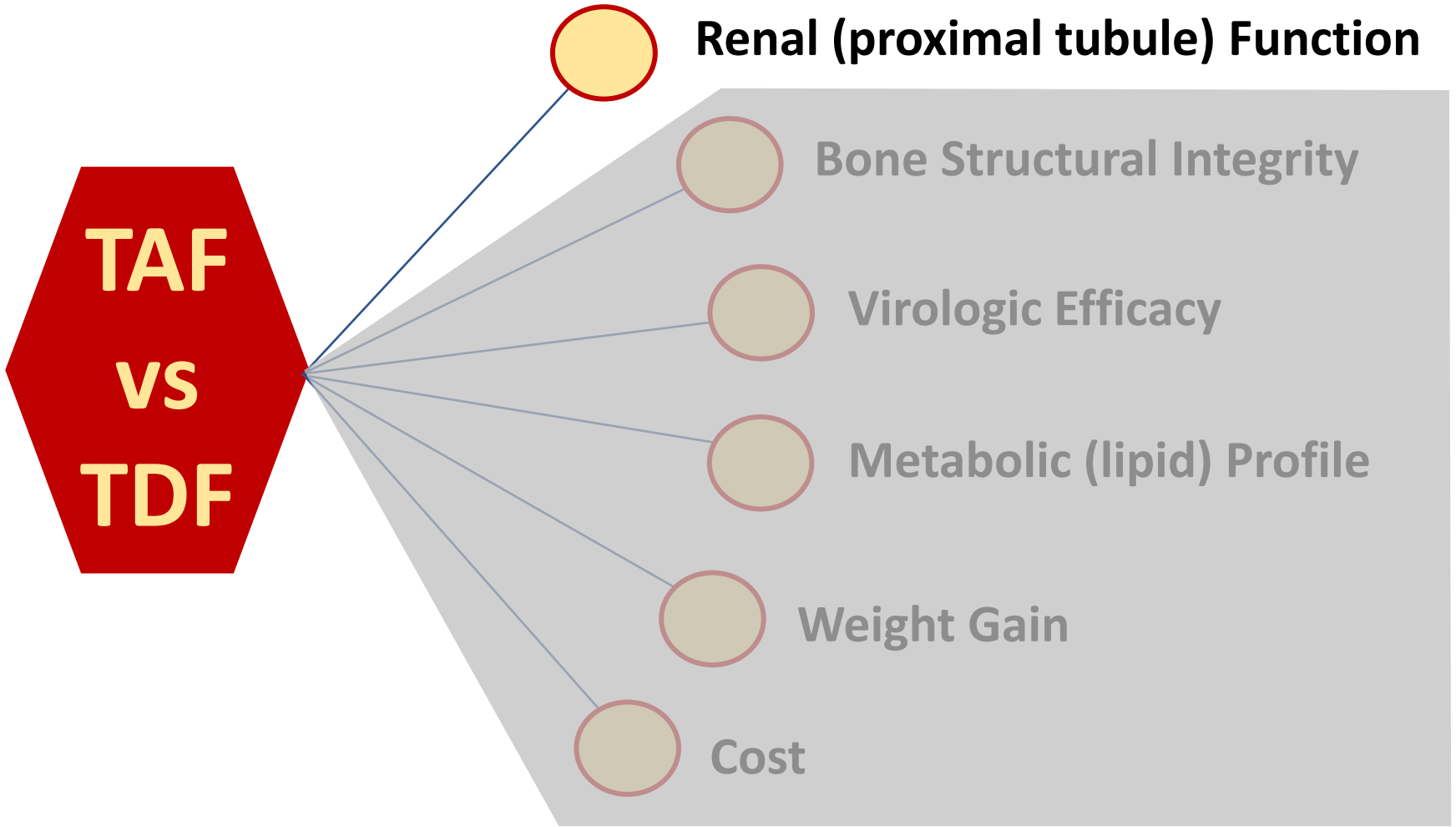
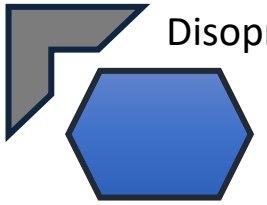
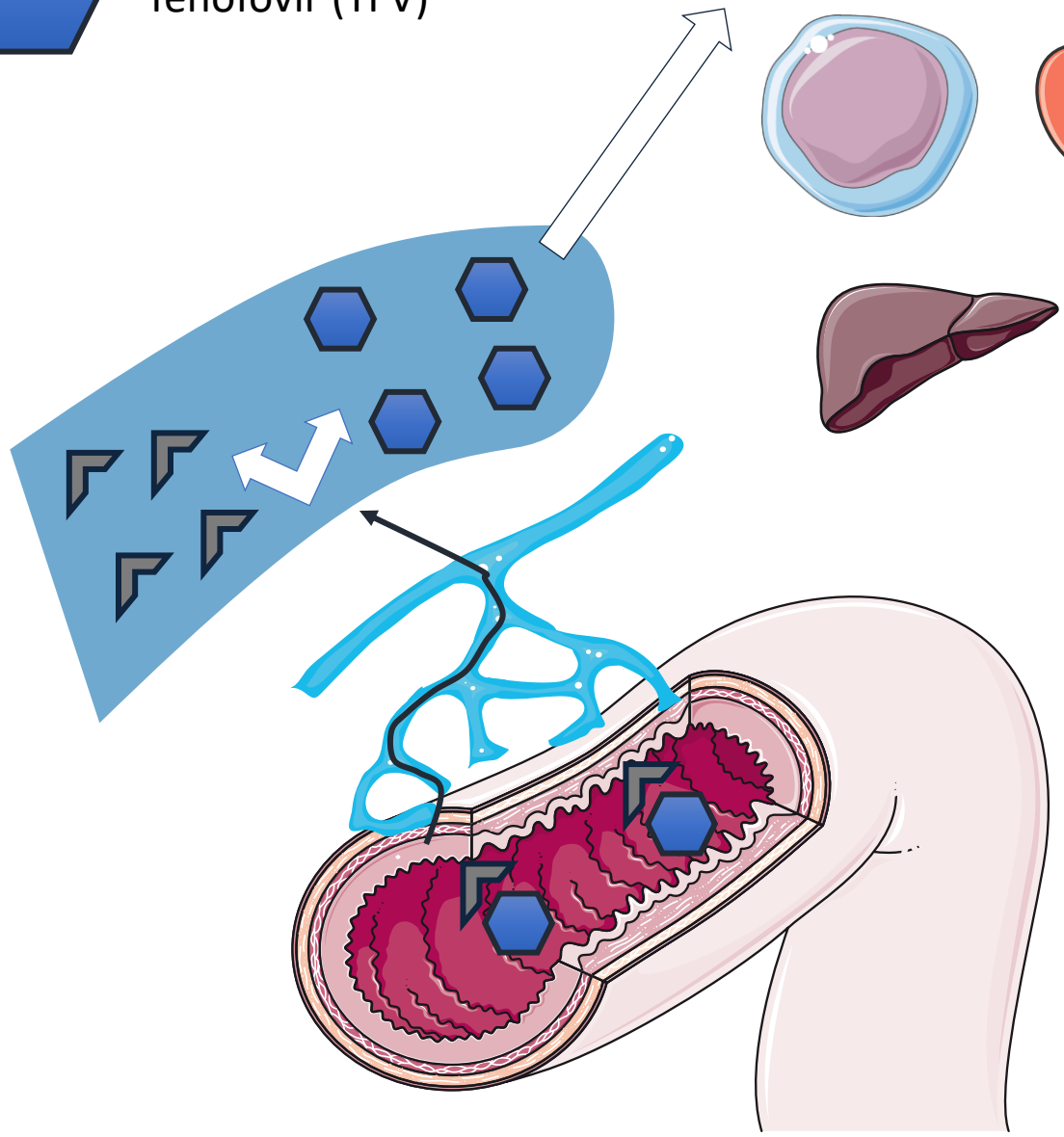


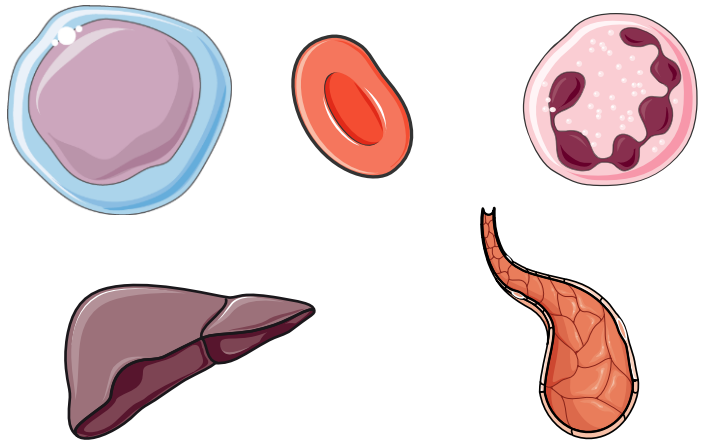


Disoproxil fumarate salt

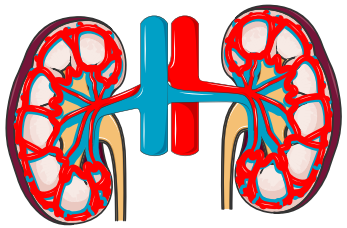
Tenofovir (TFV)

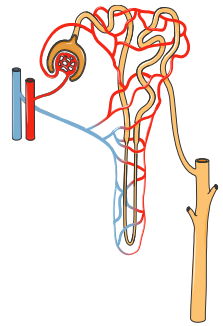
Wide spectrum of human cells

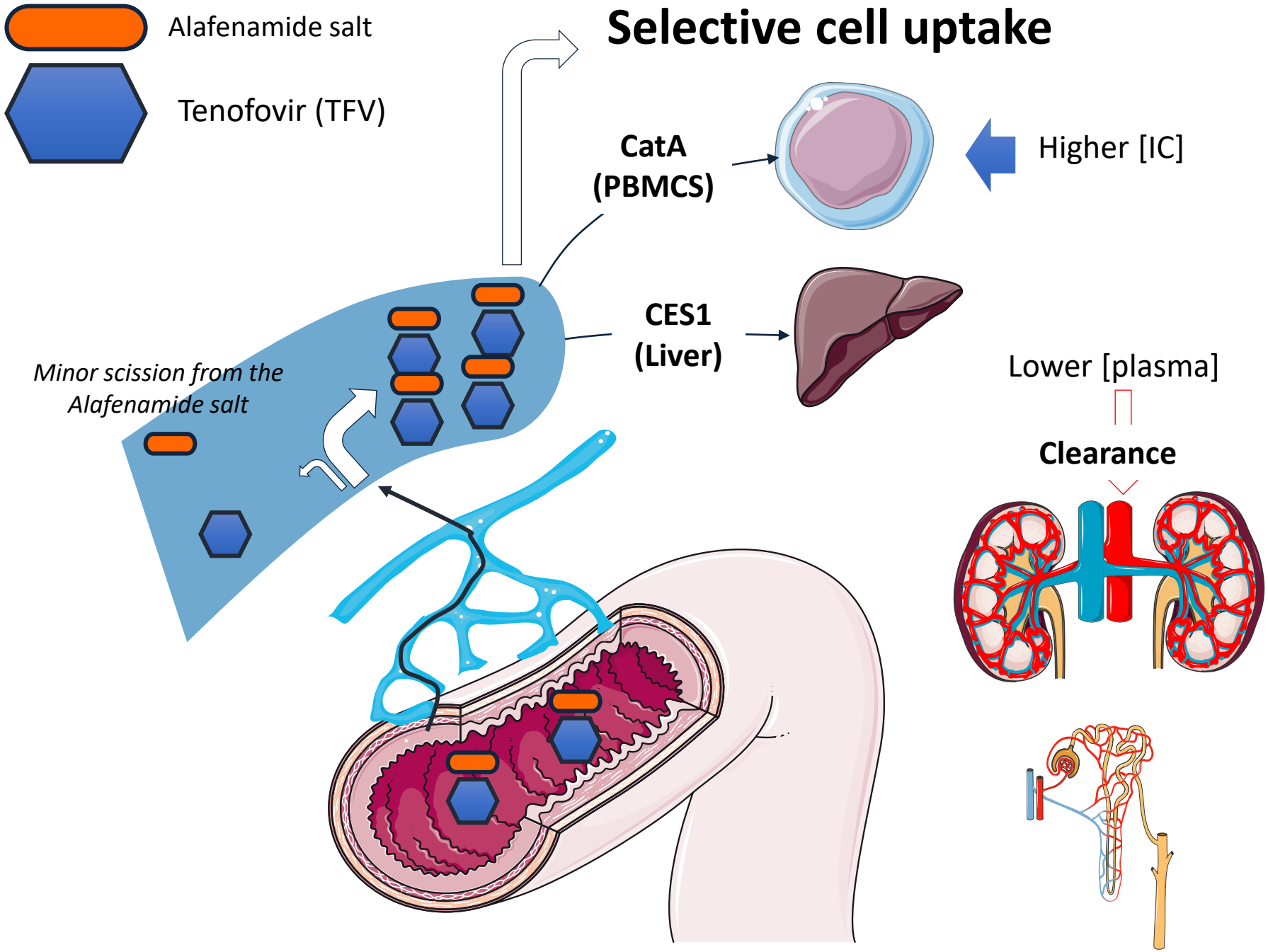




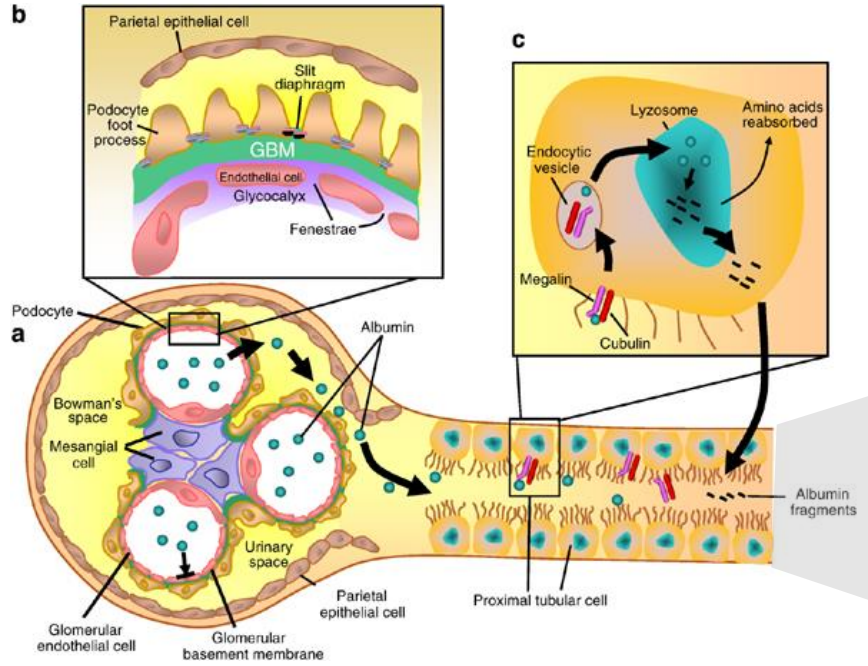
Clearance

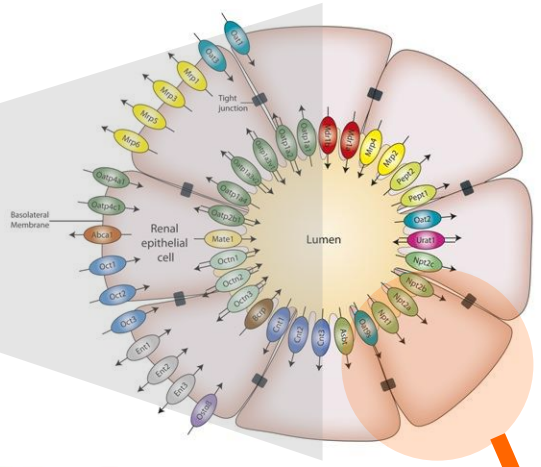


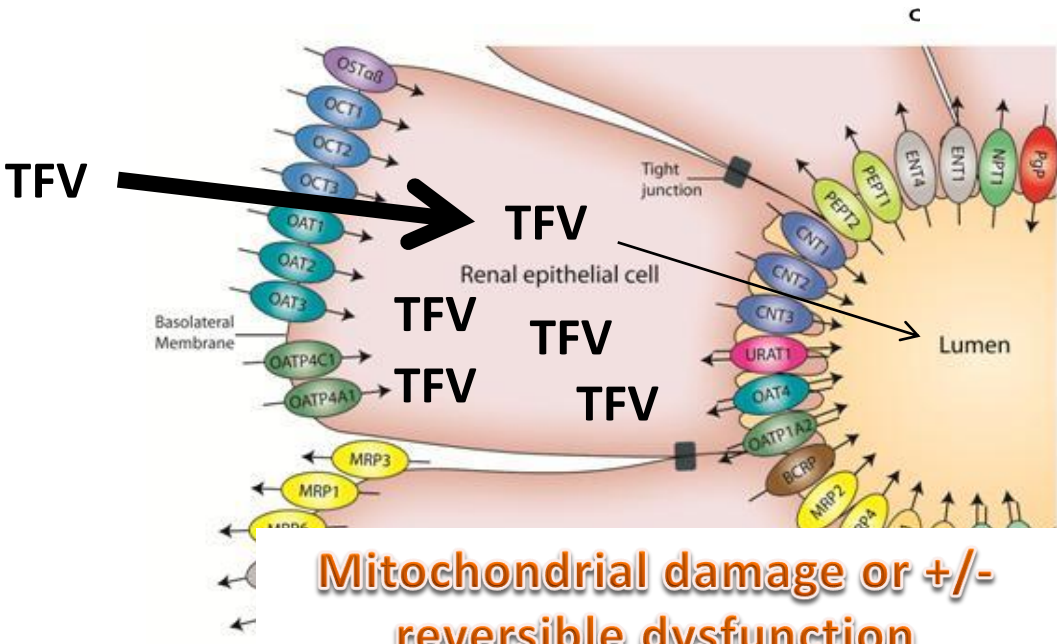



Alafenamide salt
Tenofovir (TFV)
Selective cell uptake
CatA
(PBMCS)
Higher [IC]
CES1
(Liver)
Minor scission from the
Alafenamide salt
Lower [plasma]
Clearance

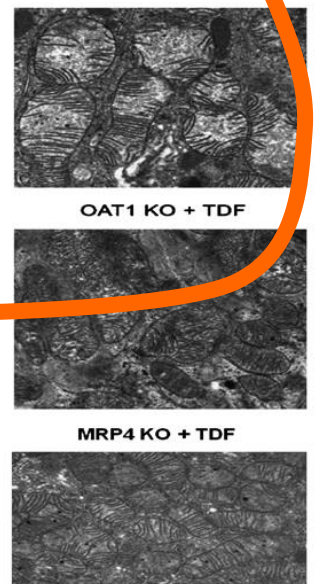
Renal accumulation of TFV and the resulting effects on the function of the proximal tubule are caused by **highly efficient uptake** from plasma and **less rapid efflux** into urine.







Mitochondrial damage or +/- reversible dysfunction



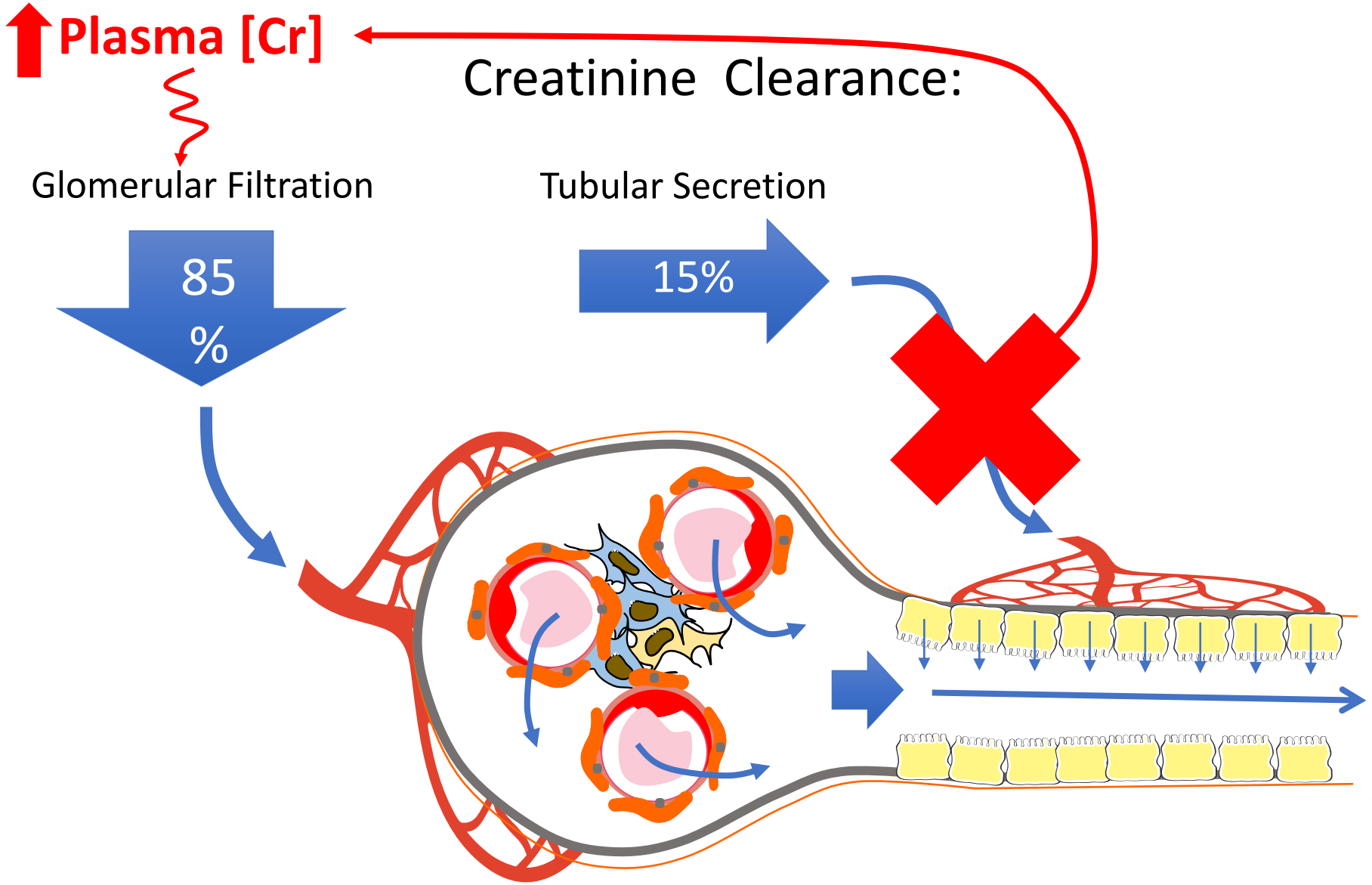
Tenofovir disoproxil fumarate-associated renal tubular dysfunction: noninvasive assessment of mitochondrial injury

Ryan Samuels, et al. AIDS 2017, 31:1297–1301

The mtDNA 'common deletion' mutation was detectable significantly more commonly in the urine of TDF exposed study participants compared with unexposed (13/22 TDF$_þ$ study participants **(59%),** 4/21 TDF$_⍰$ **(19%),** P 1⁄4 0.01).

The presence of mtDNA mutations in the context of TDF exposure adds weight to the hypothesis that *TDF-associated renal damage is at least in part mitochondrially mediated*.

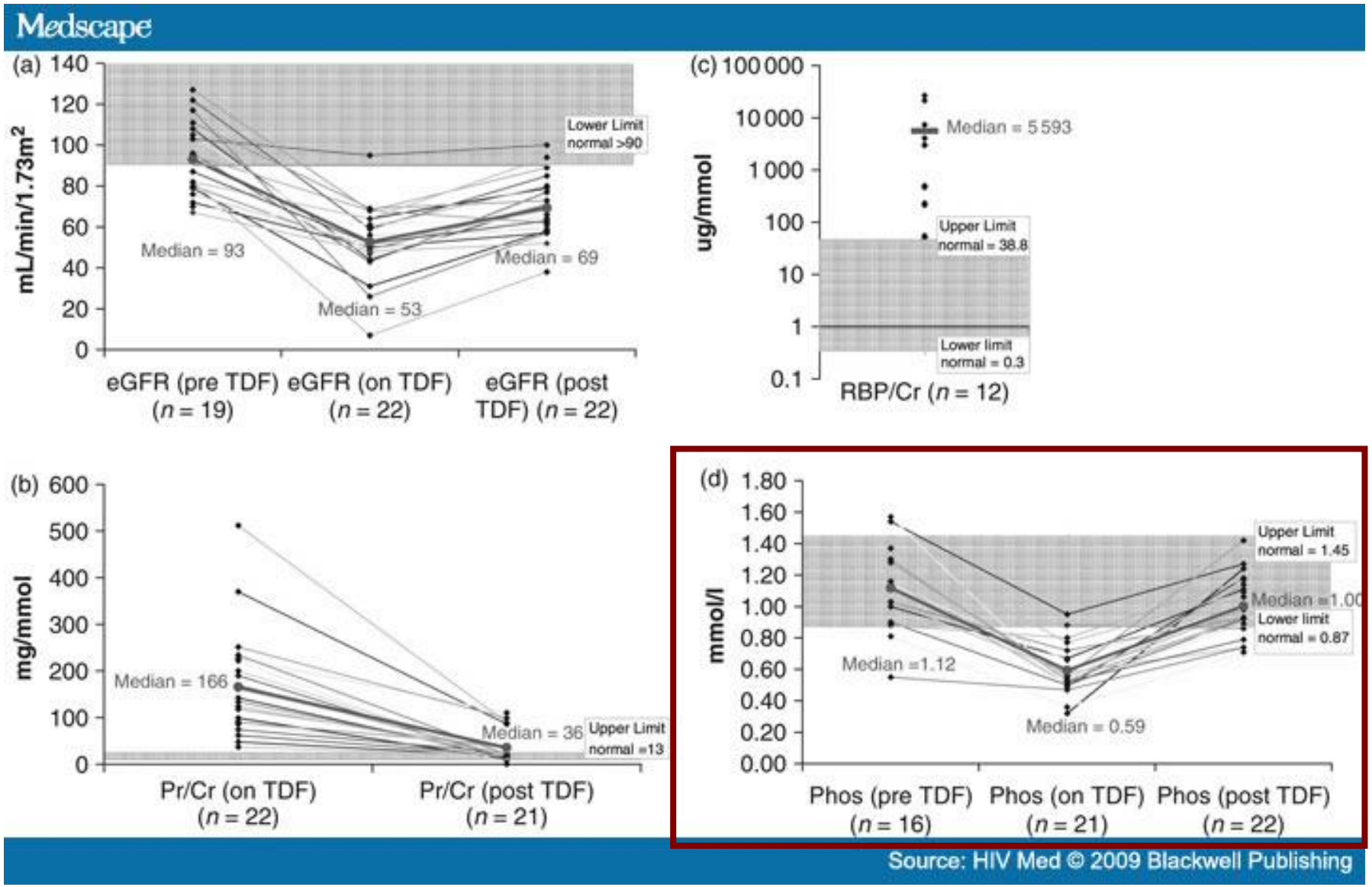
Stray, K.M., et al..AAC 2013; 57; 4982-4989.



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

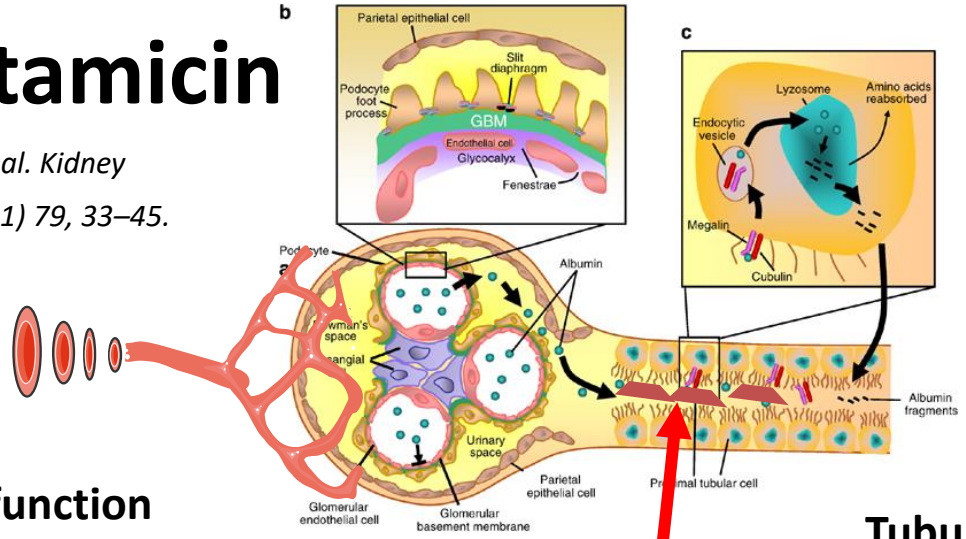
Tenofovir-associated Renal and Bone Toxicity

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.*



Gentamicin

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



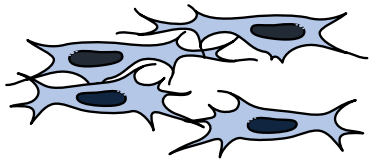
Tubular dysfunction
(decreased reabsorption of low-molecular weight proteins, calcium phosphates, electrolytes)

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

Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials

Samir K. Gupta, et al. AIDS 2019, 33:1455–1465

Our integrated analysis included 9322 adults and children with HIV (n1⁄46360 TAF, n 1⁄4 2962 TDF) with exposure of 12 519 person-years to TAF and 5947 to TDF.

Table 1. Baseline demographic and clinical characteristics.

Characteristic		TAF, $N=6360$	TDF, $N=2962$	Total, $N=9322$
Age (years)		41 (7, 80)	42 (18, 79)	42 (7, 80)
Sex	Male	4966 (78%)	2436 (82%)	7402 (79%)
	Female	1394 (22%)	526 (18%)	1920 (21%)
Race	White	3796 (60%)	1884 (64%)	5680 (61%)
	Black	1799 (28%)	739 (25%)	2538 (27%)
	Asian	373 (6%)	181 (6%)	554 (6%)
	Other	376 (6%)	153 (5%)	529 (6%)
	Declined to respond	16 (<1%)	5 (<1%)	21 (<1%)
Ethnicity	Hispanic or Latino	1188 (19%)	537 (18%)	1725 (19%)
Treatment status	Naive	2191 (34%)	975 (33%)	3166 (34%)
	Experienced	4169 (66%)	1987 (67%)	6156 (66%)
CrCl (ml/min)		108.8 (91.2, 129.6)	107.7 (90.9, 128.4)	108.6 (91.1, 129.3)

Data are median (IQR) or *n* (%), except for age, which is median (range). CrCl, creatinine clearance; IQR, interquartile range; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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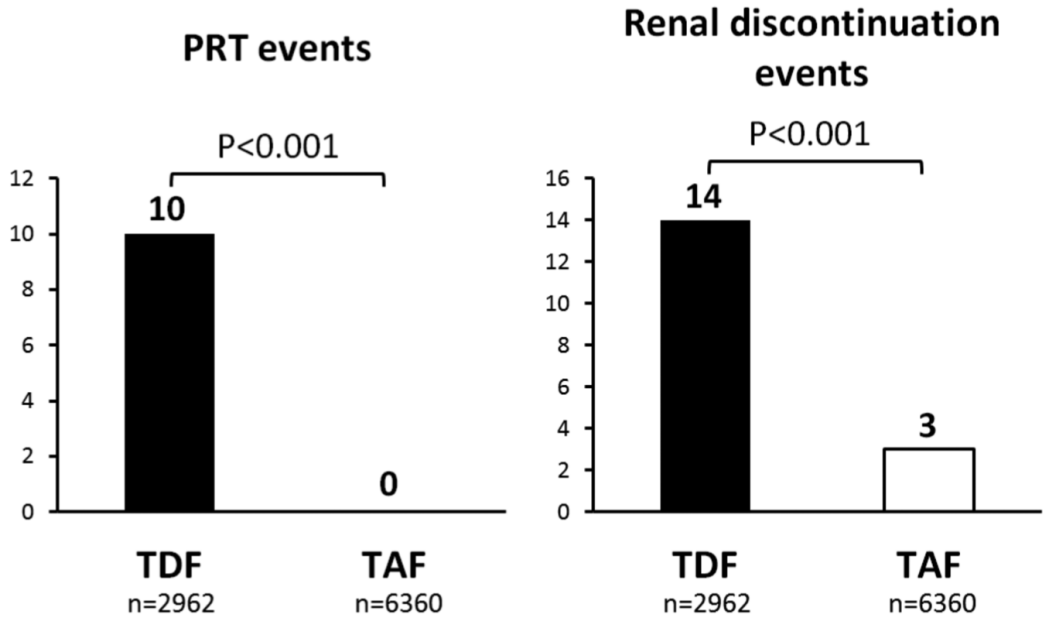

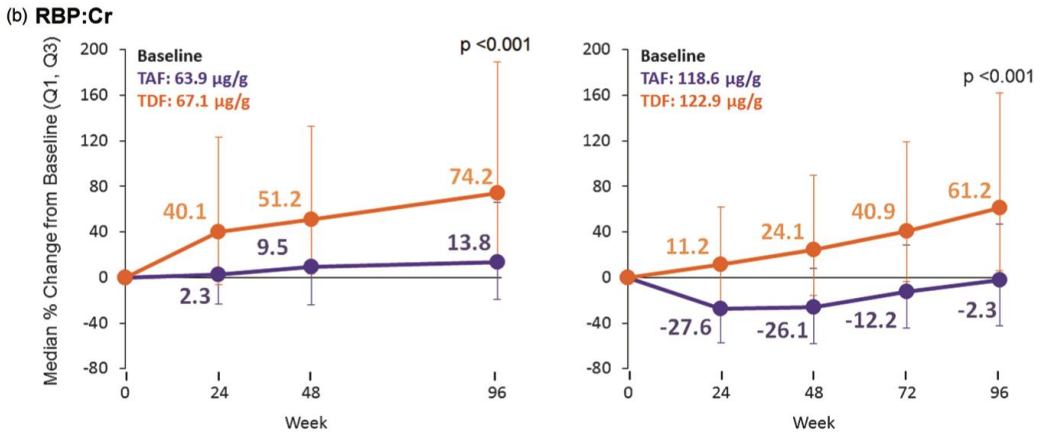

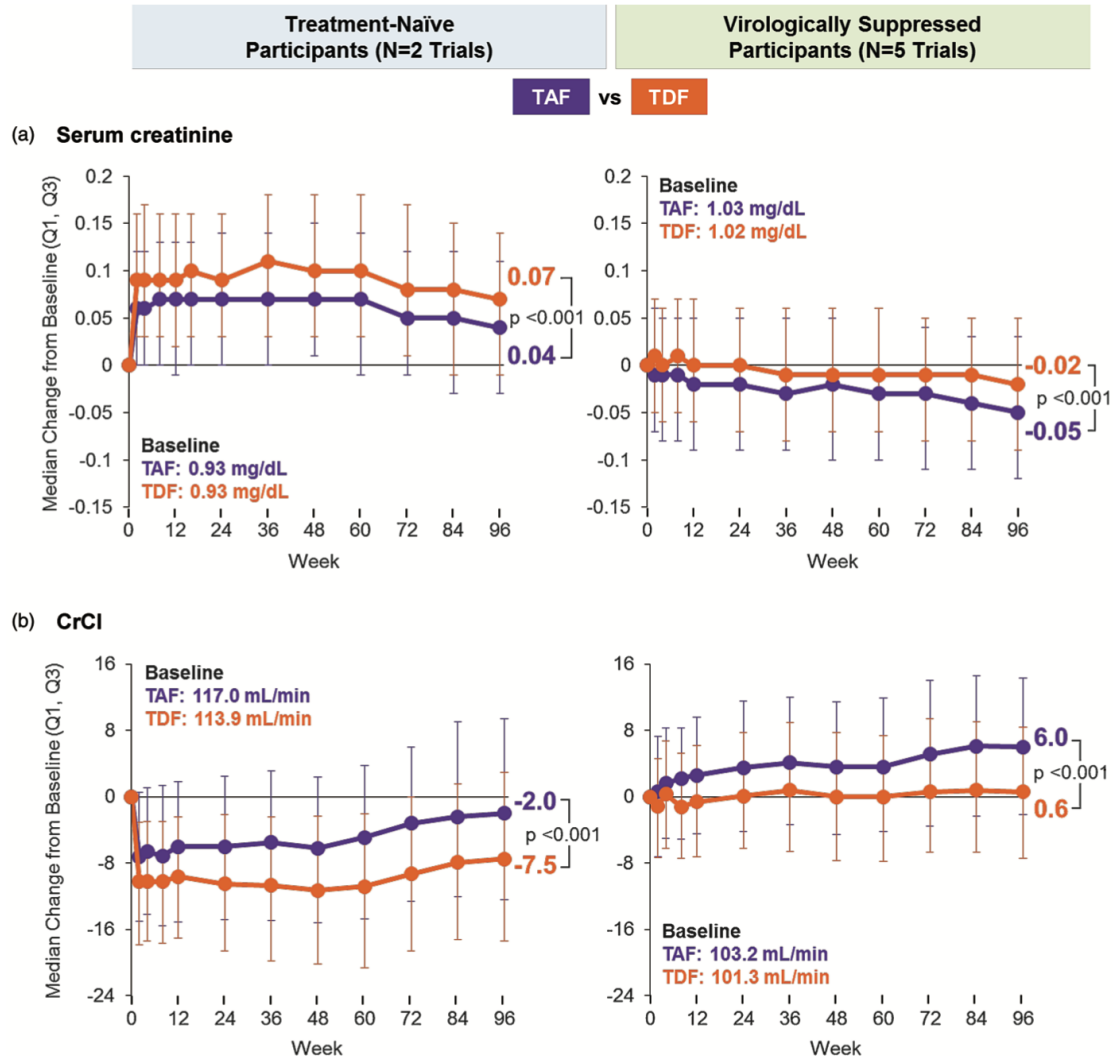

TDF intake:
52.4 months (24 – 87.1)

289 patients

eCrCl:
89.4 mL/min (78.6 – 105.9)

NNRTIs : 155 (53.6%)
PIs : 118 (40.8%)
INSTIs : 16 (5.5%)

Median age: 45.8 years (39.5 – 51.8)
Men: 207 (71.6%)
Caucasian: 246 (85.4%)
Median CD4+ T - cells: 547/uL (417 – 699)
HIV < 50 c./mL: 271 (93.8%)

Calcagno A, et al. AIDS 2016; 30: 915-919

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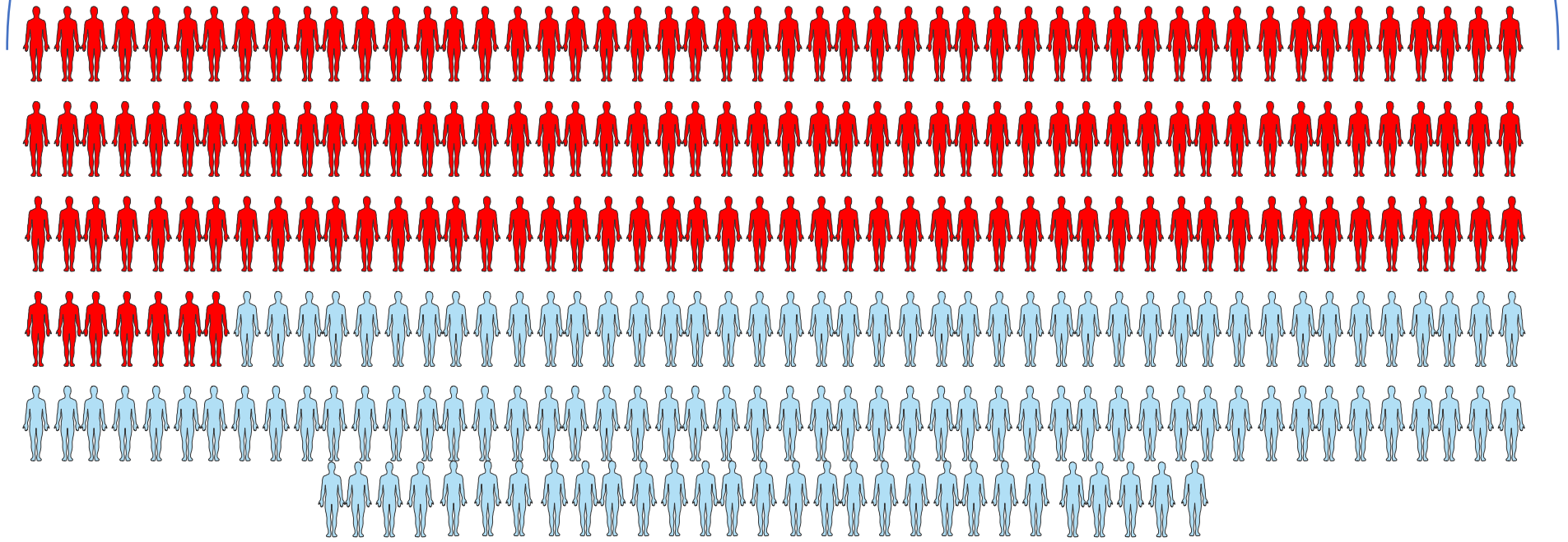
89.4 mL/min (78.6 – 105.9)



Abnormally high uRBP/uCr was found in 157 patients (54.3%)

Tubular dysfunction was proportionally associated to reduced TFV urinary clearance

Calcagno A, et al. AIDS 2016; 30: 915-919

AIDS

Kidney Disease and HIV Volume **25** Issue **1** February/March **2017**

Perspective

by Wyatt CM

Kidney Disease and HIV Infection

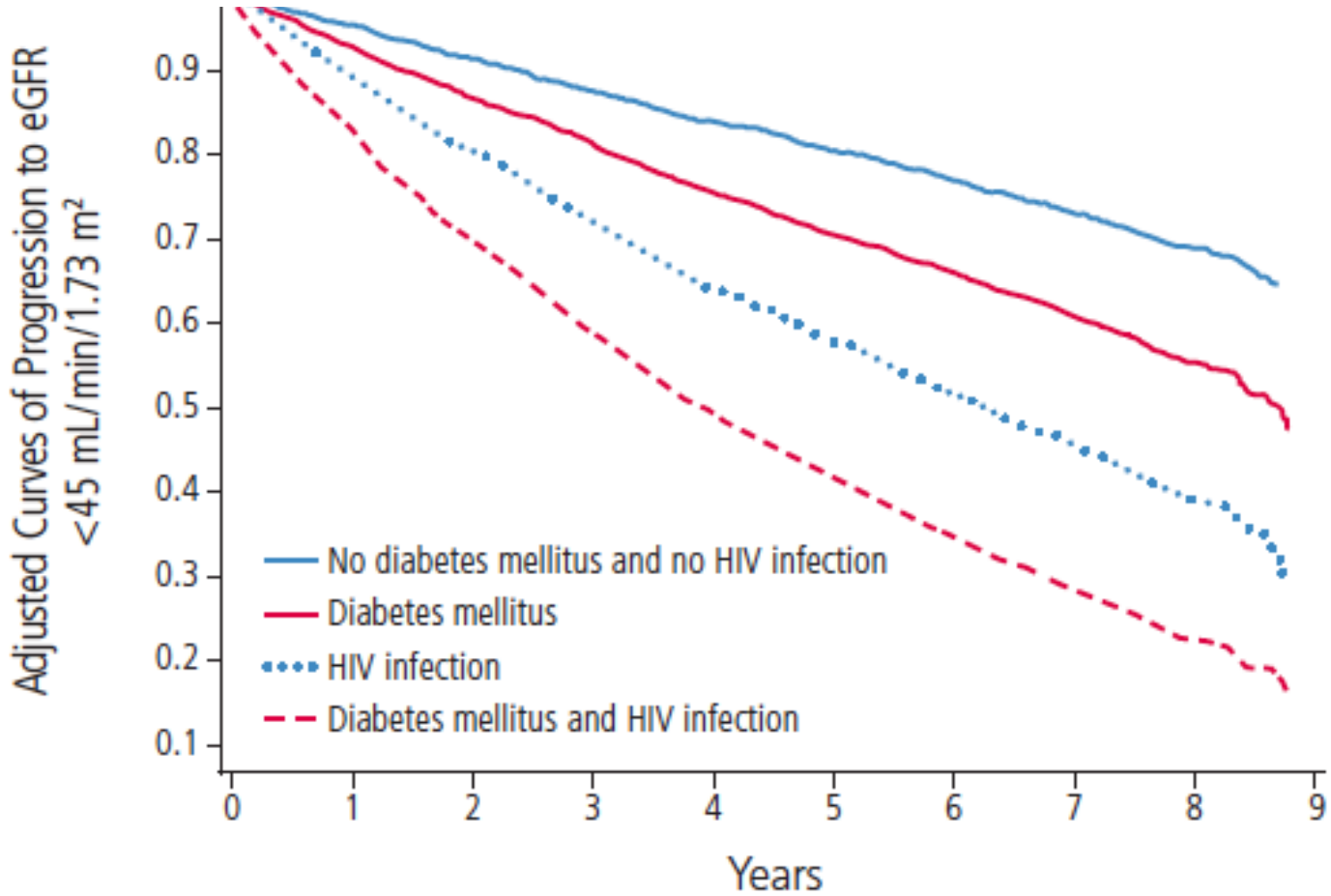


Figure 2. Additive effect of HIV infection and diabetes on progression of chronic kidney disease. Adapted from Medapalli et al.[9]

Lancet 2013; 382: 339–52

Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention

Ron T Gansevoort, Ricardo Correa-Rotter, Brenda R Hemmelgarn, Tazeen H Jafar, Hiddo J Lambers Heerspink, Johannes F Mann, Kunihiro Matsushita, Chi Pang Wen

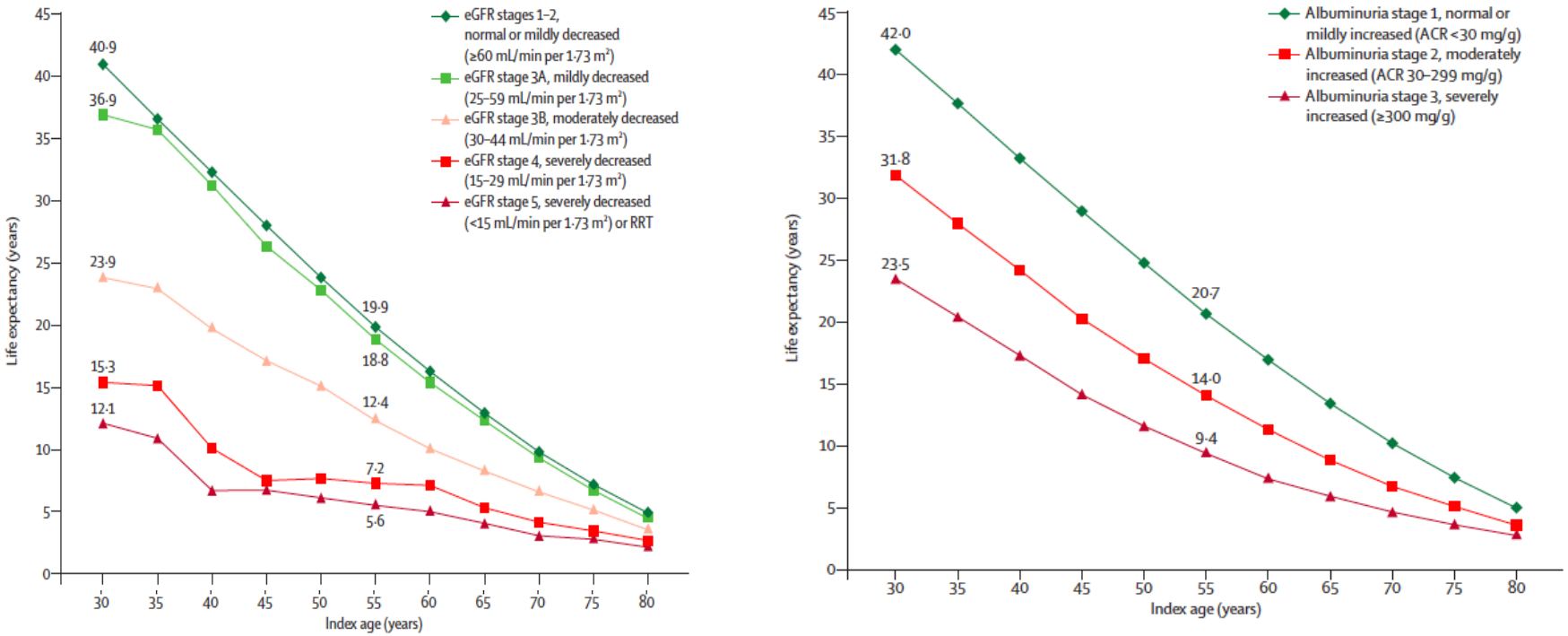


Figure 2: **Life expectancy, according to chronic kidney disease stages (Canadian data)**
(A) eGFR stages and (B) albuminuria stages. Data are adjusted per eGFR and albuminuria stage for sex to the WHO world average in 2000–05. eGFR=estimated glomerular filtration rate. RRT=renal replacement therapy. Based on data in references 24 and 25 (appendix pp 1–2).

Global Kidney Disease 5

Lancet 2013; 382: 339–52

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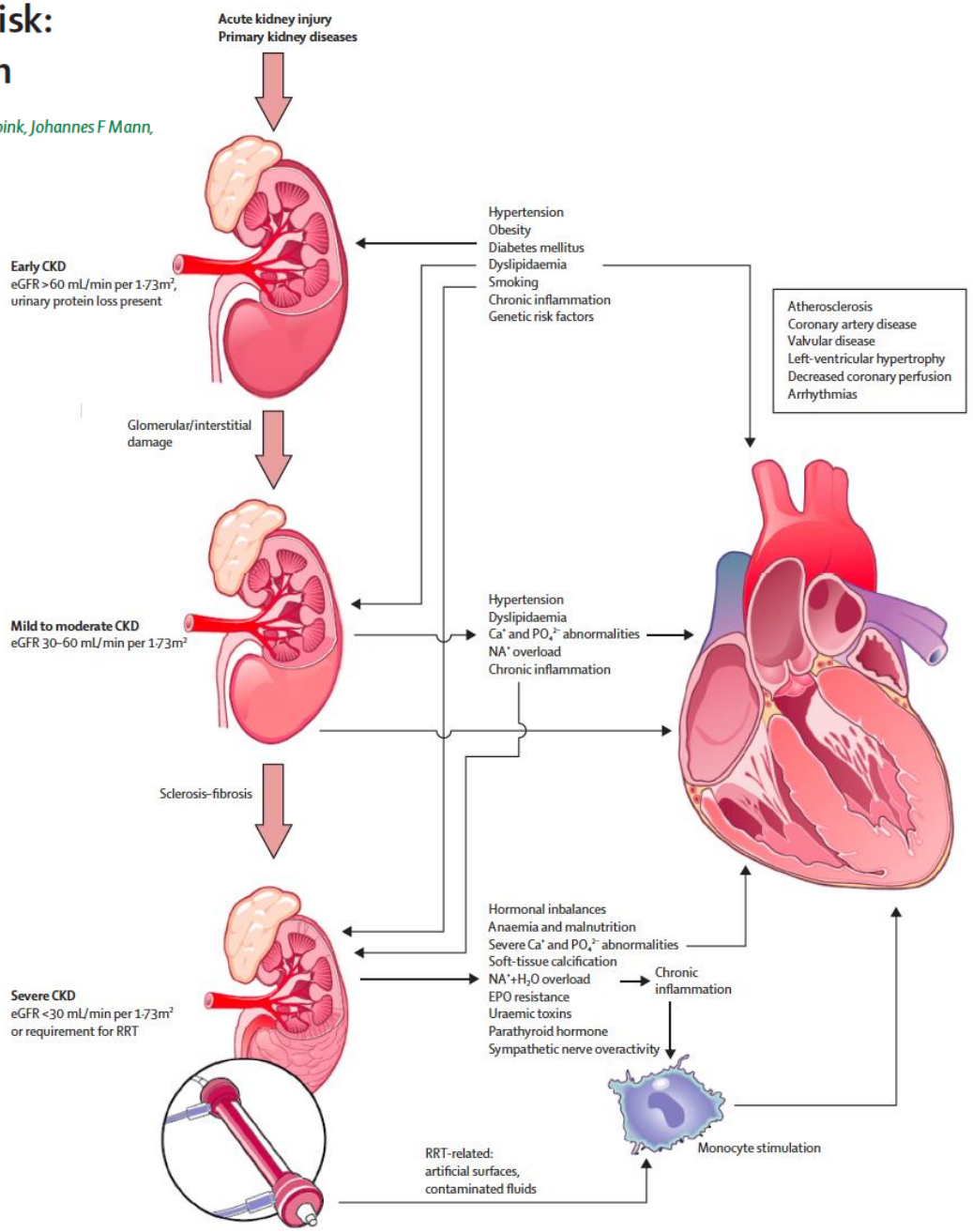
Ron T Gansevoort, Ricardo Correa-Rotter, Brenda R Hemmelgarn, Tazeen H Jafar, Hiddo J Lambers Heerspink, Johannes F Mann, Kunihiro Matsushita, Chi Pang Wen

Pathophysiological interactions between kidney and heart in chronic kidney disease.

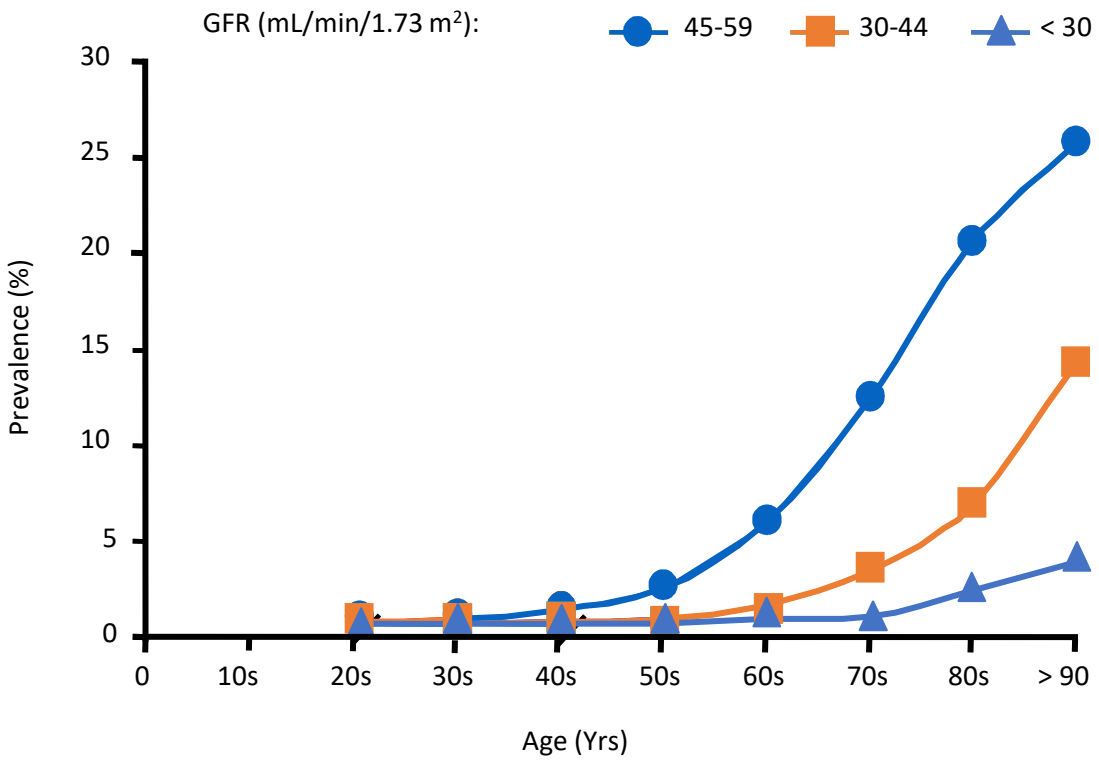
CKD contributes to decreased cardiac function, cardiac hypertrophy and increased risk of cardiovascular adverse events.

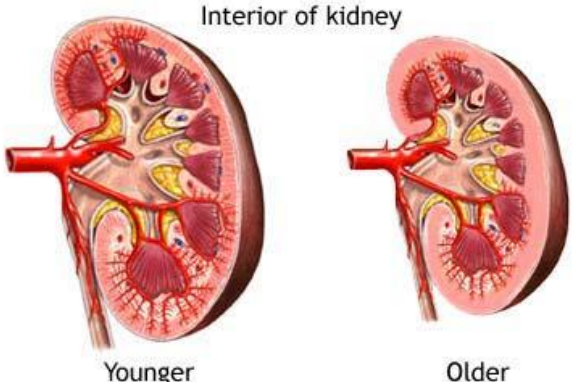
eGFR = estimated glomerular filtration rate
CKD = chronic kidney disease
RRT = renal replacement therapy



RENAL CHANGES ASSOCIATED WITH AGING

Age is a critical variable in the Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) which are used for estimating GFR for drug dosing





Decreased GFR

- kidney mass
- nephron size
- nephron number
- glomerular surface area
- tubular function
- renal blood flow

Hallan SI, et al. Br Med J. 2006; 333:1047.

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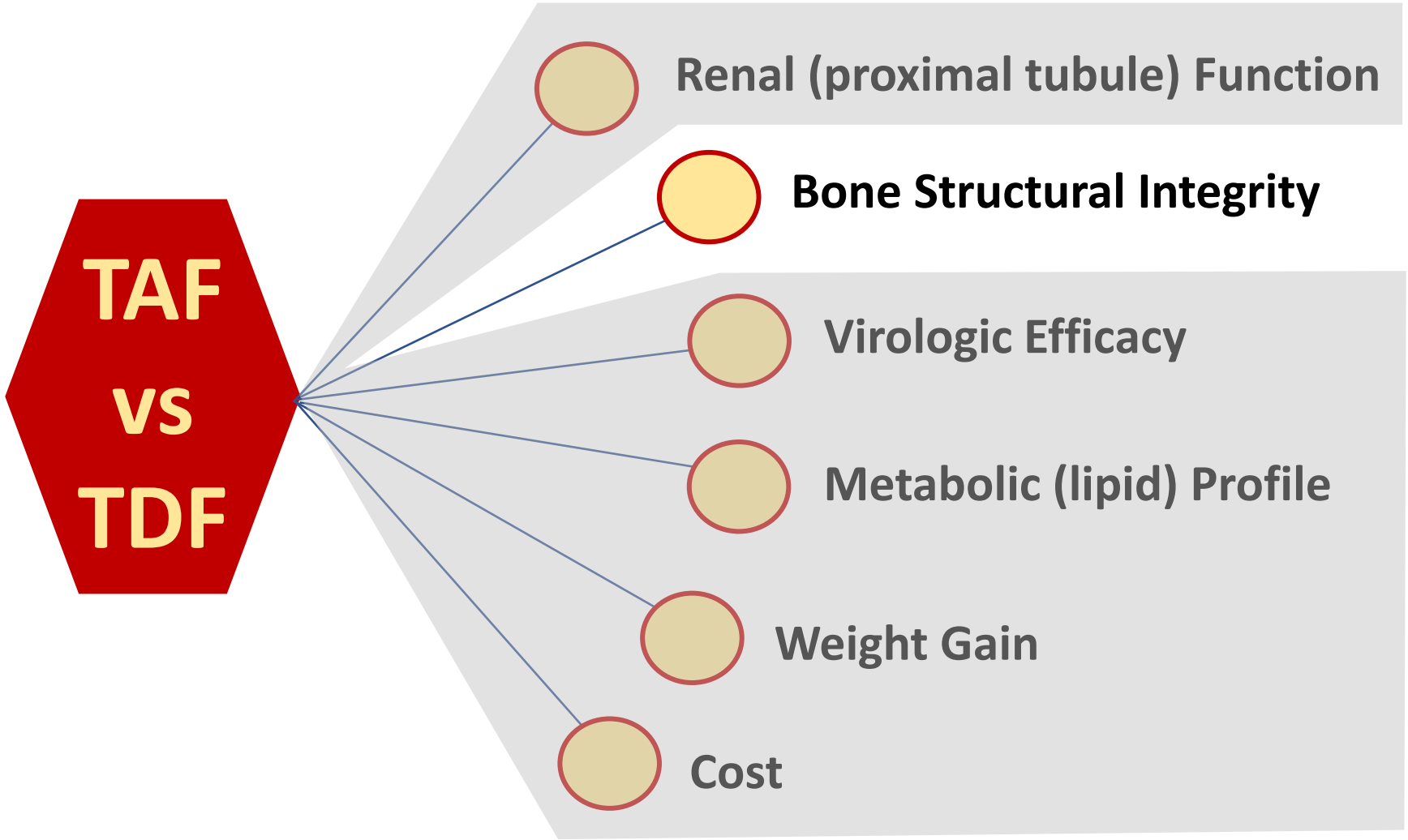
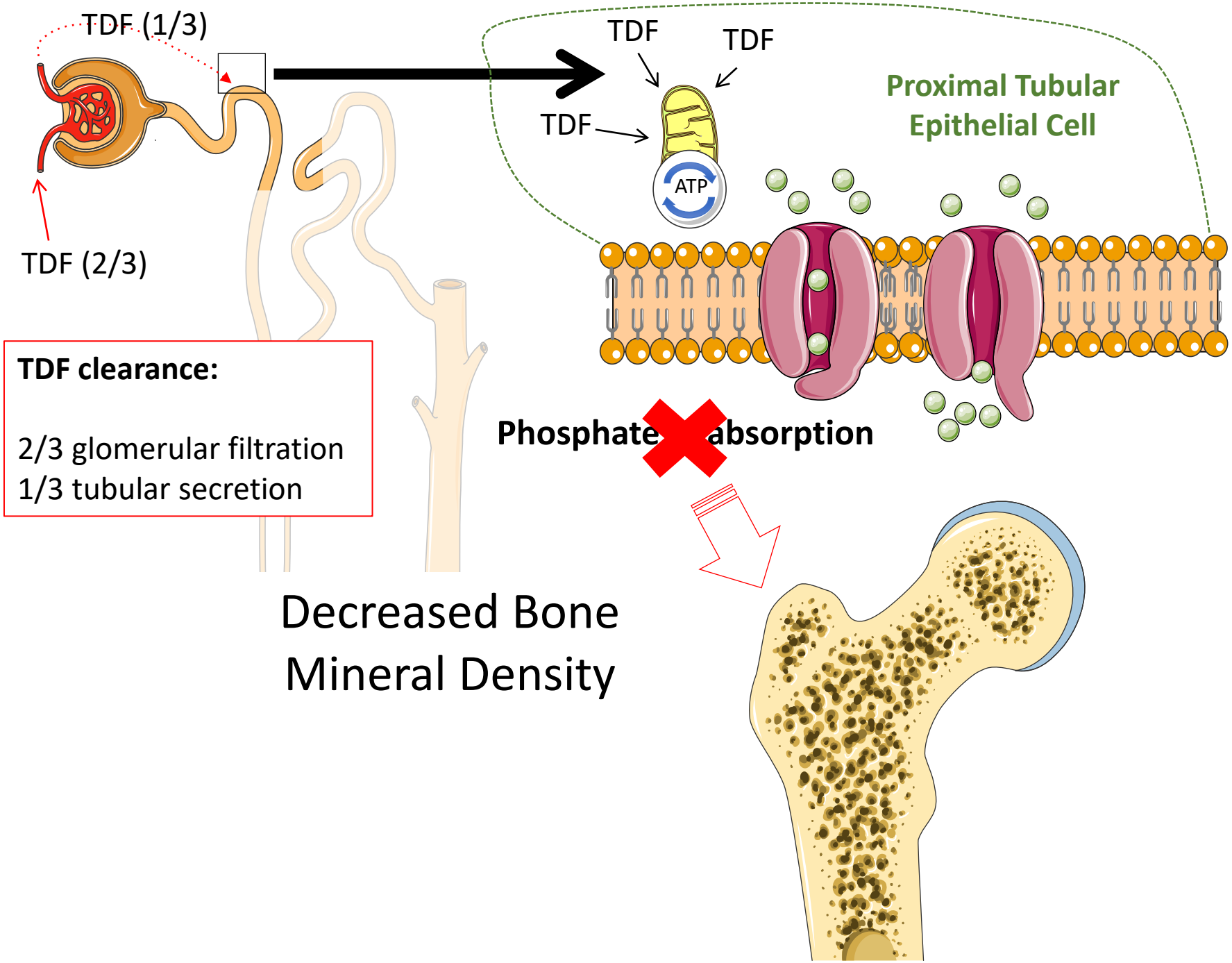




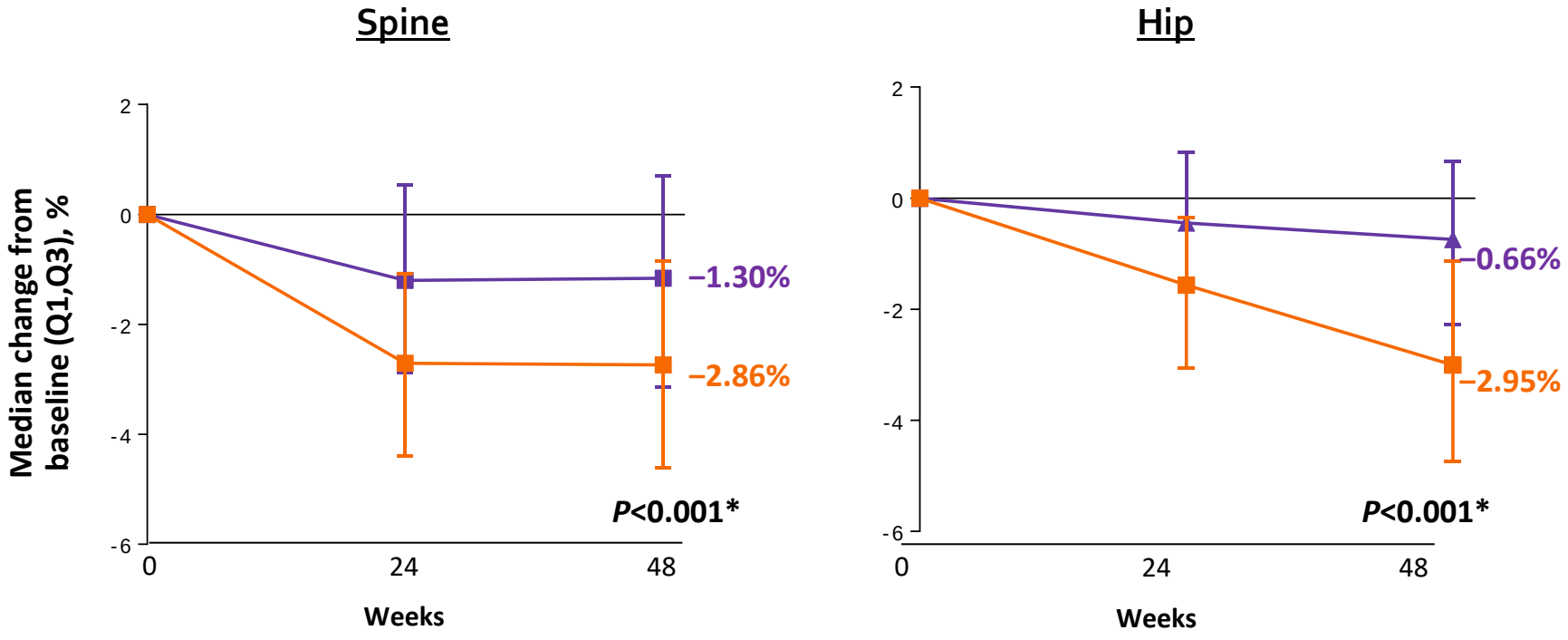
TDF clearance:

2/3 glomerular filtration
1/3 tubular secretion

Decreased Bone Mineral Density

Studies 104 and 111: ART-naive patients, Week 48 combined analysis

Changes in spine and hip BMD through Week 48



E/C/F/TAF	n=845	797	784	836	789	780
E/C/F/TDF	n=850	816	773	848	815	767

*Comparison of E/C/F/TAF vs E/C/F/TDF at Week 48

Significantly less decreases in spine and hip BMD in the E/C/F/TAF group at Week 48

BMD = bone mineral density

Sax P et al. Lancet. 2015 Jun 27;385(9987):2606–15

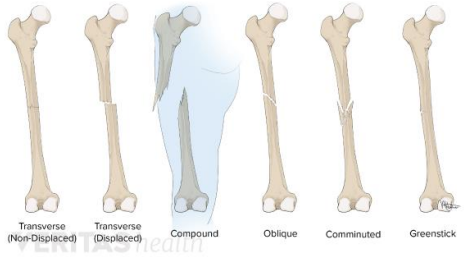
Antiretrovirals, Fractures, and Osteonecrosis in a Large International HIV Cohort

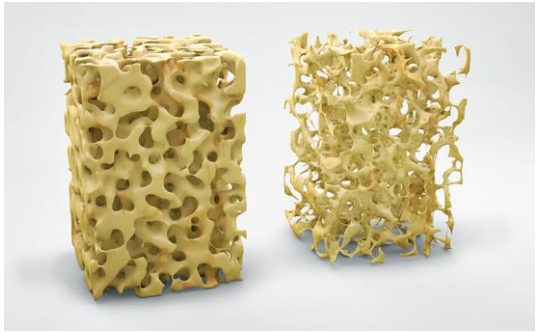
Clinical Infectious Diseases

MAJOR ARTICLE

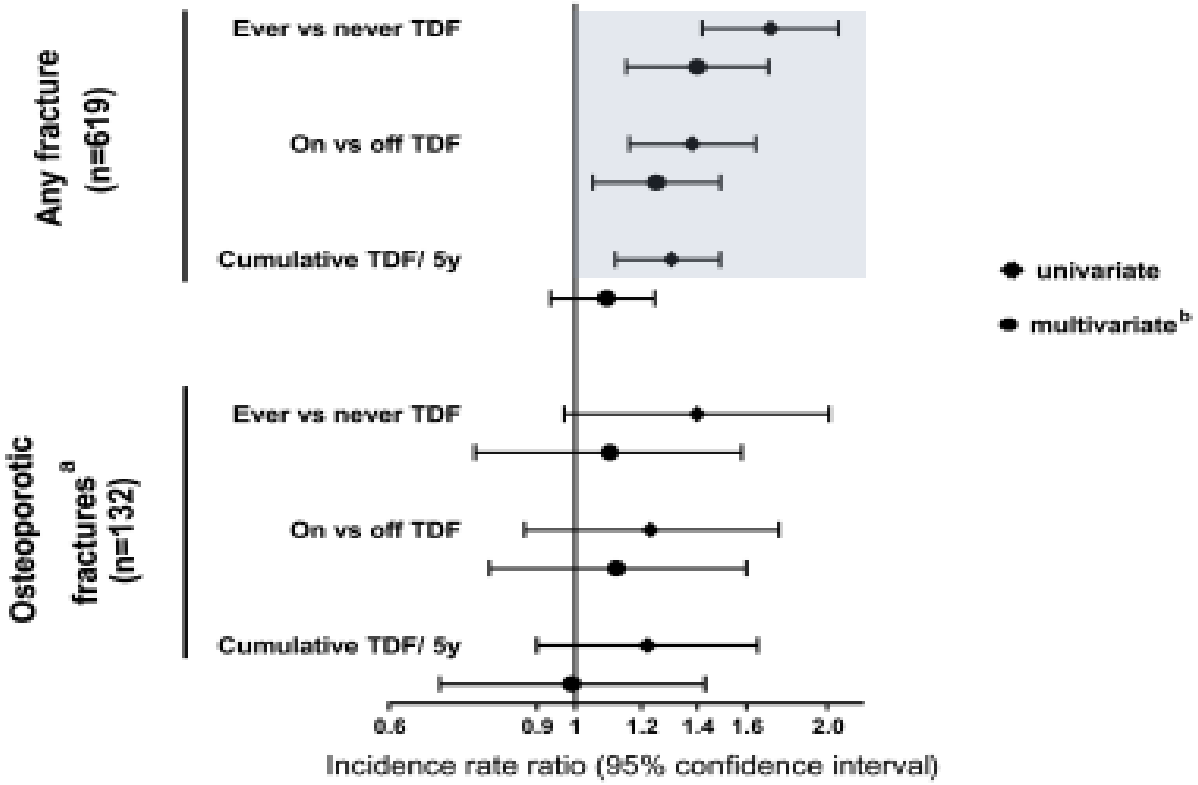
Álvaro H. Borges,[1,2] Jennifer Hoy,[3] Eric Florence,[4] Dalibor Sedlacek,[5] Hans-Jürgen Stellbrink,[6] Vilma Uzdaviniene,[7] Janez Tomazic,[8] Panagiotis Gargalianos-Kakolyris,[9] Patrick Schmid,[10] Chloe Orkin,[11] Court Pedersen,[12] Clifford Leen,[13] Christian Pradier,[14] Fiona Mulcahy,[15] Anna Lisa Ridolfo,[16] Therese Staub,[17] Fernando Maltez,[18] Rainer Weber,[19] Leo Flamholc,[20] Galina Kyselyova,[21] Jens D Lundgren,[1] and Amanda Mocroft[22]; for EuroSIDA

Clinical Infectious Diseases® 2017;64(10):1413–21





Effect of TDF exposure on risk of any fracture and of osteoporotic fractures[a]



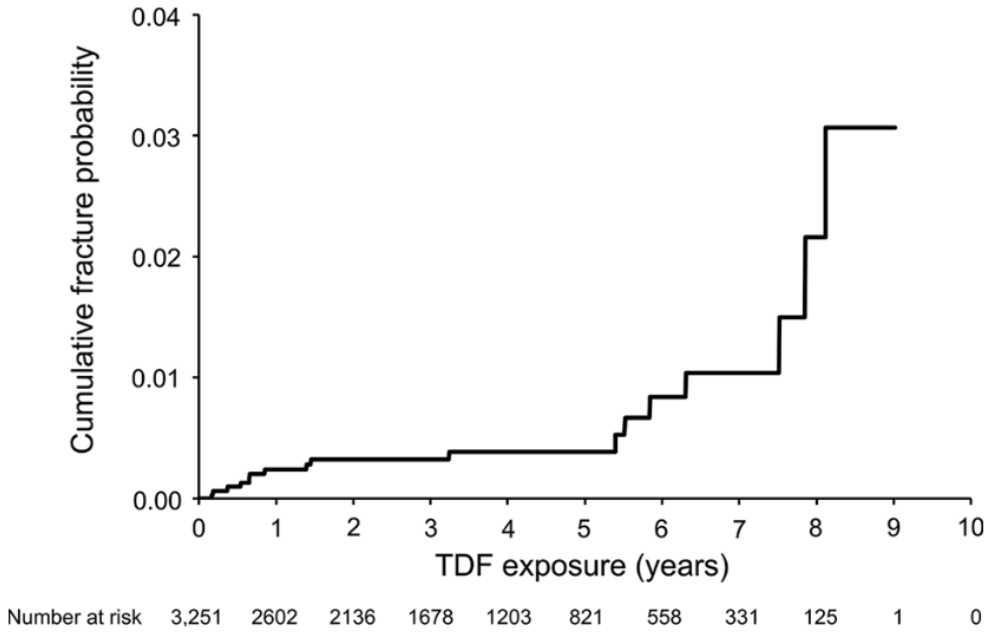
[a] grouped as fractures of the spine, arm, wrist and hip
[b] adjusted for demographics, HIV-specific variables and co-morbidities

Osteoporosis-Related Fractures in HIV-Infected Patients Receiving Long-Term Tenofovir Disoproxil Fumarate: An Observational Cohort Study

Ayami Komatsu, et al. Drug Saf (2018) 41:843–848

- A total of 3251 patients who received TDF or TDF/emtricitabine between April 2004 and March 2013 were analyzed in this study.
- The fracture rate was 13.5 per 10,000 PY in males and 42.2 per 10,000 PY in females.
- The mean age for male patients with osteoporosis-related fracture was **43.2 years**, whereas it was 65.7 years in female patients.
- The cumulative probability of osteoporosis-related fracture increased after ≥ 5 years of TDF exposure.

Conclusions. Among HIV-infected patients in Japan, treatment with TDF for ≥ 5 years increases the risk of bone fractures in **younger men**, in addition to that seen in older post-menopausal women.



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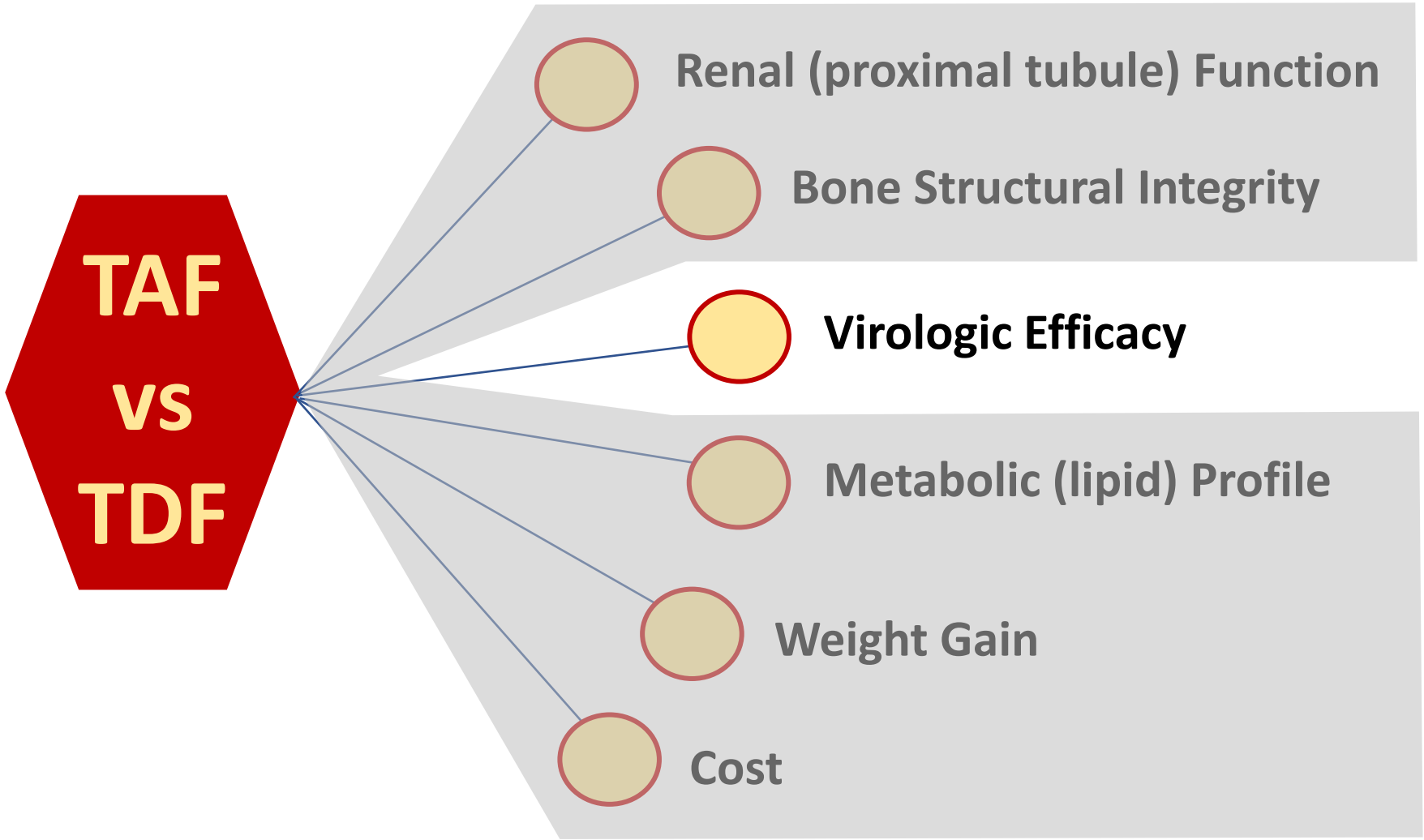
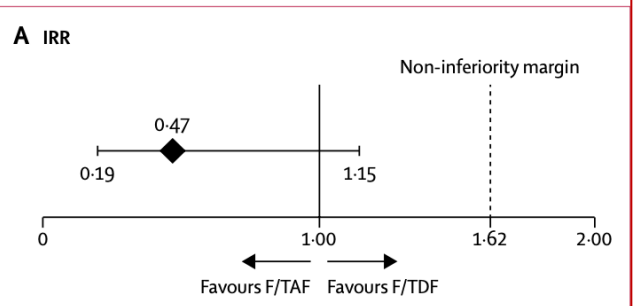
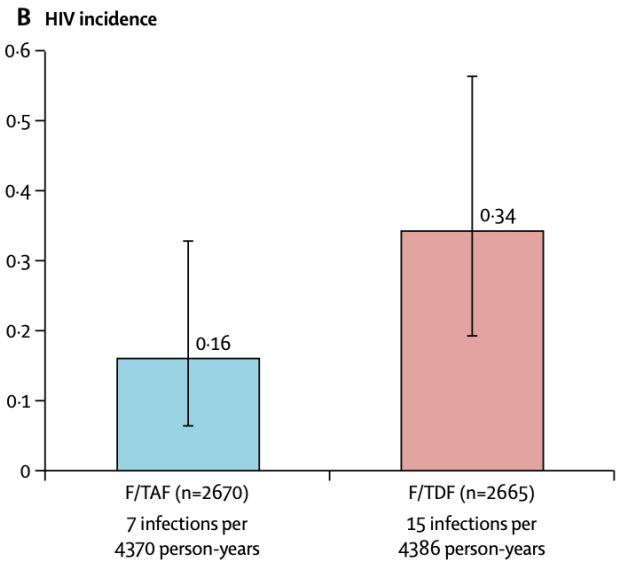
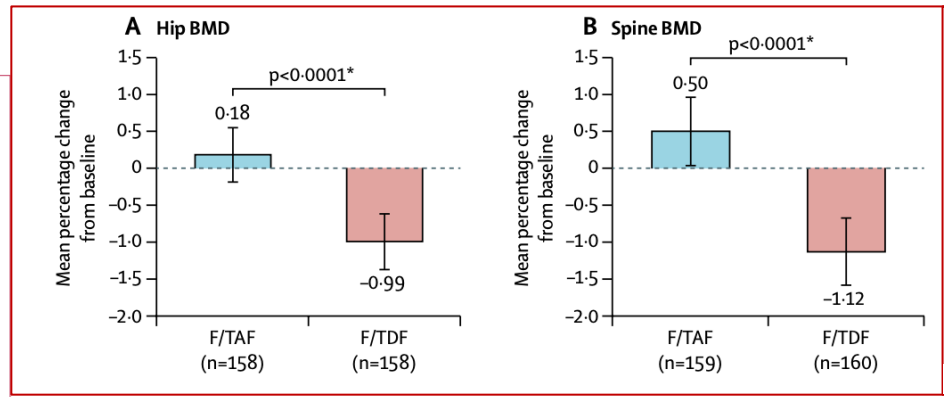


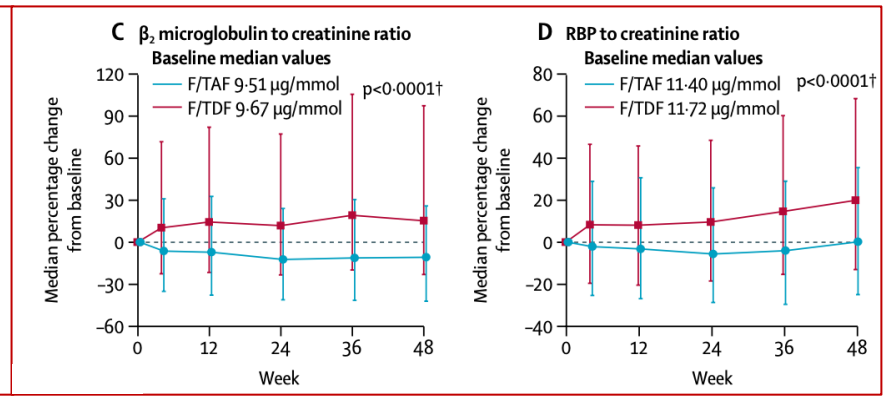
Emtricitabine and tenofovir alafenamide *vs* emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial

Kenneth H Mayer, et al. ***Lancet*** **2020; 396: 239–54**









	Emtricitabine and tenofovir alafenamide group (n=2694)	Emtricitabine and tenofovir disoproxil fumarate group (n=2693)
Grade 3 or 4 laboratory abnormality (≥1% in either group)		
Any	196 (7%)	206 (8%)
Increased alanine aminotransferase§	39 (1%)	40 (2%)
Increased amylase§	34 (1%)	46 (2%)
Increased aspartate aminotransferase§	63 (2%)	51 (2%)
Hyperglycaemia, fasting§	12 (<1%)	17 (1%)
Increased LDL, fasting§	51 (2%)	18 (1%)
Glycosuria§	19 (1%)	32 (1%)

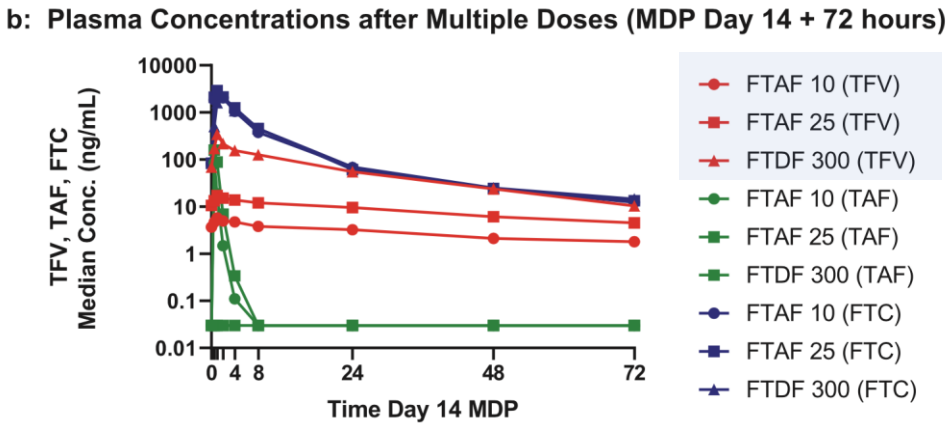
Safety and Pharmacokinetics of a Tenofovir Alafenamide Fumarate-Emtricitabine based Oral Antiretroviral Regimen for Prevention of HIV Acquisition in Women: A Randomized Controlled Trial

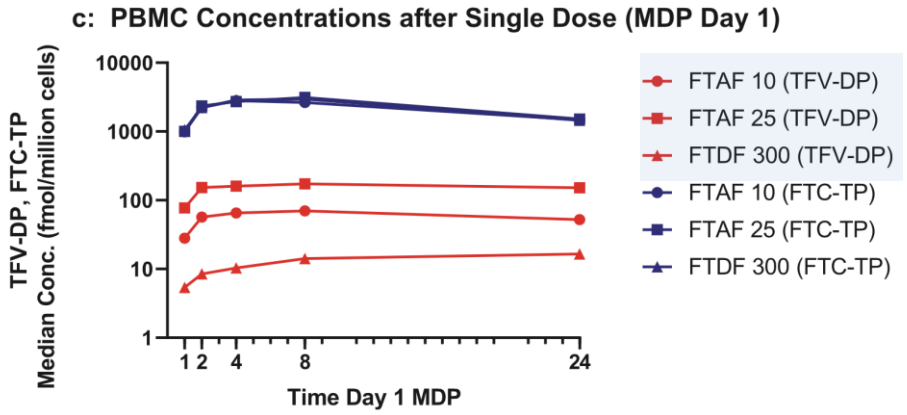
Andrea R. Thurman, et al. EClinicalMedicine 36 (2021) 100893

	Single Dose			Multiple Dose			
	F/TAF (200/25) n=12	F/TDF (200/300) n=12	Total n=24	F/TAF (200/10) n=26	F/TAF (200/25) n=24	F/TDF (200/300) n=25	Total n=75
Age, Mean (SD)	34.1 (7)	37.7 (7)	35.9 (7)	33.2 (7)	34.6 (8)	32.8 (9)	33.5 (8)
Body-mass index, kg/m^2 Mean (SD)	28.3 (4)	26.7 (4)	27.5 (4)	26.7 (4)	27.0 (4)	26.8 (4)	26.8 (4)

TFV concentrations area under curve (AUC) were ~20 fold lower following F/TAF versus F/TDF.

TFV- diphosphate (TFV-DP) AUC concentrations in PBMCs were 7-fold higher with F/TAF25 versus F/TDF.





Median TFV-DP concentrations in vaginal tissue (4hours post last dose) were approximately 6-fold higher with F/ TAF25 versus F/TDF. TFV and
TFV-DP were lower with F/TAF versus F/TDF in rectal tissue.

96 weeks treatment of tenofovir alafenamide *vs.* tenofovir disoproxil fumarate for hepatitis B virus infection

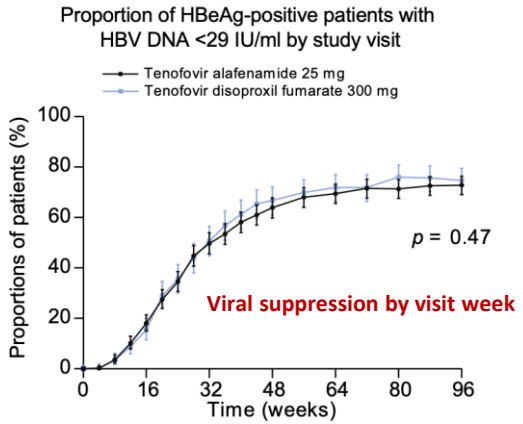
JOURNAL OF HEPATOLOGY

Kosh Agarwal, et al. Journal of Hepatology 2018 vol. 68; 672–681

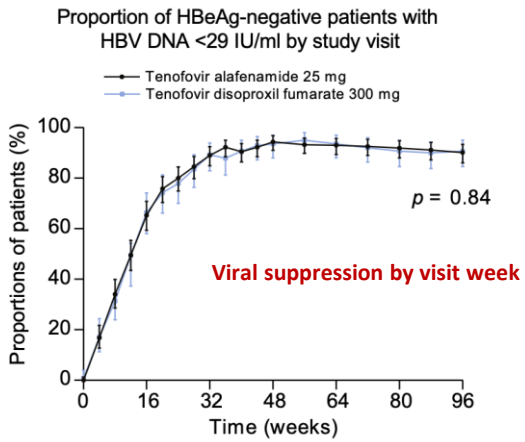
Research Article
Viral Hepatitis

In two international trials, patients with chronic HBV infection were randomized 2:1 to receive 25 mg TAF or 300 mg TDF in a double-blinded fashion.

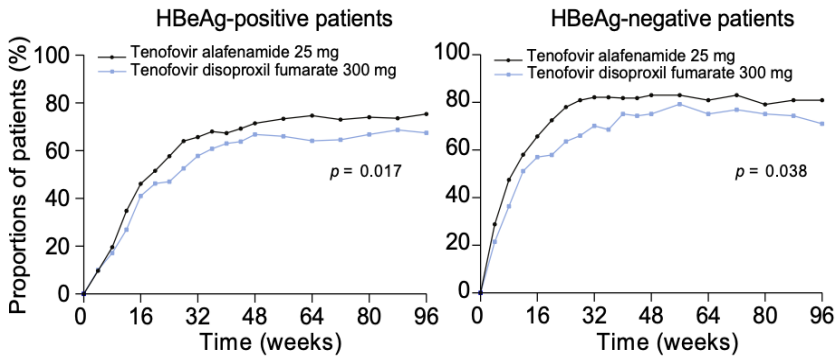
One study enrolled HBeAg- positive patients (423 vs 218) and the other HBeAg-negative (257 vs 127)patients.



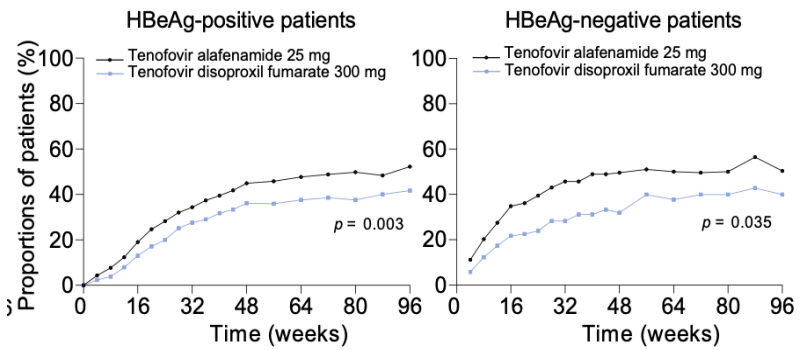
Viral suppression by visit week

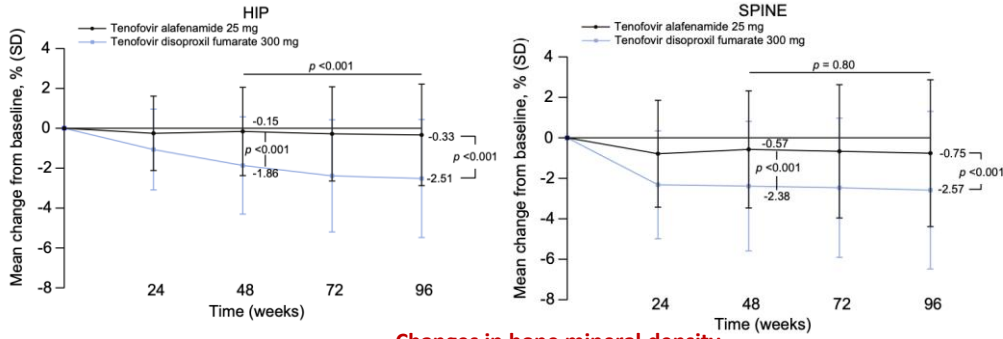


Viral suppression by visit week

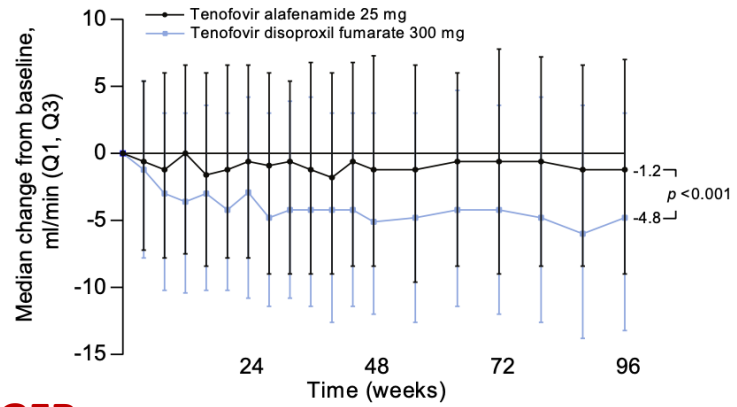


ALT Normalization by visit week





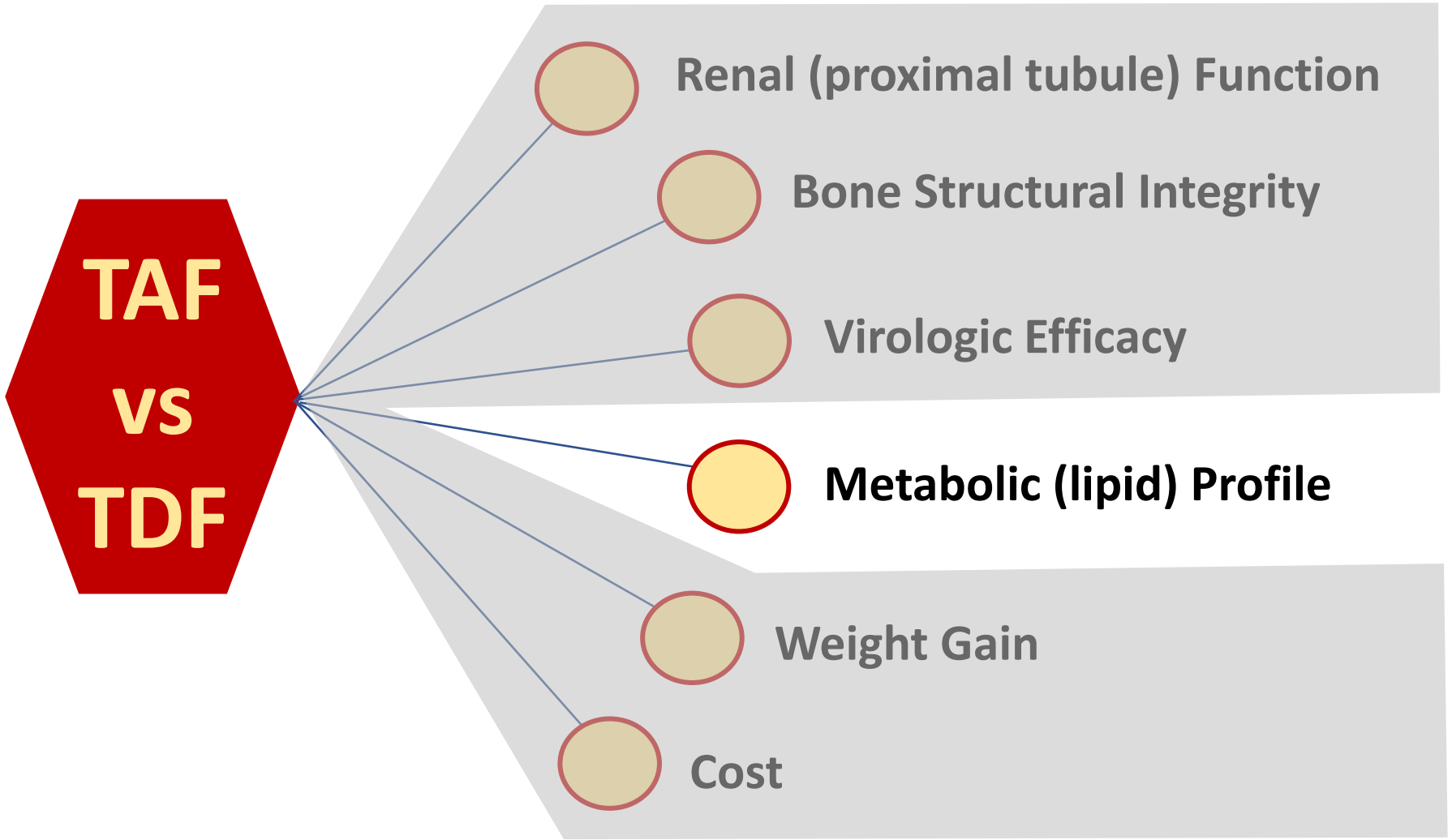
Changes in bone mineral density



eGFR

At present *Tenofovir* (TFV) pro-drugs position is that of the third component of , conventional triple drug regimens, whose main alternatives are dual regimens

Two pro-drugs are available and the main issues concerning the TAF vs TDF comparison are:



Atherosclerotic Cardiovascular Disease Risk Profile of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate

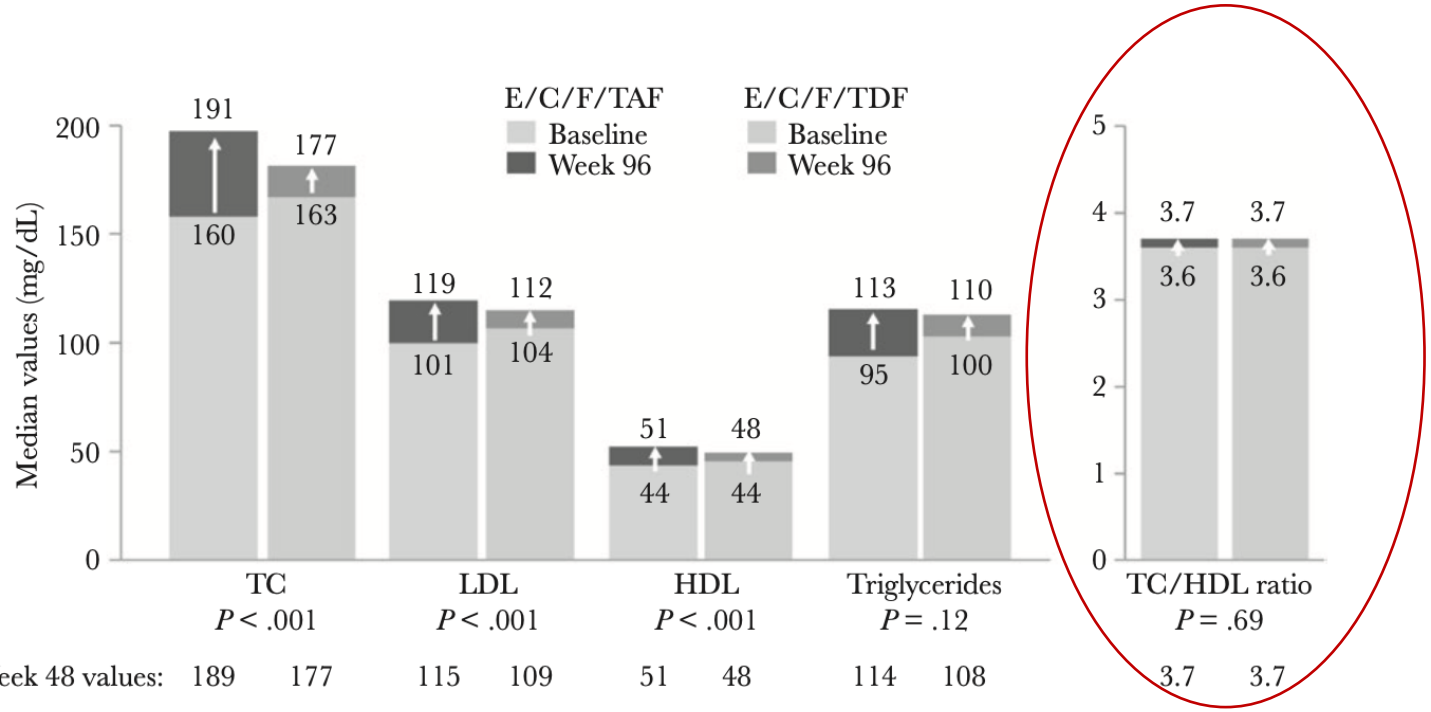
Gregory D. Huhn, et al. Open Forum Infectious Diseases, Nov 2019

IDSA Infectious Diseases Society of America | hivma hiv medicine association

Open Forum Infectious Diseases

MAJOR ARTICLE

- Participants (N = 1744) were randomized (1:1) to initiate TAF or TDF, each coformulated with elvitegravir/cobicistat/emtricitabine (studies GS-US-292-0104 and GS-US-292-0111).
- Eligibility for statin therapy and estimated 10-year ASCVD risk among adults aged 40–79 years treated with TAF or TDF for 96 weeks (W96) were analyzed based on American College of Cardiology/American Heart Association Pooled Cohort Equations. Categorical shifts in 10-year ASCVD risk from <7.5% to ≥7.5% by W96 on TAF versus TDF were calculated.



Eligibility for high-intensity statin therapy were similar for TAF versus TDF groups (19% vs 21%; *P* = .47).

Conclusions. Lipid changes with TAF as part of coformulated regimens **do not substantively affect CVD risk profiles** compared with TDF.

Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials

Clinical Infectious Diseases
MAJOR ARTICLE

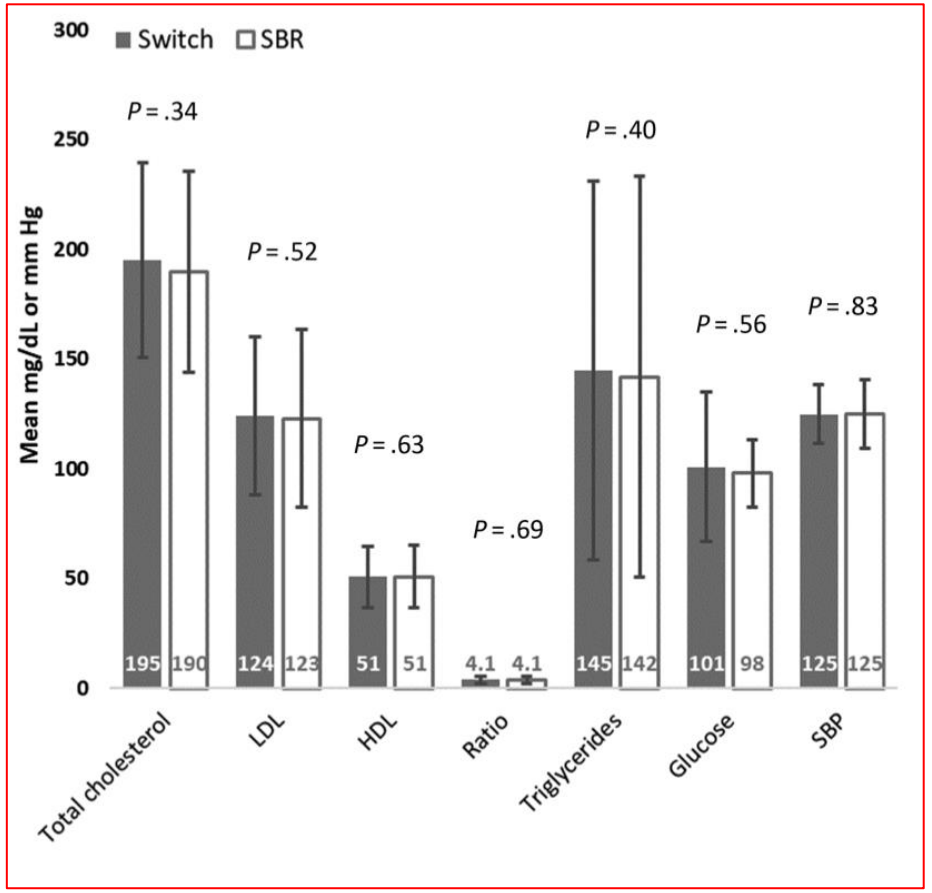
Kristine M. Erlandson, et al. Clinical Infectious Diseases 2021;73(8):1440–51

Metabolic Impact of Weight Gain in Switch Study Participants

Absolute values and changes in **cholesterol components** and **systolic blood pressure** were similar between switch and SBR participants who experienced ≥10% weight gain.

Participants with ≥10% weight gain had **small reductions in high-density lipoprotein cholesterol**; other metabolic parameters were largely stable.

Treatment-emergent AEs related to **diabetes** or **hyperglycemia** were not significantly greater among those with ≥10% compared with <10% weight gain (rate ratio, 1.52; 95% confidence interval, .70 to 3.27; *P* = .29;).



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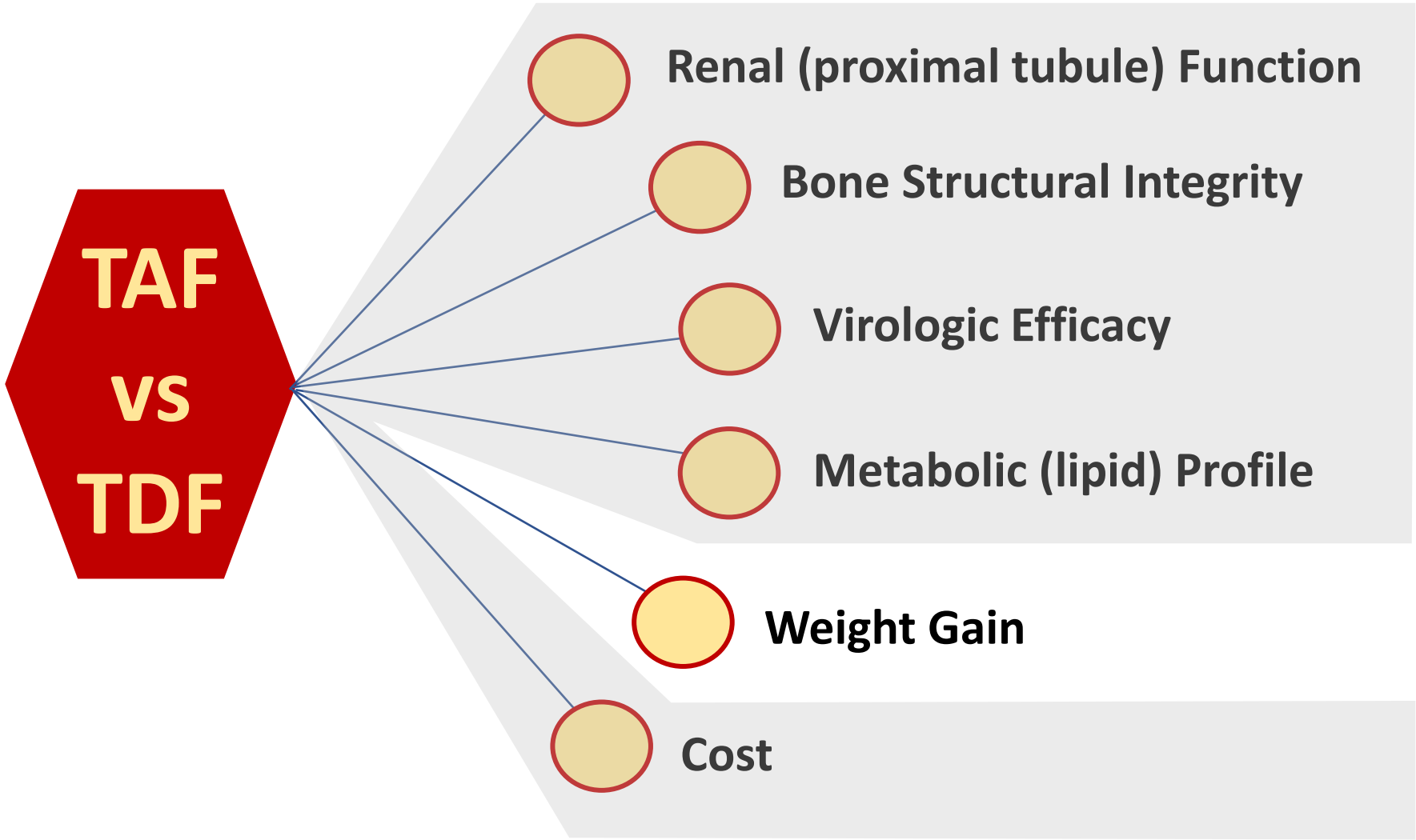

Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials

Clinical Infectious Diseases
MAJOR ARTICLE

Kristine M. Erlandson, et al. Clinical Infectious Diseases® 2021;73(8):1440–51

BACKGROUND

In a pooled analysis of 8 randomized, controlled trials of first-line ART, INSTI-based initial therapy was associated with greater weight gain than nonnucleoside reverse transcriptase inhib- itor (NNRTI)– or protease inhibitor (PI)–based ART (*Sax PE,et al. Clin Infect Dis **2020**; 71:1379–89).*

Several observational studies have shown **significant weight gain in PWH who switched to newer ART regimens** (*Kerchberger AM, et al. Clin Infect Dis **2020**; 71:593–600, . Taramasso L, et al. Open Forum Infect Dis **2020**; 7:ofaa195, . Taramasso L, et al. AIDS **2020**; 34:877–81*). **while others have not** (*Burns JE, et al. AIDS **2020**; 34:109–14, . McComsey GA, et al. CROI 4–7 March 2019, Seattle, WA. Poster abstract 671, . Verboeket SO, et al. EACS 2019, Basel, Switzerland. Abstract PS3/6*).

Trend of increasing obesity prevalence among people living with and without HIV (*Crum-Cianflone N, et al. PLoS One **2010**; 5:e10106, Coetzee L, et al. J Int AIDS Soc **2019**; 22:e25364*).

Prior studies have identified factors associated with weight gain that are:

- HIV-related (viral load, CD4 count),
- host-related (Black race, female sex, baseline weight, genetics, comorbidities, non-ART medications),
- ART-related.

Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials

Clinical Infectious Diseases
MAJOR ARTICLE

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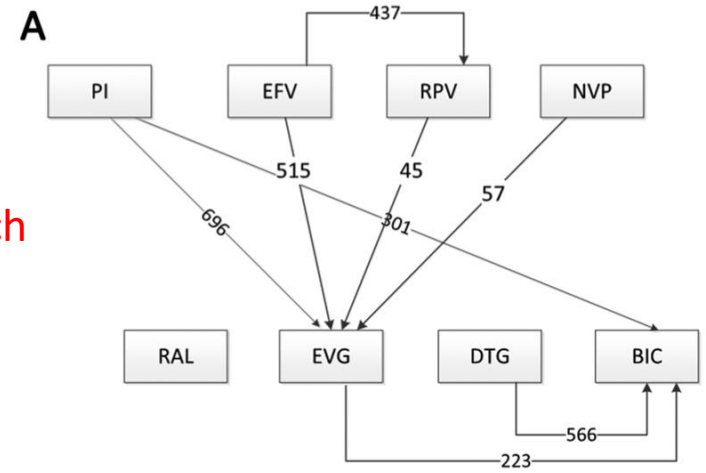
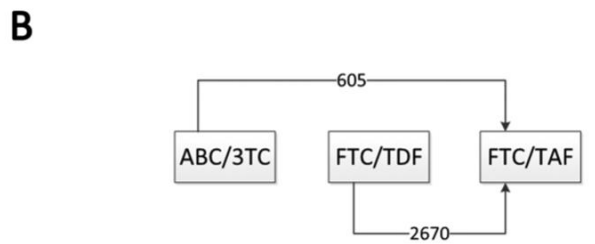
In the pooled dataset of 12 trials with 11 456 person-years of follow-up:

- 4166 were randomized to switch ART
- 3150 to continue SBR.

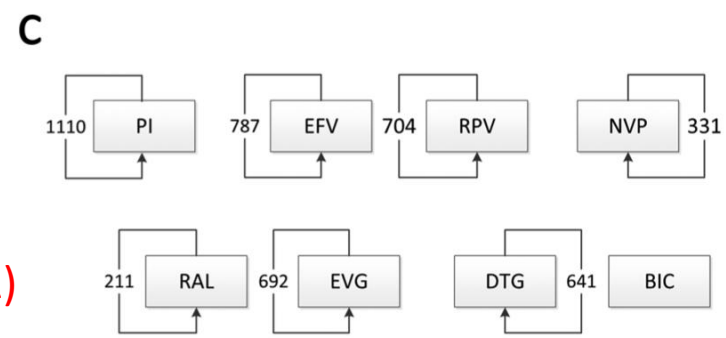
third-agent switch

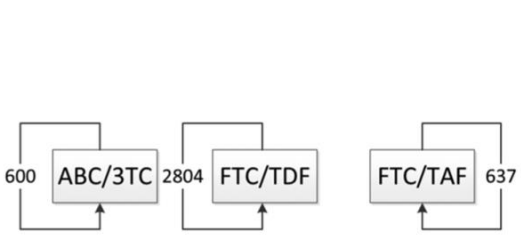




nucleotide reverse transcriptase inhibitor (NRTI) switch

third-agent stable baseline regimen (SBR)





NRTI SBR

Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials

Clinical Infectious Diseases
MAJOR ARTICLE

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In a linear mixed effects model, only BMI category and age were associated with weight gain.

Compared with participants with obesity at baseline, being underweight or having a normal BMI was associated with **0.8 kg greater** weight gain, and being overweight was associated with a **0.5 kg greater** weight gain (both $P < .0001$). Younger participants had **0.4 kg greater** weight gain than older participants (≤ vs >35 years; $P = .0014$).

RESPOND Bansi-Matharu L et al. CROI abstract 507, 2021.

Weight gain of at least 7% of BMI was also associated with being **underweight** at baseline (OR 2.10, 95% CI 1.91-2.31) and **Black ethnicity** (OR 1.59, 95% CI 1.45-1.74).

Trio: McComsey G et al. CROI abstract 503, 2021.

Weight gain of at least 10% was more likely in **people underweight or normal weight** at baseline (aRR 2.3, 95% CI 1.7-3.1).

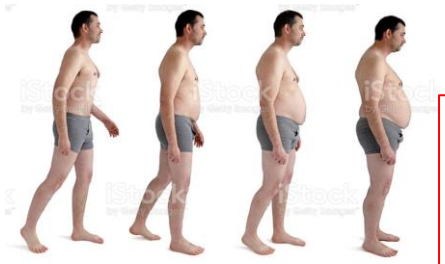
HIV Outpatients Study: Palella F et al. CROI abstract 504, 2021.

Demographic factors or **baseline weight did not affect** the rate of weight gain.

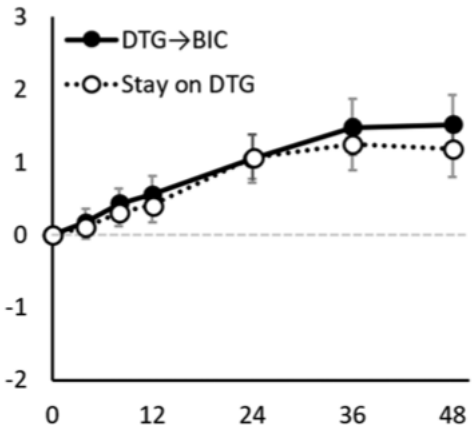
Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials

Clinical Infectious Diseases
MAJOR ARTICLE

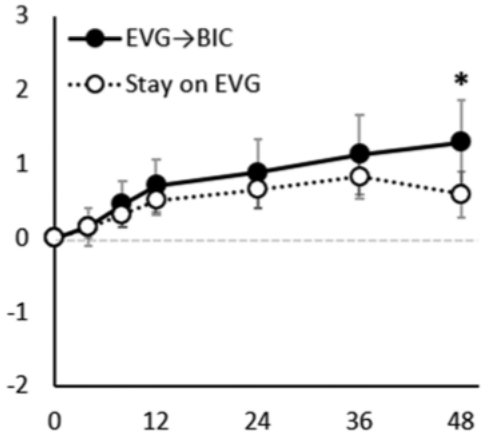
Kristine M. Erlandson, et al. Clinical Infectious Diseases 2021;73(8):1440–51



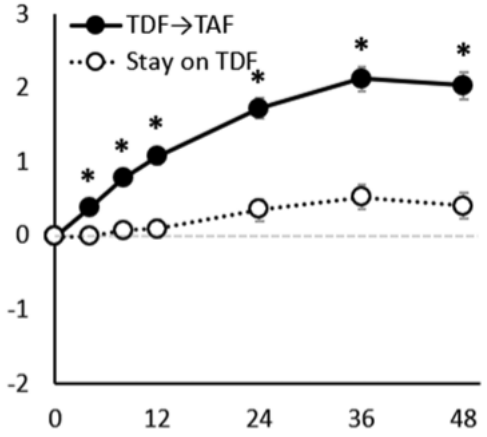
Switch from DTG to BIC was not significantly different from remaining on DTG:

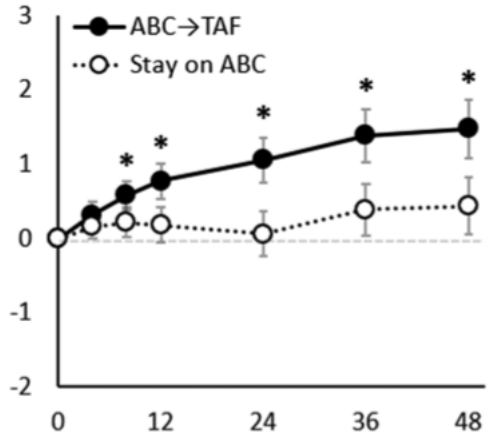


Switch from EVG/c to BIC was associated with a 0.7 kg greater weight gain at week 48 compared with no switch (*P* = .034;):

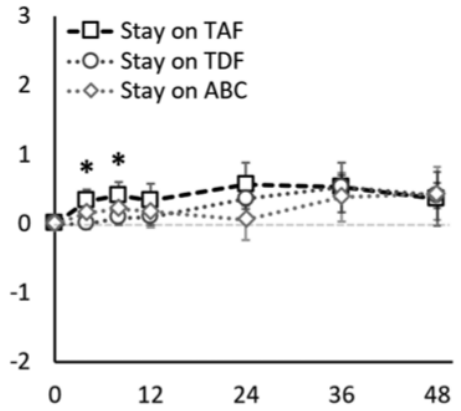


Weight gain was seen when switching from TDF:





Participants who stayed on TDF or ABC had weight changes similar to those who remained on TAF:



WEIGHT – SUPPRESSIVE EFFECTS OF TDF

Preexposure prophylaxis (PrEP) trials suggest an initial weight-suppressive effect of TDF:

- In iPrEX, participants who took emtricitabine (F)/ TDF had initial weight loss followed by a weight gain trajectory similar to the placebo arm.
- A similar pattern was observed in DISCOVER and HPTN 083, where the F/TDF arm exhib- ited initial weight loss, followed by a weight gain trajectory similar to the F/TAF and cabotegravir (CAB) arms, resulting in 1–1.5 kg greater weight gain in the F/TAF and CAB arms.

GEMINI & TANGO:

- The potential for TDF to suppress weight gain is also supported by the GEMINI 1 and 2 studies, where treatment-naive PWH randomized to DTG + lamivudine (3TC) gained more weight than those taking DTG + F/TDF (3.7 vs 2.4 kg at week 144).
- Switch from TAF-containing regimens to DTG/3TC led to similar weight gain as staying on TAF-containing ART in the TANGO study.

- Glidden DV, et al. Clin Infect Dis **2018**; 67:411–9.
- Mayer KH, et al. Lancet **2020**; 396:239–54.
- Landovitz RJ. 2Third International HIV Conference (AIDS 2020: Virtual), abstract OAXLB0101, **2020**.
- Cahn P, et al. HIV Drug Therapy, Glasgow, 5–8 October 2020; P018.
- Eckard AR, McComsey GA. Curr Opin Infect Dis 2020; 33:10–9.

- Drugs like EFV, COBI, RTV and TDF have a consistent negative impact on body weight (weight suppressants….), and such an effect might have significantly biased the interpretation of the results of studies in which antiretrovirals were virtually the sole variables investigated….

- The higher the number of variables considered in body weight/metabolic studies, the lesser appears to be the responsibility of either INSTIs or TAF

- Fat increase in those who experienced weight gain following INSTIs and/or TAF introduction suggests a rather favourable re-distribution

Contribution of INSTI, BMI, physical activity or caloric intake to weight gain in PWH

Guaraldi G[1], Milic J[1], Malagoli A[1], Carli F[1], Menozzi M[1], Franconi I[1], Raimondi A[1], Ciusa G[1], Masi V[1], Belli M[1], Guaraldi S[1], Mussini C[1], Brown TT[2], Lake JE[3], Erlandson K[4]

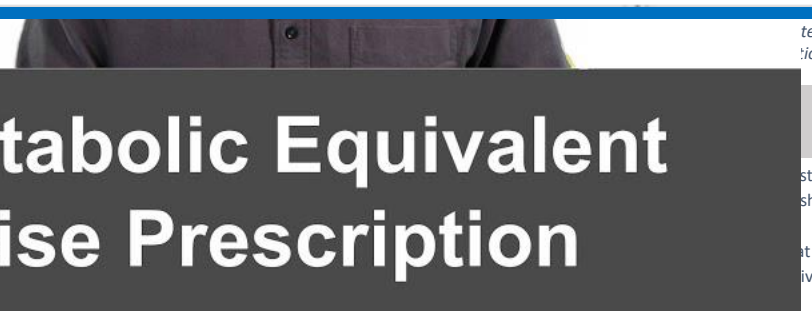
[1] Modena HIV Metabolic Clinic, University of Modena and Reggio Emilia, Modena, Italy; [2] Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University, Baltimore, Maryland; [3] University of Texas Health Sciences Centre, Houston, Texas, USA; [4] University of Colorado, Department of Medicine, Aurora, CO

675

Our findings suggest that WG is mostly influenced by pre-existing weight, low physical activity and immunological status:

- ✓ The most relevant risk factor for WG was baseline BMI>25. Not only obesity, but even overweight at baseline should be avoided in order to prevent WG during follow up.
- ✓ The second most relevant risk factor for WG was MET<600 at baseline. At a clinical level, these data suggest that a dedicated counselling should be offered in all ART experienced PWH that recommends a moderate to intense physical activity (MET>600) to prevent WG, for example suggesting:
  - 3 or more days of vigorous intensity activity and/or walking of at least 30 minutes per day , OR
  - 5 or more days of moderate intensity activity and/or walking of at least 30 minutes per day , OR
  - 5 or more days of any combination of walking, moderate intensity or vigorous intensity activities
- ✓ High CD4/CD8 ratio suggests potential immunologic mechanisms linked to weight gain.

This study was not powered to address clinical significance of WG, but we did not observe that the already high proportion of co-morbidities at baseline changed over time in weight gainers.



Vivo Phys. MET - Metabolic Equivalent for Exercise Prescription

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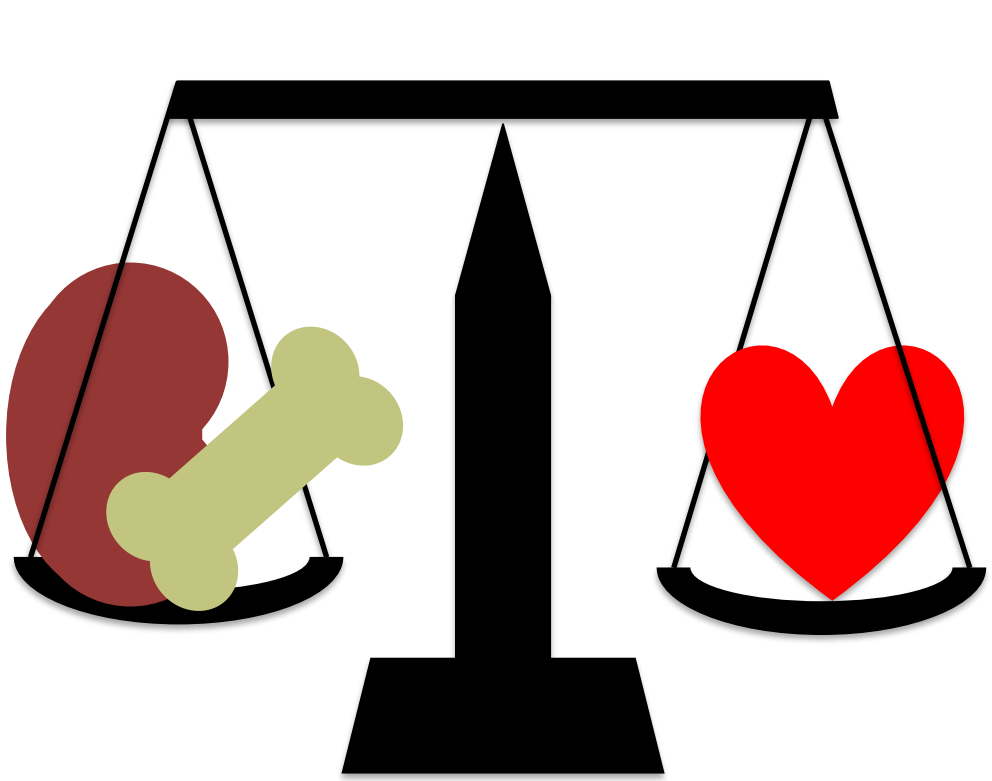
Corresponding author: Giovanni Guaraldi, MD - giovanni.guaraldi@unimore.it

Have We Progressed Past "Classic" ART-Associated AEs?



Non-Modifiable Risk Factors

Modifiable Risk Factors

Modified from:

Solomon. Curr Opin HIV AIDS. 2015;10:219. Masters. Expert Rev Clin Pharmacol. 2019;12:1129.

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Simone Mornese Pinna

Enrica Borgogno

Silvia Scabini

Giancarlo Orofino

Valeria Ghisetti

Valeria Avataneo

Alessandra Manca

Ilaria Zedda

Alice Ianniello

Elisa De Vivo

Luca Paglietti

Miriam Antonucci

Mattia Trunfio

Elena Salvador

Walter Rugge

Acknowledgments

THE UNIVERSITY *of* LIVERPOOL

LIVERPOOL:

David Back

Saye Khoo

Andy Owen

Marco Siccardi

ST STEPHEN'S AIDS TRUST

LONDON:

Marta Boffito

Margherita Bracchi

ROMA:

Andrea Antinori

Giuseppe Ippolito