Case Discussion : Switching ART

August, 27 2022

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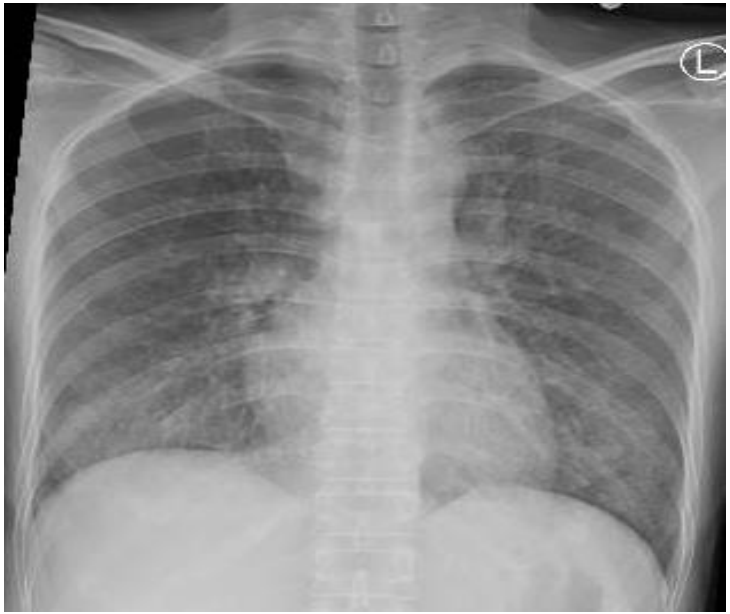
Case 1 : A 47-year-old woman

- Diagnosed with AIDs and PCP in 4/2022, presented with dyspnea for 10 days w/o fever, admitted 6-11/4/22
- CD4 lymphocytes 20 cells/µL (2%), Serum CrAg, HBsAg, anti-HCV, Syphilis Ab: negative



Treatment: TMP/SMX and prednisolone

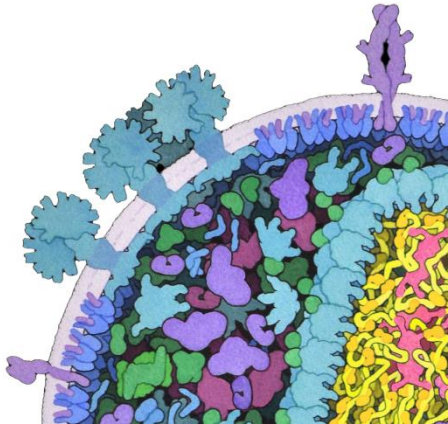
↓ 3wks

27/4/22: TMP/SMX induced agranulocytosis with *E. coli* acute pyelonephritis and septicemia
Treatment:
- Cefepime >> ciprofloxacin total 14 days (27/4-9/5/22)
- Dapsone for PCP prophylaxis 3/5/22

- TDF/3TC/DTG was started 6/5/22

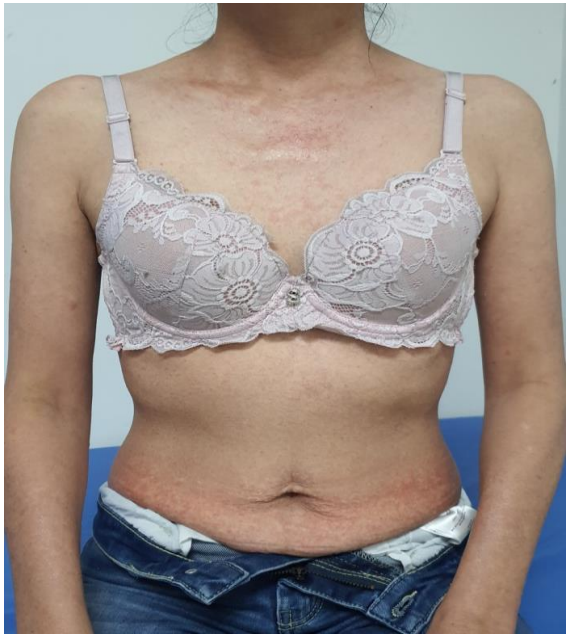
47-year-old woman

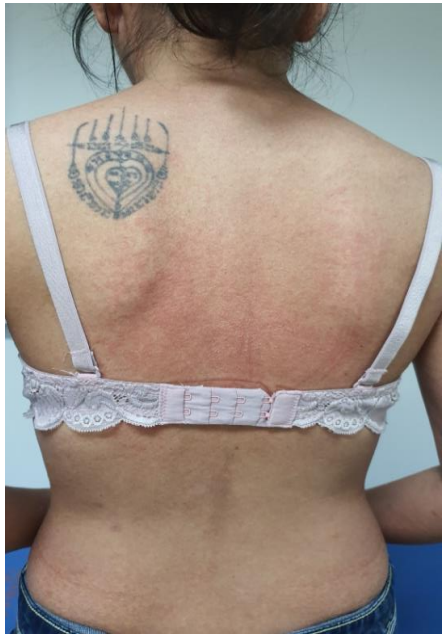
- 6/5/22 เริ่มกินยา TDF/3TC/DTG
- 10/5/22 มีผื่นแดงขึ้นที่แขนและขาสองข้าง ไม่แสบไม่คัน ไม่เป็นตุ่มน้ำ ผื่นหายไปเอง
- 12/5/22 ผื่นเริ่มขึ้นที่ลำตัว ริมฝีปากแห้งและแดง ผิวแห้งและลอกทั่ว ๆ กินยาแก้แพ้ ผื่นจางลง
- 15-16/5/22 มีผื่นลักษณะเดิม ผื่นจางลงเองหลังกินยาแก้แพ้
- 24/5/22 เริ่มมีผื่นขึ้นที่แขนขาสองข้าง ภายใน1 วัน เริ่มลามมาที่ตัว หน้าปาก **เจ็บมุมปาก มีแผลในปาก** วัดไข้ได้ 37.5 ไม่มีปวดท้องหรือคลื่นไส้อาเจียน
- 27/5/22 มาโรงพยาบาล visit ARI clinic เนื่องจากรู้สึกเพลีย เจ็บคอ ผื่นขึ้นทั้งตัว
- Physical examination: **generalized maculopapular rash, injected conjunctiva and lips**
- **Diagnosis: Steven-Johnson Syndrome (SJS) suspected culprit drug: DTG**
- **Treatment: prednisolone and antihistamine, discontinue TLD and dapsone 1/6/22**



47-year-old woman

- 8/6/22: MP rash improved >> the culprit drug should be DAPSONE !!
- TDF/3TC/DTG was restarted





- 10/6/22: MR rash at chest, abdomen and back, no mucosal involvement
- Normal CBC and LFT

- TDF/3TC/DTG was discontinue
- Prednisolone and CPM were started lesions improved in 7 days

- 17/6/65 start TDF/FTC/EFV + CPM + prednisolone
- 28/6/65 **recurrent MP rash**

What is the most appropriate management ?

Intolerance of DTG-containing ART Regimens

- Cohort study, Natherland
- 556 patients
- Median F/U time: 225 days

- **85 patients (15.3%)**: DTG was stopped
- **Neuropsychiatric AE**
- Combination with ABC show higher risk

Table 1. Reported adverse reactions leading to discontinuation of dolutegravir[a].

Adverse drug reaction	*n* (%)
Sleep disturbance, insomnia	31 (5.6)
Gastrointestinal complaints	21 (3.8)
Joint, tendon and/or muscle pain	11 (2.0)
Psychological/psychiatric symptoms[b]	14 (2.5)
Neurologic symptoms	10 (1.8)
General malaise (headache and severe fatigue)	24 (4.3)
Respiratory tract complaints	5 (0.9)
Other	9 (1.6)

[a]Numbers and percentages do not add up to total because multiple negative side effects were diagnosed or reported in 31 (39%) patients who stopped dolutegravir for this/these reason(s); in 11 (14%) patients more than two negative side effects were reported.
[b]Including **depression, anxiety, agitation, emotional instability** and one case of **psychosis.**

GJ de Boer Mark et al. AIDS, 2016

Adverse Events of RAL and DTG

- Swiss HIV Cohort Study, 2006-15, 4041 patients
- Toxicity occurred in 5.07% of patients treated with RAL and 3.85% with DTG
- Neuropsychiatric complaints are most common AE
  - DTG: n = 33 (1.7%)
  - RAL: n = 13 (0.6%)

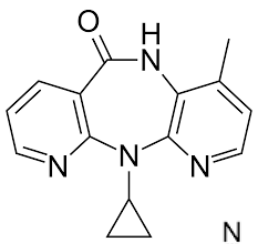
	Raltegravir $N=2091$		Dolutegravir $N=1950$		
	n	%	*n*	%	*P* value
Male	1474	70.5	1455	74.6	0.003
Age, median (IQR)	48	41–54	48	40–54	0.447
White ethnicity	1752	83.8	1566	80.3	0.004
Treatment modification	364	17.4	204	10.5	<0.0001
Treatment failure	10	0.48	2	0.10	0.028
Toxicity					
Total	106	5.07	75	3.85	0.060
Gastrointestinal	6	0.29	19	0.97	0.005
Liver	2	0.10	7	0.36	0.098
Lipids	12	0.57	1	0.05	0.003
Neuropsychiatric	13	0.62	33	1.69	0.001
Kidney	3	0.14	0	0.00	0.251
Hematologic	9	0.43	2	0.10	0.046
Allergy	16	0.77	4	0.21	0.011
IRIS	6	0.29	1	0.05	0.076
Other	39	1.87	8	0.41	<0.0001
Convenience					
Total	210	10.04	92	4.72	<0.0001
Patient's wish	54	2.58	44	2.26	0.502
Physician's decision	94	4.50	26	1.33	<0.0001
Treatment simplification	62	2.97	22	1.13	<0.0001
Pregnancy	3	0.14	11	0.56	0.023
Other	25	2.97	18	1.13	0.399
No information	10	0.48	6	0.31	0.390

Elzi L et al. AIDS, 2017

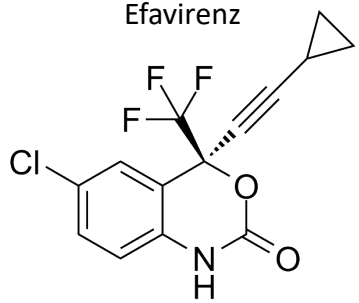
NNRTI Cross Hypersensitivity

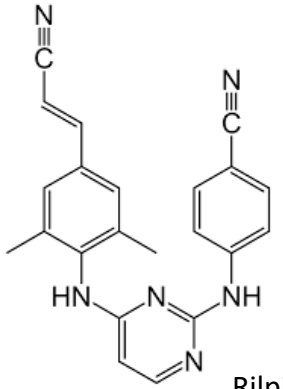
- Efavirenz-associated rash: 4.6-20%
  - SJS, TEN: 0.1%
- Nevirapine-associated rash: 15% to 32%
  - SJS and TEN: 0.3-0.37%
- Switch from nevirapine to efavirenz: recurrent rash = 12.6%
- Switch from efavirenz to nevirapine: recurrent rash = 50%
- Rilpivirine: rarely cause drug hypersensitivity
  - Unknown incidence of cross hypersensitivity

Nevirapine



Efavirenz





Rilpivirine

Yunihastuti Evy et al. Asia Pacific Allergy 2014
Mehta U. Lancet Infect Dis, 2007

Case 2 : A 61-year-old woman

Dx HIV infection in 2547, her husband died of AIDS

Unknown BID regimen

2554
TDF/FTC+AZT+LPV/r

Poor adherence
No resistance assay result

VL Oct/63 < 20 copies/mL
CD4 664 cells/µL (24%)

Feb/64

What is the most appropriate management ?

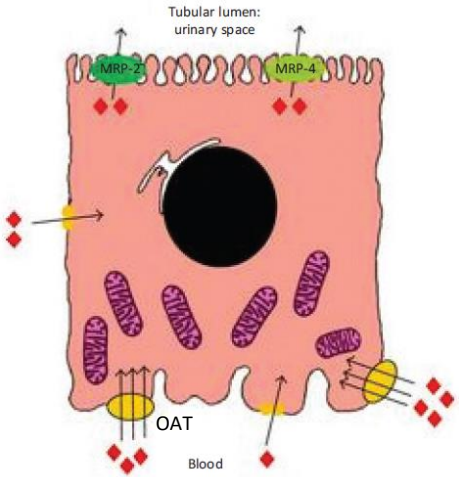
ปวดตามตัว ปวดหลัง เป็น ๆ หาย ๆ เป็นปี มีอาการปวดหลังมากตั้งแต่ ก.พ.64 จนต้องเดินด้วย walker ปวดเวลาขยับตัว

Blood Chem			
Cr	0.6 mg/dL	PO_4	0.6 mg/dL (2.5-4.5)
Na	134 mmol/L	Ca	9.7 mg/dL
K	2.9 mmol/L	VitD	23 ng/mL
Cl	100 mmol/L	FBS	102 mg/dL
CO_2	22 mmol/L	ALP	280 IU/L

Urinalusis	
Glu	1+
pH	6
RBC	0-1
WBC	0-1
Pro	1+
Spec.	1.21

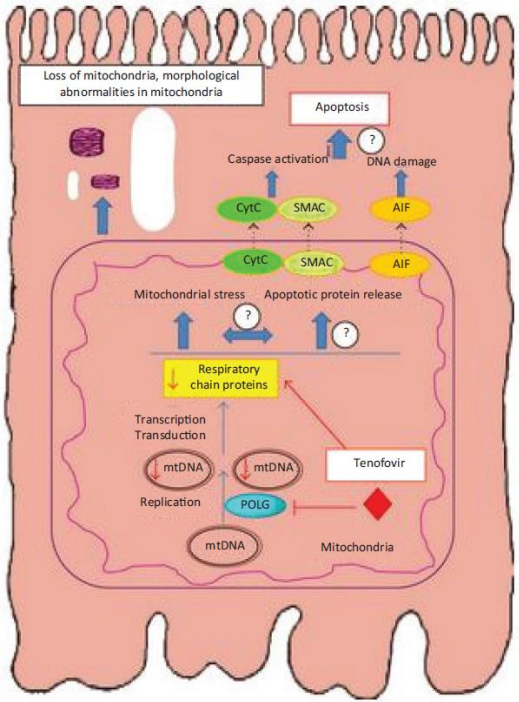
Tenofovir Disoproxil Fumarate and Renal Tubular Cell

- Tubular secretion is estimated at 20% – 30% of total excretion of TDF



OAT: Organic aion transporter
MRP: multidrug resistance protein

Probenicid, ritonavir, NSAIDs, and antiherpes: acyclovir alter OAT and MRP function



- Proximal tubule functions
  - **Reabsorption** of glucose, uric acid, amino acids, small proteins (such as vit D-binding protein and β2-microglobulin) and phosphate
  - **Secretion** of hydrogen ions
  - **Synthesis** of calcitriol
- Proximal tubule damage
  - Proximal RTA
  - Fanconi's syndrome
  - Bone loss
  - Vitamin D deficiency

Venter WDF et al. Southern African Journal of HIV Medicine, 2018

The safety of tenofovir disoproxil fumarate

- A tenofovir DF expanded access program (EAP) was initiated in 2001-2005, postmarketing surveilence, 10 343 patients, Australia, Europe and US

Table 2. Serious adverse events from the expanded access program (EAP)[a] and most common serious adverse drug reactions[b] from the postmarketing safety database.

Adverse event	Expanded access program [$n = 10343$ (3700 person-years)] No. (%)	Expanded access program [$n = 10343$ (3700 person-years)] Incidence per 100 000 person-years	Reporting rate[c] per 100 000 person-years in postmarketing safety database (455 392 person-years)
Specific categories of interest[d,e]			
Bone abnormalities	12 (0.1)	324	1.1
Lactic acidosis	13 (0.1)	351	4.2
Mitochondrial toxicity	1 (<0.1)	27	1.5
Neuropathy	6 (<0.1)	162	0.7
Pancreatitis	48 (0.5)	1,297	5.5
Renal[e]			
Any renal serious adverse event	56 (0.5)	1514	43.3[‡]
Renal failure	32 (0.3)	865	24.2
Renal other	11 (0.1)	297	4.0
Serum creatinine increase/blood urea nitrogen increase[f]	10 (<0.1)	270	5.1
Fanconi/renal tubular disorder/hypophosphatemia/glycosuria	7 (<0.1)	189	22.4
Nephrogenic diabetes insipidus	1 (<0.1)	27	2.2
Nephritis	0 (0)	0	2.4
Proteinuria	0 (0)	0	2.2

- Graded increase in Cr = 2.2%

Risk factors

- ↑ serum Cr
- Nephrotoxic med
- Low BW
- Advanced age
- lower CD4

Nelson MR et al. AIDS, 2007

Common Laboratory Indicators of Proximal Tubule Dysfunction

Common Laboratory Indicators of Proximal Tubular Dysfunction	
Abnormality	**Definition of Abnormality**
Serum Abnormalities	
Hypokalemia	Serum potassium concentration below laboratory reference range
Low serum bicarbonate	Serum bicarbonate concentration below laboratory reference range
Hypophosphatemia	Serum phosphorous concentration below laboratory reference range
Urine abnormalities	
Urine glucose on dipstick	Glycosuria in the absence of diabetes, or in diabetics with well-controlled blood glucose
Fractional excretion of phosphate	<10% is normal and >20% is abnormal
Tubular maximum for phosphate corrected for GFR	Lower than reference value (normal, 2.8–4.4 mg/dL)
Fractional excretion of uric acid	<15% is normal and >20% is abnormal
Urine albumin-to-protein ratio	uAPR <0.4 suggests predominantly tubulointerstitial disease, whereas uAPR >0.4 suggests predominantly glomerular disease
Abbreviations: GFR = glomerular filtration rate; uAPR, urine albumin-to-protein ratio;	

Other Markers of Early Tubular Dysfunction

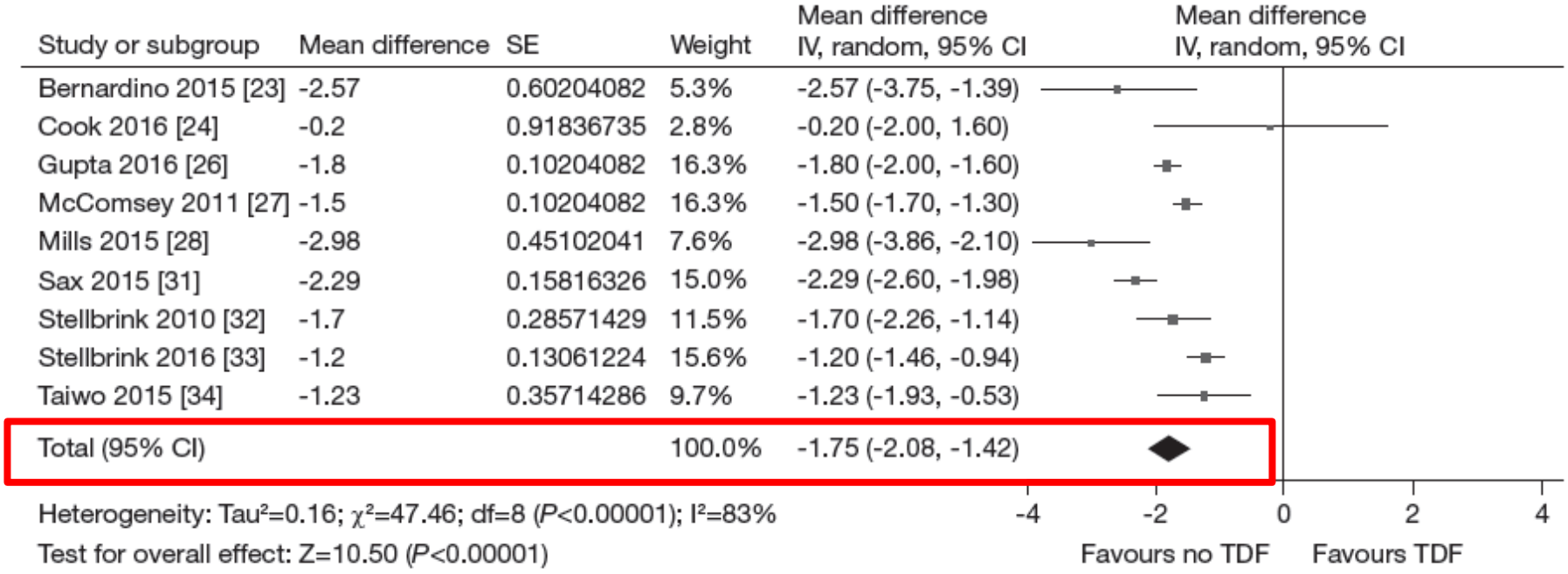
- Neutrophil Gelatinase-Associated Lipocalin (NGAL)
- Alpha-1 Microglobulin (A1M)
- Beta 2-Microglobulin (B2M)
- Retinol Binding Protein (RBP)

https://www.hiv.uw.edu/

Fiseha T and Gebreweld A. Biochemistry Research International, 2016

The Effect of TDF on BMD

- Systematic review and meta-analysis, HIV patients, HBV patients and PrEP



HIV patients: Total hips at 48 weeks

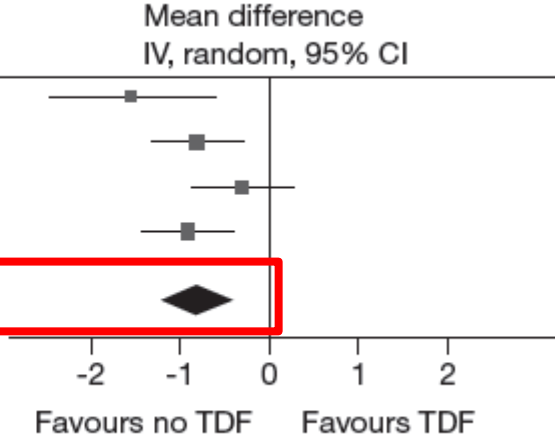
Baranek B et al. Antiviral Therapy, 2020

PrEP patients: Total hips at 48 weeks

Study or subgroup	Mean difference	SE	Weight	Mean difference IV, random, 95% CI
Kasonde 2014 [17]	-1.55	0.4744898	14.1%	-1.55 (-2.48, -0.62)
Liu 2011 [11]	-0.8	0.255	29.6%	-0.80 (-1.30, -0.30)
Mirembe 2016 [18]	-0.303	0.284	26.7%	-0.30 (-0.86, 0.25)
Mulligan 2015 [12]	-0.92	0.255	29.6%	-0.92 (-1.42, -0.42)
Total (95% CI)			100.0%	-0.81 (-1.22, -0.40)

Heterogeneity: Tau²=0.08; χ^2=5.76; df=3 (*P*=0.12); I²=48%

Test for overall effect: Z=3.89 (*P*=0.0001)

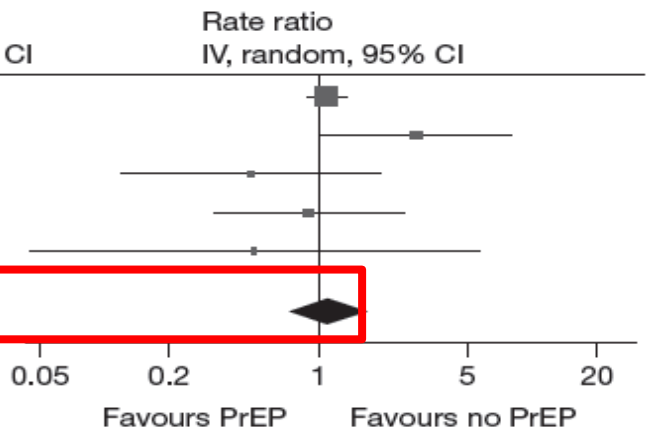


PrEP patients: Fracture (1-4 years F/U)

Study or subgroup	Log [rate ratio]	SE	Weight	Rate ratio IV, random, 95% CI
Choopanya 2013 [15]	0.09532257	0.11159349	58.3%	1.10 (0.88, 1.37)
Grohskopf 2013 [16]	1.0631542	0.51639778	14.9%	2.90 (1.05, 7.97)
Molina 2015 [19]	-0.72467506	0.70710678	8.8%	0.48 (0.12, 1.94)
Thigpen 2012 [1]	-0.10177436	0.51754917	14.8%	0.90 (0.33, 2.49)
Van Damme 2012 [20]	-0.6868945	1.22474487	3.2%	0.50 (0.05, 5.55)
Total (95% CI)			100.0%	1.12 (0.72, 1.74)

Heterogeneity: Tau²=0.07; χ^2=5.40; df=4 (*P*=0.25); I²=26%

Test for overall effect: Z=0.50 (*P*=0.62)



Baranek B et al. Antiviral Therapy, 2020

The Effect of TDF on BMD

- TDF-containing regimens lead to an approximately ***1–3% greater*** BMD loss compared to non-TDF containing regimens

- Mechanism:
  - Effects on osteoblast
  - ***Fanconi's syndrome***
  - TDF may affect ***vitamin D and PTH metabolism*** >> ***increased bone turnover***

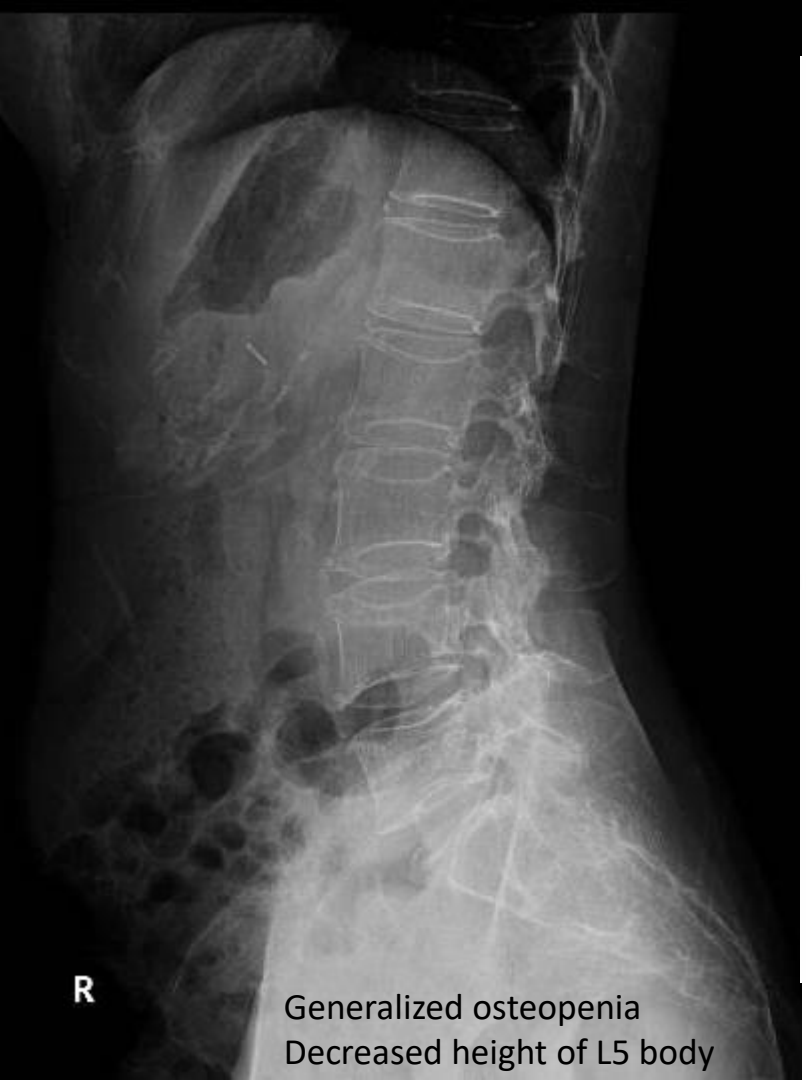
- Some studies reported increase fractures in HIV patients who were treated with TDF

Grant and Cotter. Curr Opin HIV AIDS, 2017

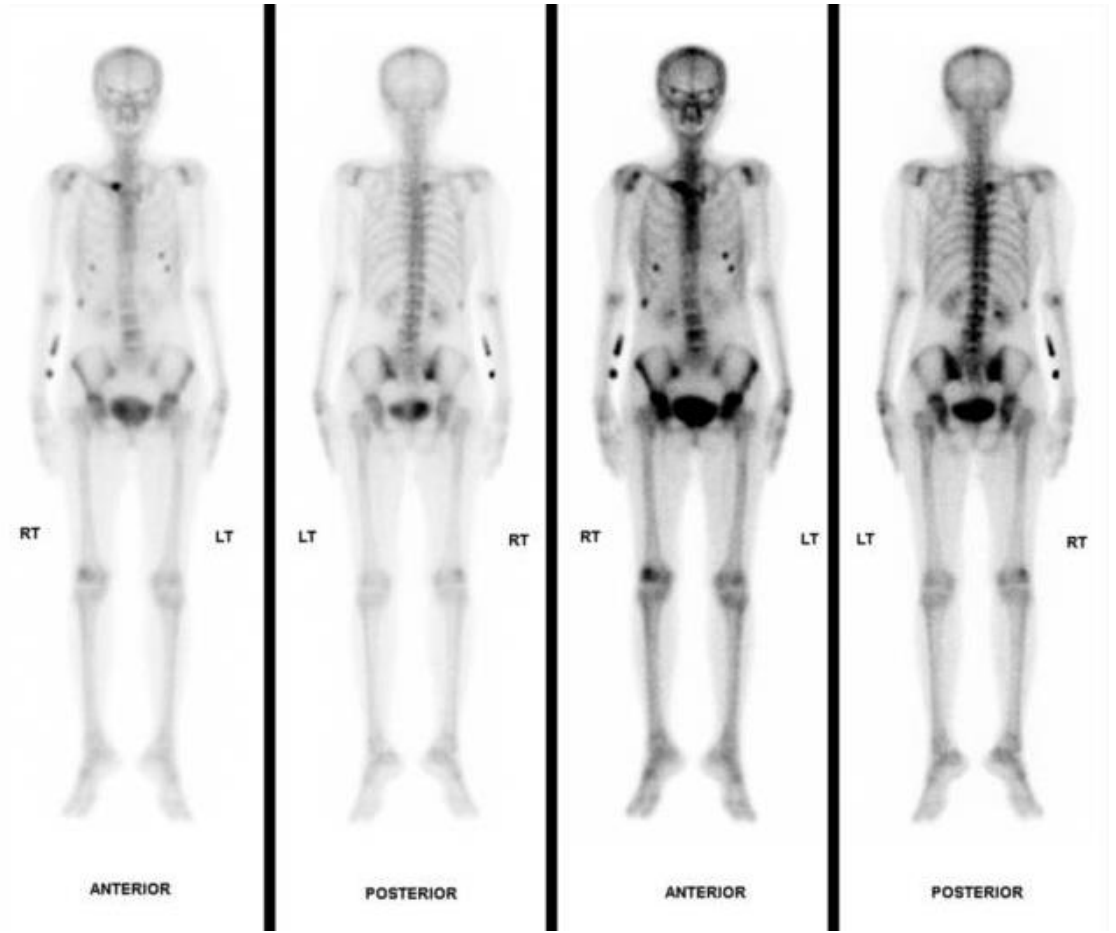
Osteomalacia and Fanconi's Syndrome

- Classical renal Fanconi syndrome characterized by ***osteomalacia***, ***metabolic acidosis*** and ***glycosuria***
- Osteomalacia occurs when ***hypophosphatemia*** leads to ***altered mineralization in regenerating bone***
- Many of the affected individuals were also receiving ***ritonavir-boosted protease inhibitors***
- Patients typically present with ***severe bone pain***, ***often around the pelvic girdle***
- Lab: proximal tubular dysfunction + ***high ALP, low BMD***
- Treatment: Vitamin D, calcium and phosphate supplement, discontinue TDF
- Improve in 2 weeks to 11 months

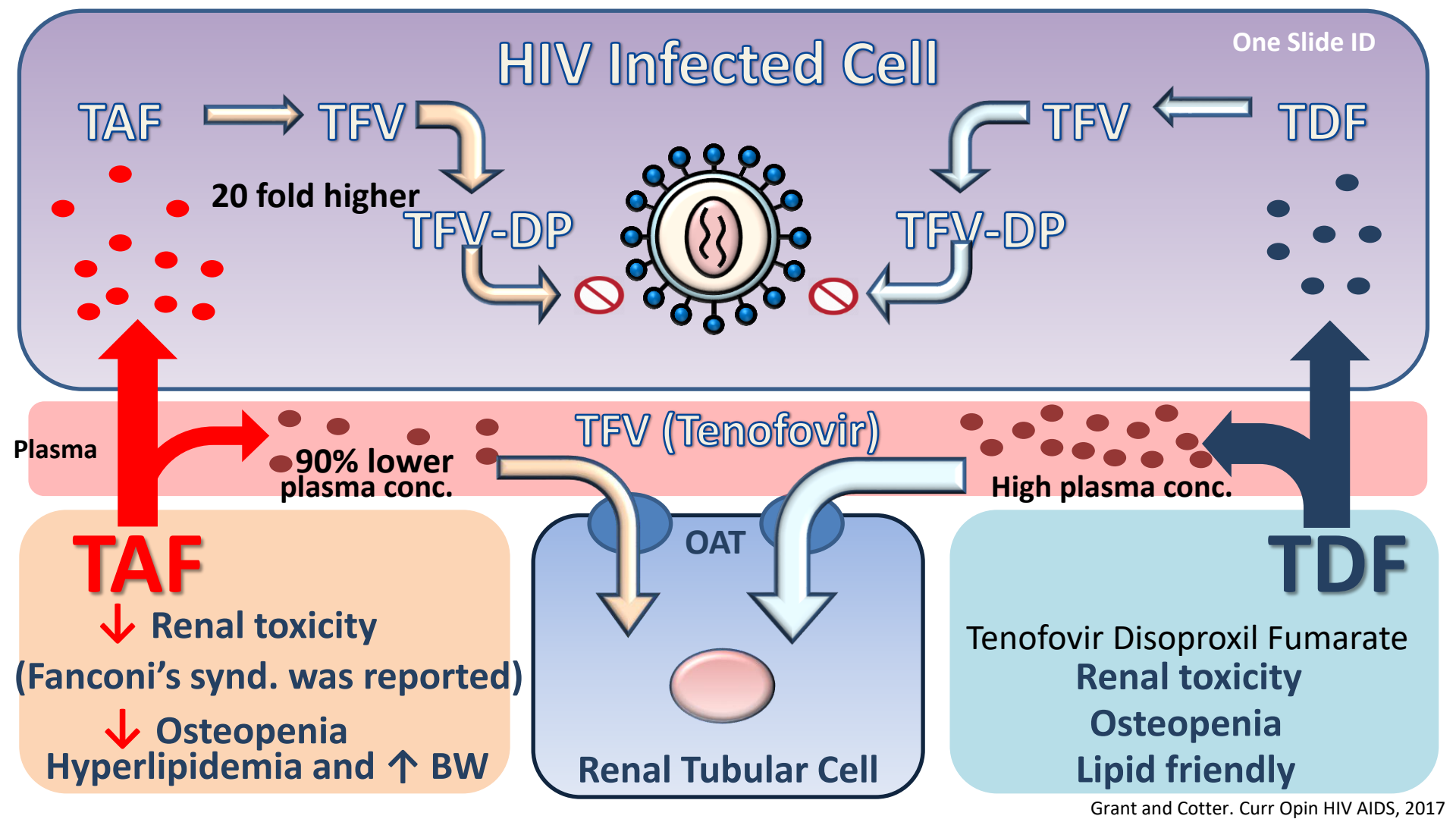
Grant and Cotter. Curr Opin HIV AIDS, 2017
Mateo L et al. Clin Rheumatol , 2016



Generalized osteopenia
Decreased height of L5 body



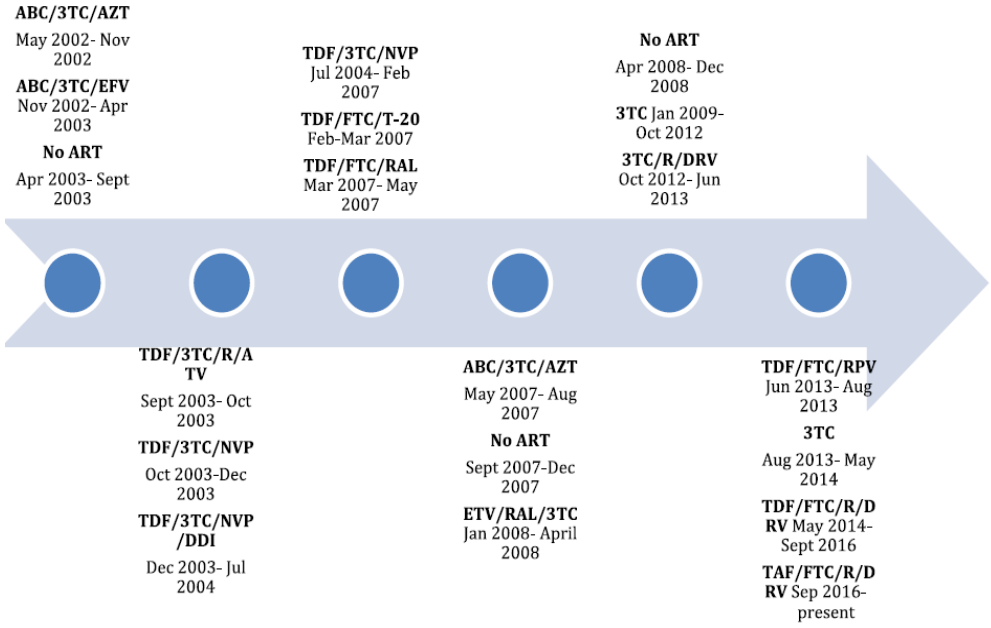
Multiple increased radiotracer uptake



Grant and Cotter. Curr Opin HIV AIDS, 2017

Fanconi syndrome due to tenofovir disoproxil fumarate reversed by switching to tenofovir alafenamide fumarate in an HIV-infected patient

Nomvuyo Z. Mothobi, Jeffrey Masters and Deborah J. Marriott



Ther Adv Infectious Dis

2018, Vol. 5(5) 91–95

Table 1. Serum biochemistry and urinalysis from TDF initiation to 14 months post switch to TAF.

	Initiation of TDF	12 months post TDF	Admission (28 months post TDF)	10 months post TAF	14 months post TAF	Normal values
Sodium, mmol/l	**132**	**130**	137	138	138	137–146
Potassium, mmol/l	4.7	3.7	**2.9**	3.7	4.8	3.5–5.2
Bicarbonate, mmol/l	26	23	**17**	26	26	22–32
Creatinine, µmol/l	42	66	**161**	108	106	60–120
eGFR, ml/min/1.73 m^2	>90	>90	**41**	65	67	>60
Phosphate, mmol/l	1.40	**0.37**	**0.29**	0.72	1.08	0.70–1.40
Random glucose, mmol/l	–	–	5.2	4.6	4.6	3.0–7.8
Urine glucose	Nil	**4+**	**4+**	–	Nil	Nil
Urine protein	Nil	**3+**	**3+**	–	**1+**	Nil
Urine casts	Nil	Nil	**1+**	–	Nil	Nil
Urine phosphate concentration, mmol/l	–	–	**32.3**	–	**9.4**	–
Urine protein concentration, g/l	–	–	**2.04**	–	**0.32**	0.00–0.10

eGFR, estimated glomerular filtration rate; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate. (Bold text- abnormal result)

Switching from TDF to TAF in ARV Regimens for Virologically Suppressed adults with HIV-1 infection

- Randomised, actively controlled, multicentre, open-label, non-inferiority trial
- TDF-containing regimen (N = 477) vs TAF-containing regimen (N=959)

	Tenofovir alafenamide group	Tenofovir disoproxil fumarate group	Difference in least square means* (95% CI)
Hip BMD change			
Number assessed	869	428	..
BMD T-score change from baseline	0·11 (0·18)	−0·02 (0·20)	0·13 (0·10–0·15); p<0·0001
Percent change from baseline	1·47% (2·71)	−0·34% (2·83)	1·81 (1·49–2·13); p<0·0001
Patients with:			
0–3% increase	486 (56%)	163/428 (38%)	p<0·0001†
>3% increase	186/869 (21%)	32 (8%)	..
Spine BMD change			
Number assessed	881	436	
BMD T-score change from baseline	0·17 (0·29)	−0·02 (0·31)	0·19 (0·16–0·23); p<0·0001
Percent change from baseline	1·56% (3·84)	−0·44% (4·14)	2·00 (1·55–2·45); p<0·0001
Patients with:			
0–3% increase	358/881 (41%)	146/436 (34%)	p<0·0001†
>3% increase	291/881 (33%)	58/436 (13%)	..

Table 2: **Changes in BMD in hip and spine from baseline to week 48**

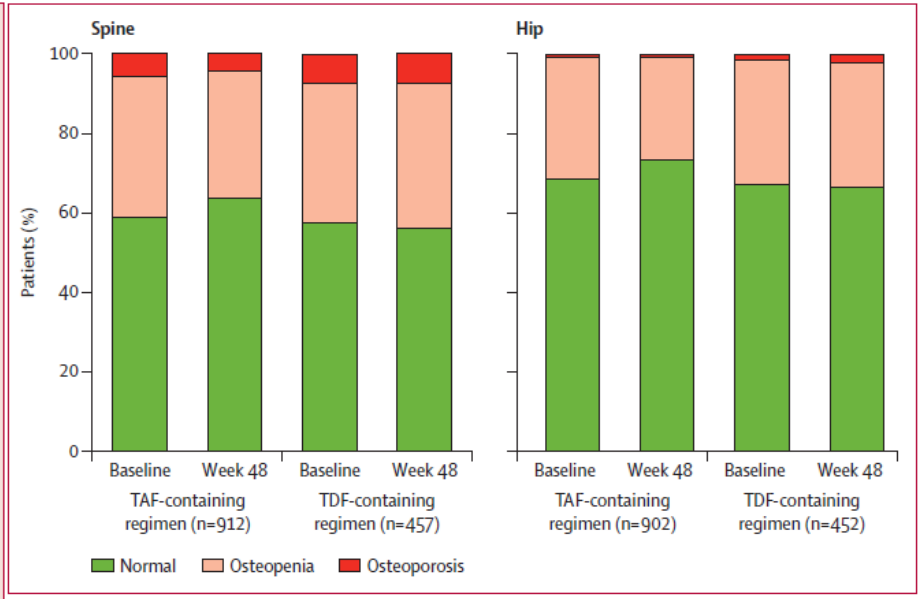


Figure 2: **Changes in osteopenia and osteoporosis (T-score defined) from baseline to week 48**
Differences between regimens were significant (p<0·0001). TAF=tenofovir alafenamide. TDF=Tenofovir disoproxil fumarate

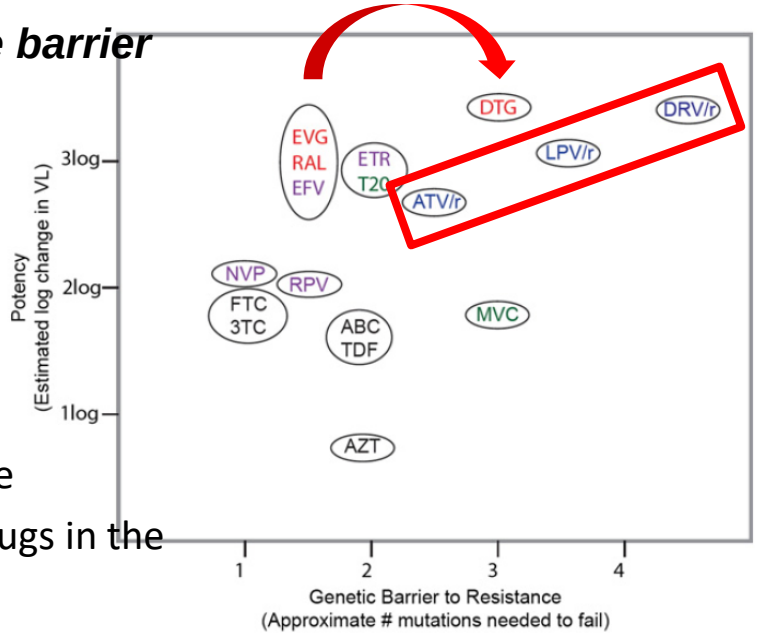
Mills A et al. Lancet Infect Dis, 2016

Key Factors to Consider for a New ARV Regimen

- ***2 fully active drugs*** if at least ***1 has a high resistance barrier***
  - ***2nd INSTI***: dolutegravir (DTG)
  - ***Boosted-PI***: darunavir (DRV)

- If both the ***2nd INSTI*** and ***boosted PI*** are fully active
  - Can be used in combination without NRTIs

- No fully active drug with a high resistance barrier is available
  - Every effort should be made to include 3 fully active drugs in the regimen
- Despite the presence of some DRM, some ARV drugs may be retained
  - NRTIs, PIs, and 2nd INSTIs



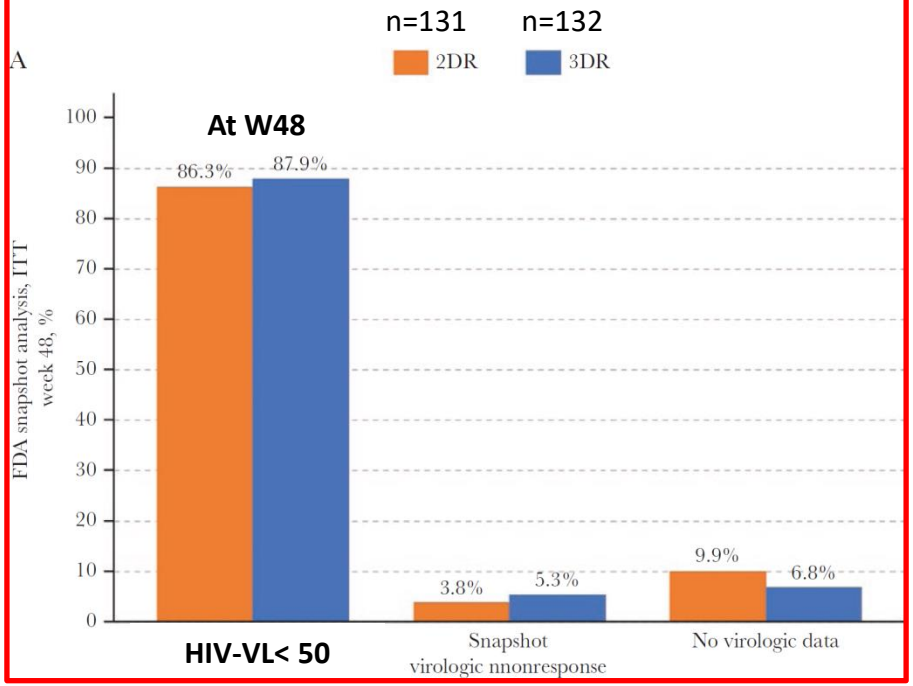
DTG + DRV/r

DHHS guideline. 2021

Dual therapy based on DTG and bDRV

Switching from **2NRTIS + bDRV** to **DTG+bDRV**

Spinner CD et al. OFID, 2020 (DUALIS), (RCT)



DTG+bDRV in treatment experienced patients

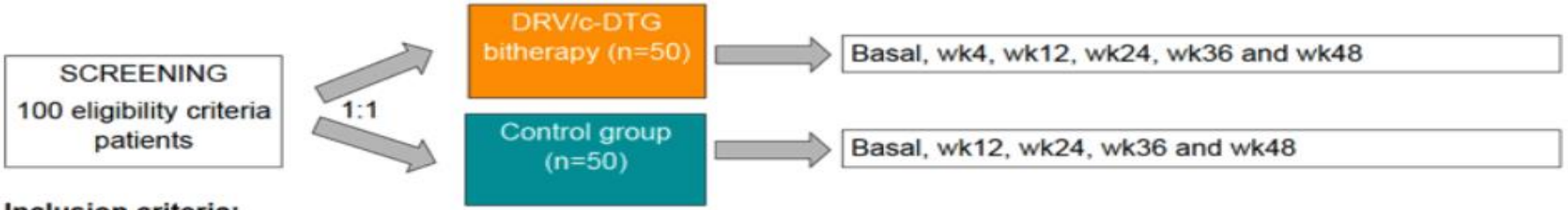
Vizcarra P et al. Antiviral Therapy, 2019 (single-arm cohort study)

- 51 patients with virologic failure to ≥ ARV classes
- DTG 50 mg + DRV/C (800/150) or DRV/r (800/100)

- At week 48
  - Efficacy was 90% (95% CI 82, 99%) in the ITT analysis
  - Efficacy was 94% (95% CI 87, 100%) in the PPT analysis
- No severe side effect

DTG+DRV/c for switching in MDR HIV-1

- Open label, multicenter, randomized pilot study



Inclusion criteria:

- Adults on ART containing at least 3 antiretroviral drugs.
- Confirmed HIV-1 RNA <50 c/ml for ≥6 months preceding the randomization.
- History of DRM against at least 2 antiretroviral classes, with no integrase-associated mutations or previous virological failure (VF) to INSTI-based regimens and no evidence of resistance to DRV (<15 points from Stanford dB score).
- Willing and able to be adherent during the study.

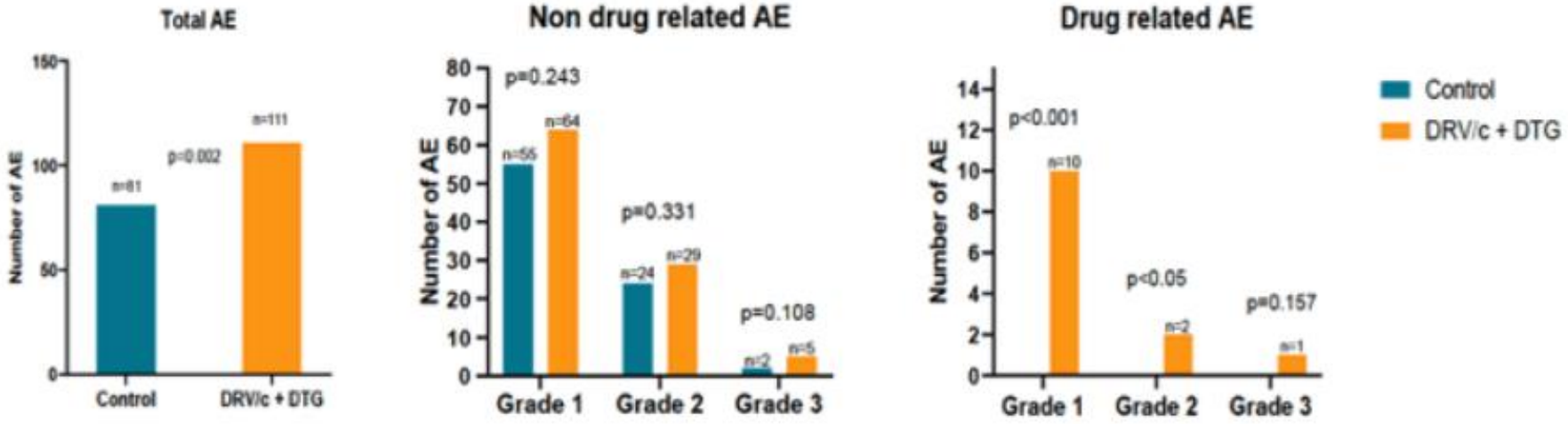
Virological outcomes

- There was **no VF in the DTG+DRV/c** group, whilst there were 2 (4.5%) VF in the control group (p=0.147)
- Genotyping test was not performed in one patient with VF. No DRM were detected in the other one.

José Ramón Santos et al. CROI 2022. Poster Abstract Submission Number 510.

DTG+DRV/c for switching in MDR HIV-1

Adverse events during follow-up



- More frequently observed AEs in the DRV/c+DTG arm has to be interpreted with caution due to open-label design.
- AEs leading to treatment discontinuation were unfrequent.

José Ramón Santos et al. CROI 2022. Poster Abstract Submission Number 510.

Dx HIV infection, motorcycle accident, BW 51 kg

Case 3 : A 34-year-old woman

2559
TDF/FTC/EFV
↓
TDF+3TC

2 days

Dizziness, nausea and vomiting

VL = 139000

Genotypic resistance assay in 2560

NNRTI: *None*

NRTI: K65R, M184V

ปลาย 2559
TDF+3TC

Fever weight loss generalized papules
Tissue PCR: Non tuberculous *Mycobacterium*

2560
AZT/3TC+EFV
REC

VL = 5961

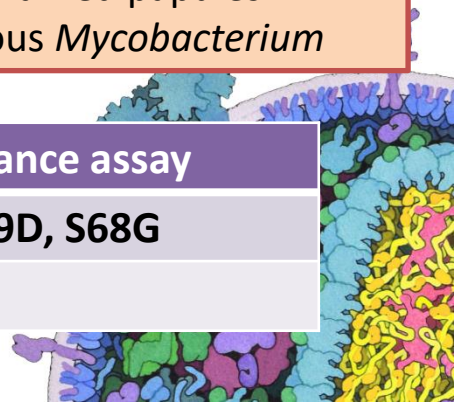
2/61 Genotypic resistance assay

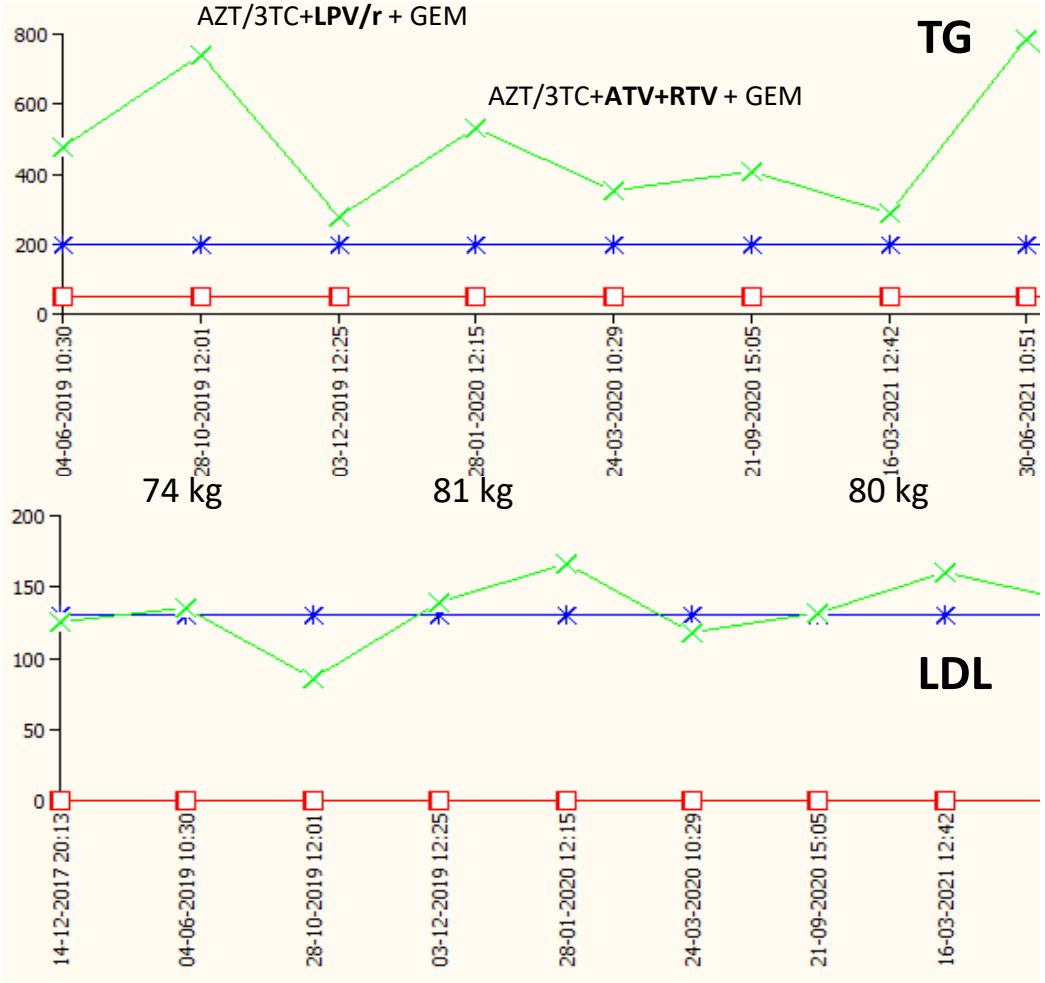
NNRTI: G190A, K103N, V179D, S68G

NRTI: M184V

2561
AZT/3TC+LPV/r
EC

VL < 20 (2561)





HIV-VL < 20
FBS 297 mg/dL
HbA1C 11.3%

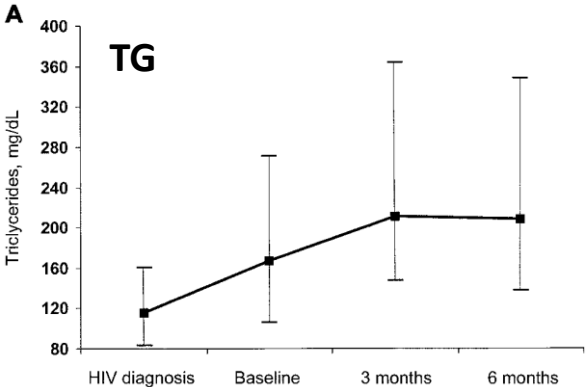
TB/DB 4.33/0.95 mg/dL
AST/ALT 51/66 U/L

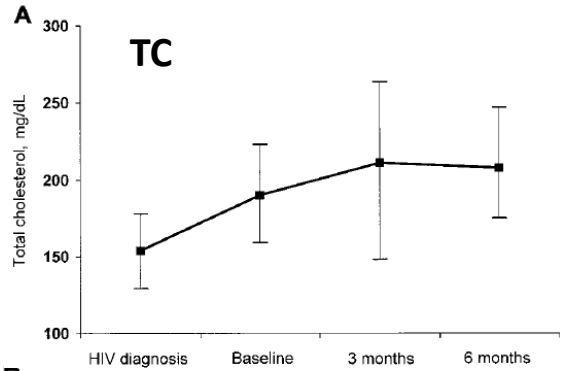
Trement
AZT/3TC+ATV+RTV
Metformin 500 mg 2x2 po pc
Glipizide 5 mg 1x1 po ac
Gemfibrozil 600 mg 1x1

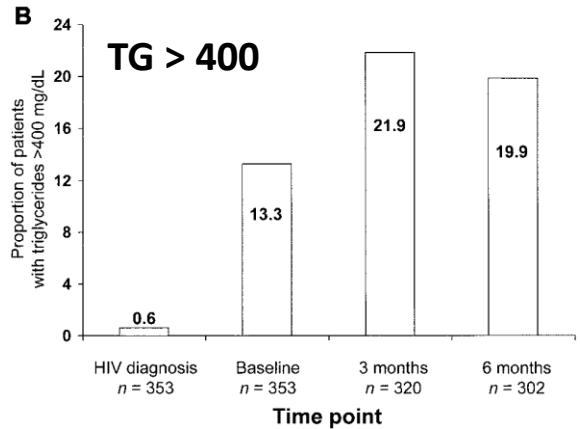
What is the most appropriate management ?

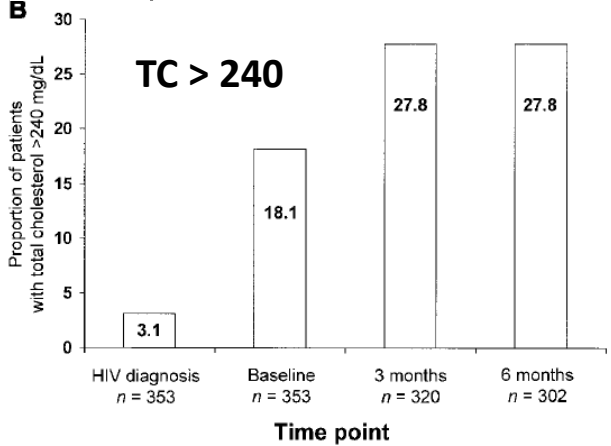
Lopinavir-Ritonavir and Metabolic Abnormalities

353 PLWHs who received LPV/r containing regimen (combine with d4T > 50%)









Hyperlipidemia; TG and TC

Unfavorable lipid profile >> ATV, DRV

Martinez E et al. CID, 2004

Effects of switching from LPV/r to ATV/r

- **Significantly ↓ triglyceride** (treatment effect 18264 mg/dl, ATV/r vs. LPV/r, P = 0.02)
- **Significantly ↓ total cholesterol** (treatment effect 23 8 mg/dl, ATV/r vs. LPV/ r, P = 0.01)

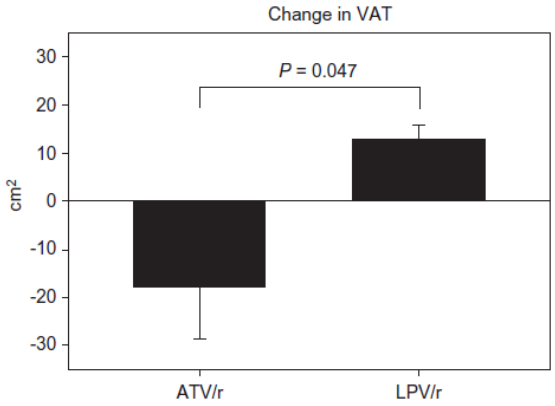
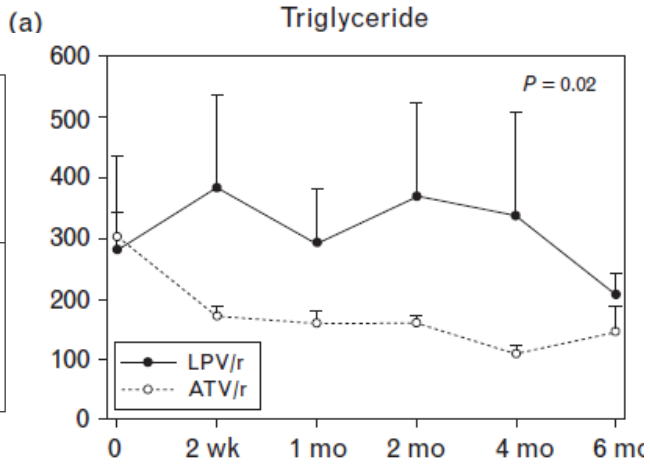
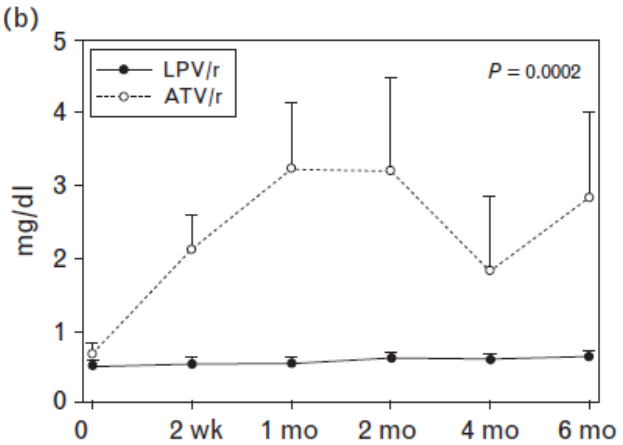


Fig. 1. Change in visceral adipose tissue after 6 months in each treatment group. $P = 0.047$ for comparison between groups by Student's t-test.

Change in visceral fat tissue



↓ TG

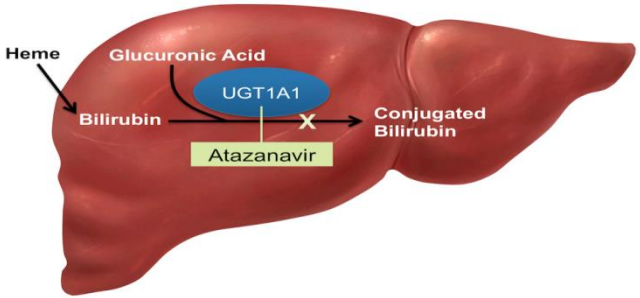


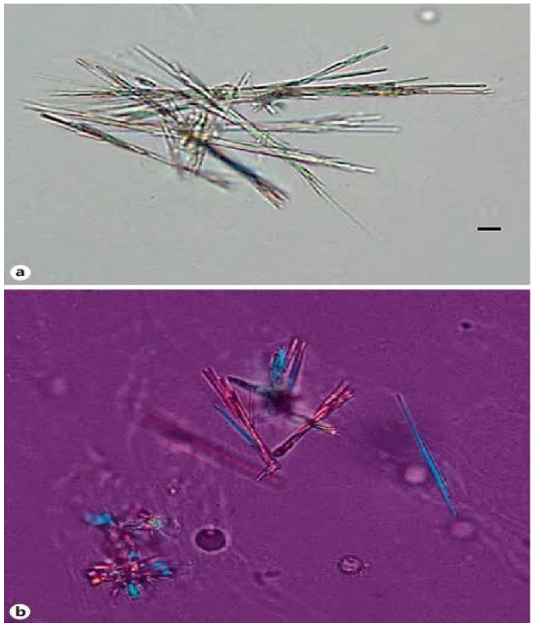
↑ Bilirubin

Stanley TL et al. AIDS, 2009

Atazanavir

- **Hyperbilirubinemia;**
  - **Cosmetic concern**
  - **Indirect bilirubin**
- **Cholelithiasis**
  - Uncommon or rare occurrence
- **Nephrolithiasis**
  - 1% of patients
  - Occurs, on average, 2 years after starting
  - Rod-shaped crystal in urine
  - **ATZ-calcium phosphate**
  - **Radiolucent**



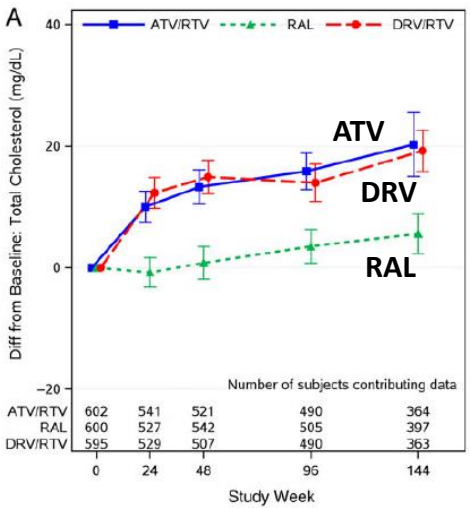


Inagagi I et al. Urologia internationalis 2013

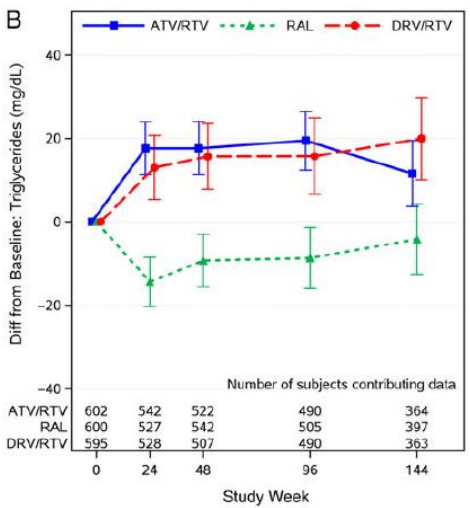
https://www.hiv.uw.edu/

Comparison of the Metabolic Effects of RTV-Boosted DRV or ATV

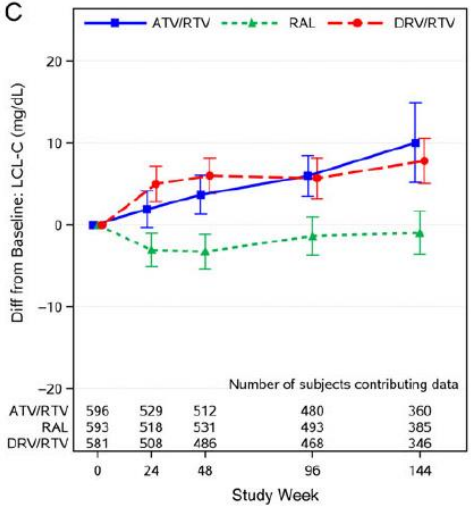
- 1797 subjects with baseline fasting data (ACTG 5257)
- Metabolic profile week 0 to 144



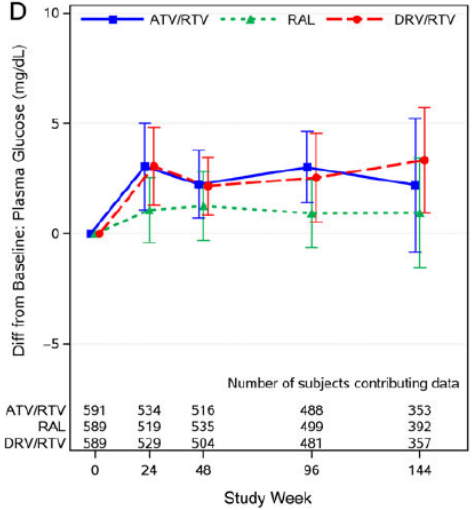
Total Cholesterol



Triglyceride



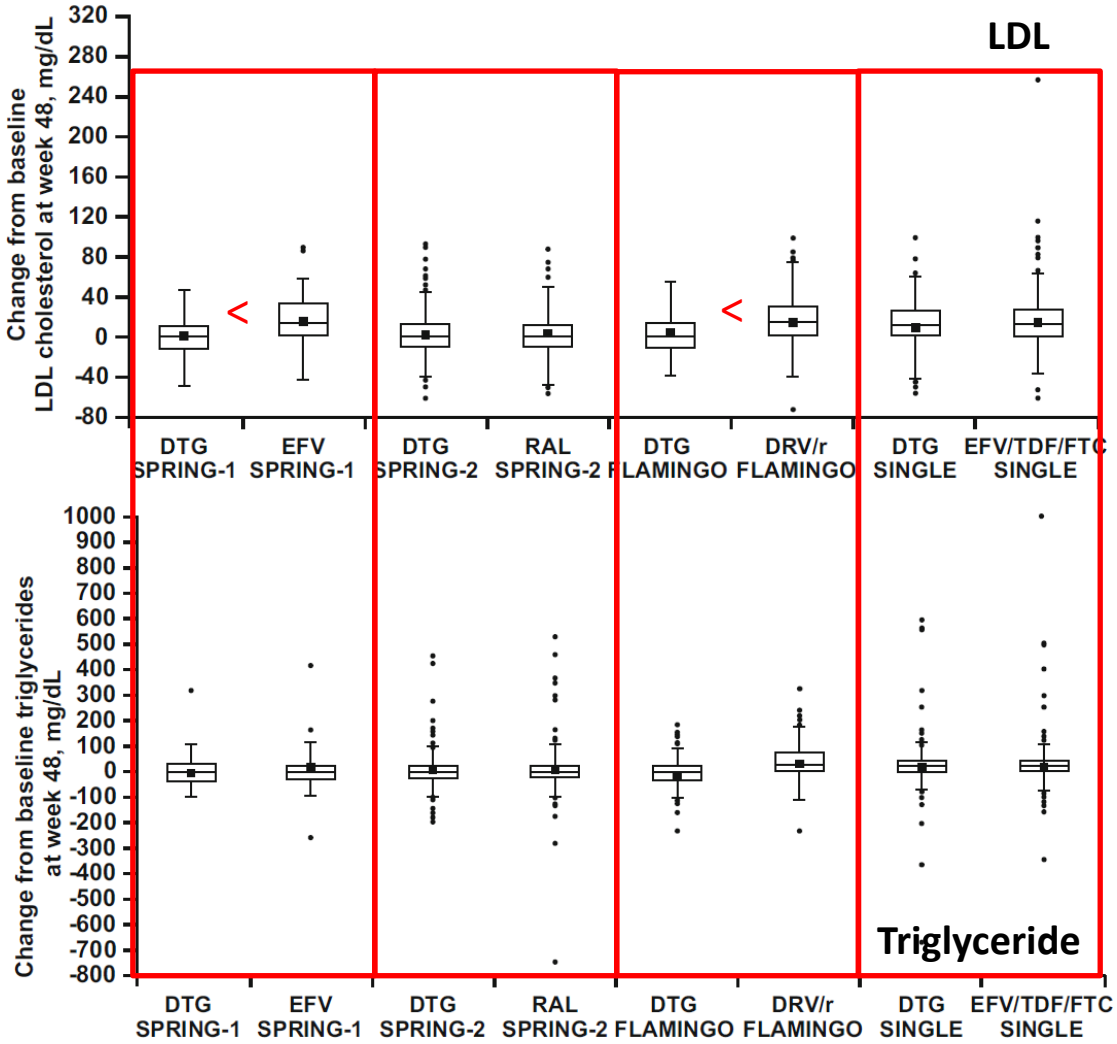
LDL



FBS

- Comparable increases occurred in TC, TG, and LDL with the boosted Pis
- Each PI had greater increases relative to raltegravir (all P ≤ .001 at week 96)

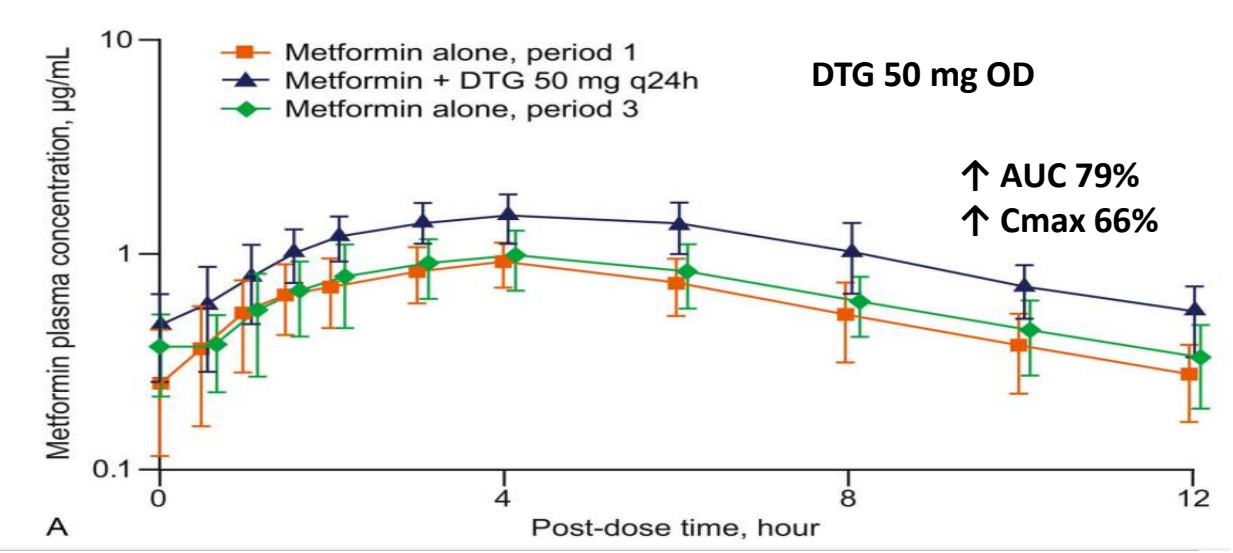
Ofotokun I et al. CID, 2015

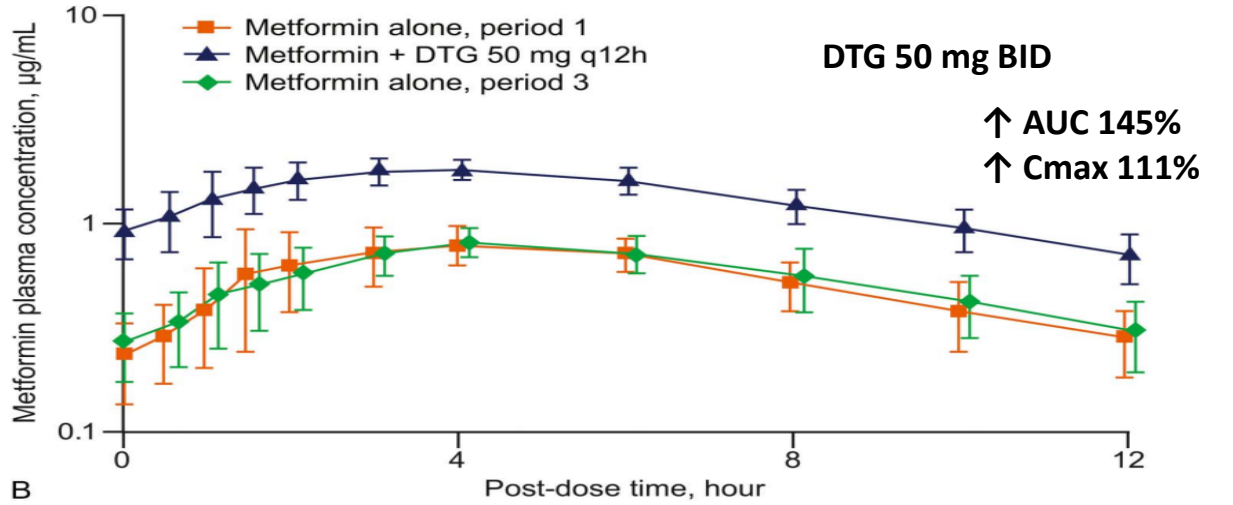


Lipid Outcomes of INSTI, EFV and DRV/r

- Lipid outcomes at 48 weeks in ART-naïve participants in four phase IIb–IIIb clinical trials
- *DTG* shows a broadly neutral effect on lipids vs *EFV and DRV*
- DTG exhibited smaller increases in TC, LDL-C, and TG (similar to RAL)

Quercia R et al. Clin Drug Investig, 2015





DTG and MFM

Mean plasma concentration–time profiles of metformin (500 mg q12h) administered with and without DTG

Period 1: metformin alone (5 d)
Period 2: metformin plus DTG (7 d)
Period 3: metformin alone (10 d)

lactic acidosis associated with plasma level > 5 mg/mL

Should not be coadministered with MFM > 1000 mg/day

Aim in this pt.: switch to DRV/c

Song IH et al. JAIDS, 2016

Case 4 : A 58-year-old man

Dx HIV infection in 2558,
pulmonary TB, no other OI, MDD

TDF/FTC
NVP

Oct/2561
CD4 350 cells/µL (20)
VL < 20 copies/mL
Cr rising from 1.1 to 1.5
CrCl 50 min/mL

ABC/3TC + NVP

Generalized MP rash

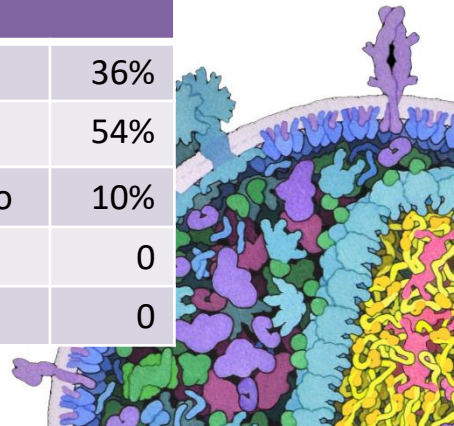
AZT/3TC + NVP

At the 3rd month
Dyspnea on exertion

What is the most appropriate management ?

Blood Chemistry and UA			
Cr	1.5 mg/dL	PO_4	1.8 mg/dL (2.5-4.5)
Na	134 mg/dL	Ca	8.2 mg/dL
K	3.6 mg/dL	Mg	2.5 mg/dL
Cl	100 mg/dL	FBS	90 mg/dL
CO_2	24 mg/dL	UA	normal

CBC			
WBC	2300 cells/µL	Neu	36%
Hb	6.2 g/L	Lym	54%
Hct	16.9%	Mono	10%
MCV	115.8 fL	Eo	0
Plt	248000 cells/µL	Ba	0



Abacavir

- **Hypersensitivity Reaction**
  - Related to **HLA-B*5701**
  - Develop within 6 weeks of starting abacavir (**median onset is 11 days**)
  - Fever, rash, malaise, gastrointestinal effects, and respiratory symptoms
  - More frequently in Caucasians than African Americans

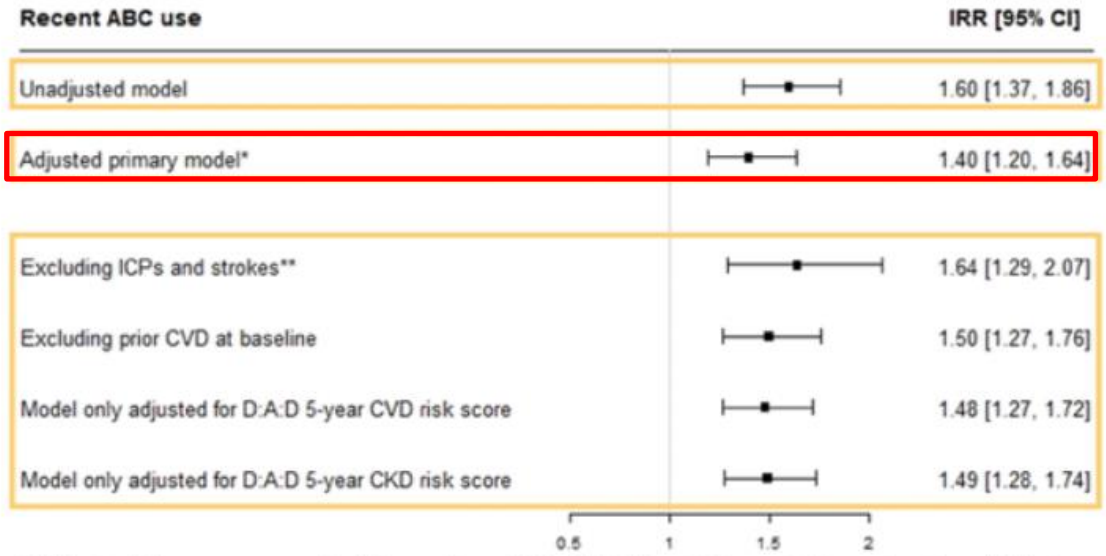
- **Other side effects**
  - > 10% Nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders

https://www.hiv.uw.edu/
Clinicalinfo.hiv.gov

Abacavir and CVD disease: RESPOND Cohort Consortium

- N= 29304, 2012, Denmark
- Median age 44 years old
- **34% were recently using ABC**; of those, 32% were on bPI
- Median F/U 6.16 years

Incidence rate ratios (IRR) of CVD: recent ABC use compared to no recent ABC use



*Adjusted for age, sex, ethnicity, region, BMI, HIV risk, CD4 count, hypertension, diabetes, AIDS, CVD, CKD, dyslipidemia (all fixed at baseline), calendar year, smoking status, exposure to INSTI, cumulative exposure to boosted lopinavir and darunavir, indinavir, didanosine and stavudine (all time updated)

**Only adjusted for age, CD4 nadir, smoking status and prior CVD

Josephine N et al. 18th EACS 2021 Oct 27-30 virtual & London, UK

Haematological Changes in Adults Receiving a AZT-Containing ARV Regimen

- Prospective cohort study in Abidjan, Ivory Coast, 498 adults, 6 months

Table 2. Lowest neutrophil count and haemoglobin level during follow-up, by baseline values of neutrophil count and haemoglobin

Baseline absolute neutrophil count	Total *n* (%)	Lowest absolute neutrophil count during follow-up				
		≥1500	1000–1499	750–999	500–749	<500
≥1500/mm³, *n* (%)	297 (100)	74 (25)	121 (41)	53 (18)	38 (13)	11 (4)
1000–1499/mm³, *n* (%)	146 (100)	7 (5)	42 (29)	49 (34)	34 (23)	14 (10)
750–999/mm³, *n* (%)	45 (100)	4 (9)	9 (20)	11 (24)	11 (24)	10 (22)
500–749/mm³, *n* (%)	9 (100)	0 (0)	0 (0)	2 (22)	5 (56)	2 (22)
<500/mm³, *n* (%)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Overall, *n* (%)	498 (100)	85 (17)	172 (35)	115 (23)	88 (18)	38 (8)

Baseline haemoglobin	Total *n* (%)	Lowest haemoglobin during follow-up				
		≥105	95–104	80–94	65–79	<65
≥105/g/l, *n* (%)	345 (100)	255 (74)	61 (18)	20 (6)	4 (1)	5 (1)
95–104/g/l, *n* (%)	89 (100)	24 (27)	40 (45)	23 (26)	0 (0)	2 (2)
80–94/g/l, *n* (%)	54 (100)	6 (11)	18 (33)	18 (33)	10 (19)	2 (4)
65–79/g/l, *n* (%)	10 (100)	0 (0)	0 (0)	6 (60)	3 (30)	1 (10)
Overall, *n* (%)	498 (100)	285 (57)	119 (24)	67 (13%)	17 (3%)	10 (2%)

Moh R et al. Antiviral Therapy. 2005

Position of 2-drug Regimens in HIV Clinical Guidelines

Naïve-to-ART Patients

	GeSIDA	EACS	DHHS	Observations
DTG + 3TC	Recommended	Recommended	Recommended	HbS Ag-negative HIV VL < 500,000 copies/mL CD 4 count > 200 cells/mm^3 HIV VL < 100,000 copies/mL
RAL + bDRV	Not recommended	Alternative	Alternative	
bDRV + 3TC	Not recommended	Not recommended	Alternative †	

Simplification in Virologically Suppressed Patients

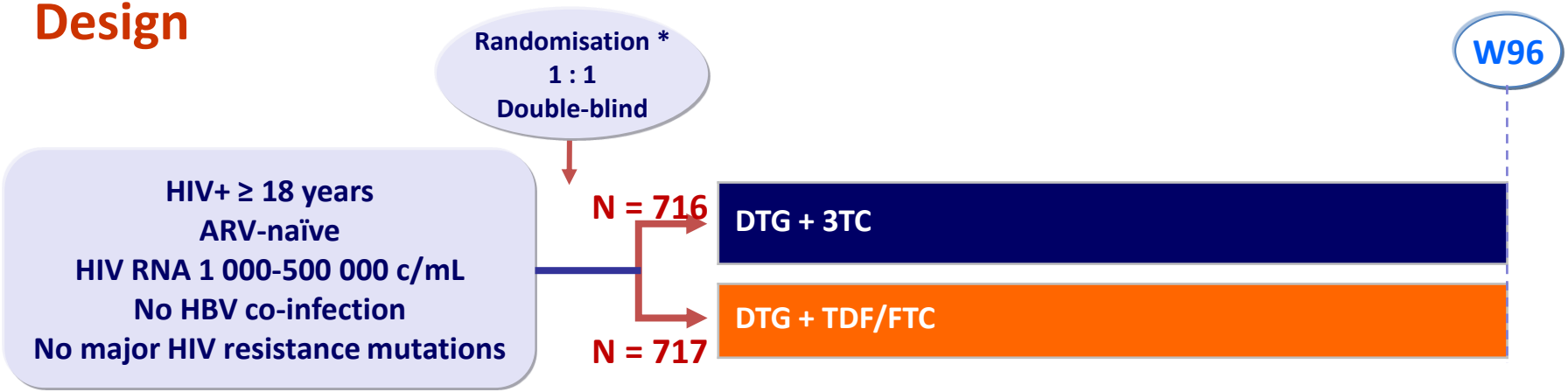
	GeSIDA	EACS	DHHS	Observations
DTG + RPV	Recommended	Recommended	Recommended	
DTG + 3TC	Recommended	Recommended	Recommended	
bPI + 3TC	Alternative	Recommended	Alternative ‡	‡ DRV is preferred over LPV and ATV
DTG + bDRV	Recommended	Alternative	Alternative	
bDRV + RPV	Not recommended	Alternative	Not recommended	

ART: anti-retroviral treatment; GeSIDA: Grupo de estudio del SIDA; EACS: European AIDS Clinical Society; DHHS: Department of Health and Human Services; HbS Ag: hepatitis B surface antigen; HIV VL: human immunodeficiency virus viral load; DTG: dolutegravir; 3TC: lamivudine; RAL: raltegravir; bDRV: boosted-darunavir; RPV: rilpivirine; bPI: boosted-protease inhibitor; DRV: davunavir; LPV: lopinavir; ATV: atazanavir. † If chronic kidney disease is present, and only DRV/r.

Pérez-González A et al. Microorganisms **2022**

GEMINI 1 & 2 Studies: DTG + 3TC vs DTG + TDF/FTC in first-line

Design



* Randomisation stratified by HIV RNA (≤ or > 100 000 c/mL) and CD4 (≤ or > 200/mm^3)

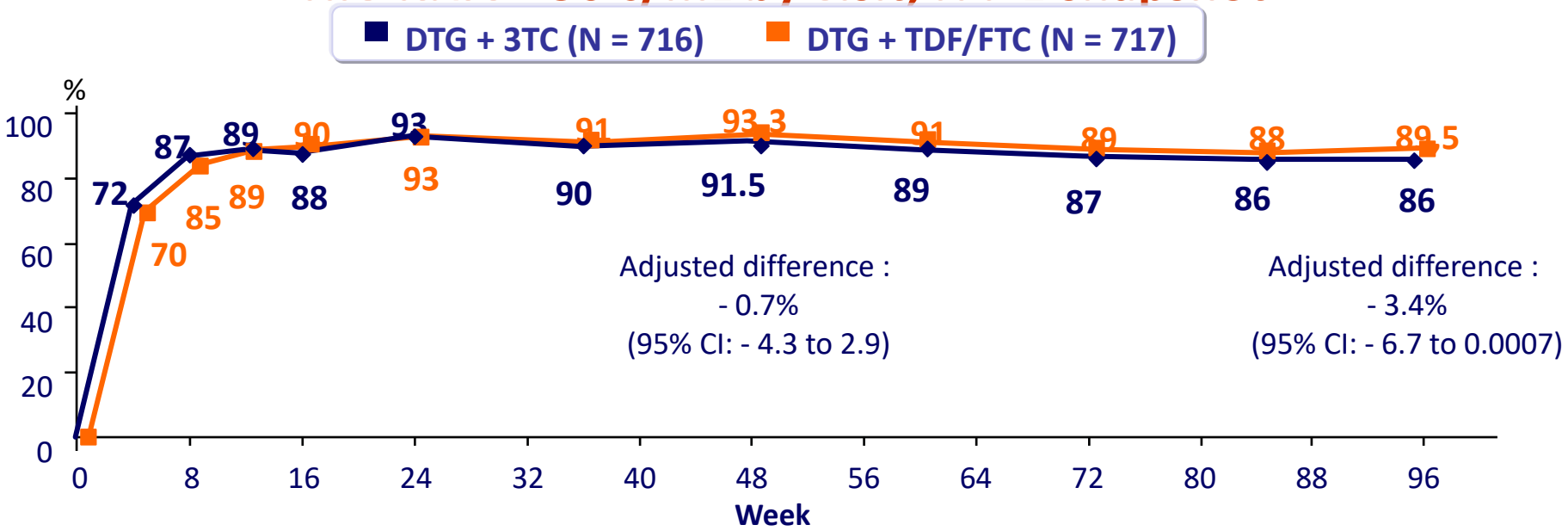
Primary endpoint

- 2 parallel studies (GEMINI-1 and GEMINI-2), each with a combined number of 710-720 patients and similar endpoint
- Proportion of patients with HIV RNA < 50 c/mL at W48, ITT-E analysis, snapshot algorithm ; non-inferiority if lower margin of a one-sided 97.5% CI for the difference = - 10%, 90% power

Cahn P. Lancet. 2019; 393(10167):143-155

GEMINI 1 & 2 Studies: DTG + 3TC vs DTG + TDF/FTC in first-line

HIV RNA < 50 c/mL by visit, ITT-E snapshot



- Mean adjusted increase in CD4 between baseline and W48
  - DTG + 3TC: + 224/mm^3
  - DTG + TDF/FTC: + 218/mm^3

GEMINI

Cahn P. Lancet. 2019; 393(10167):143-155; Cahn P, IAS 2019, Abs. WEAB0404LB

Position of 2-drug Regimens in HIV Clinical Guidelines

Naïve-to-ART Patients				
	GeSIDA	**EACS**	**DHHS**	**Observations**
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RAL + bDRV	Not recommended	Alternative	Alternative	
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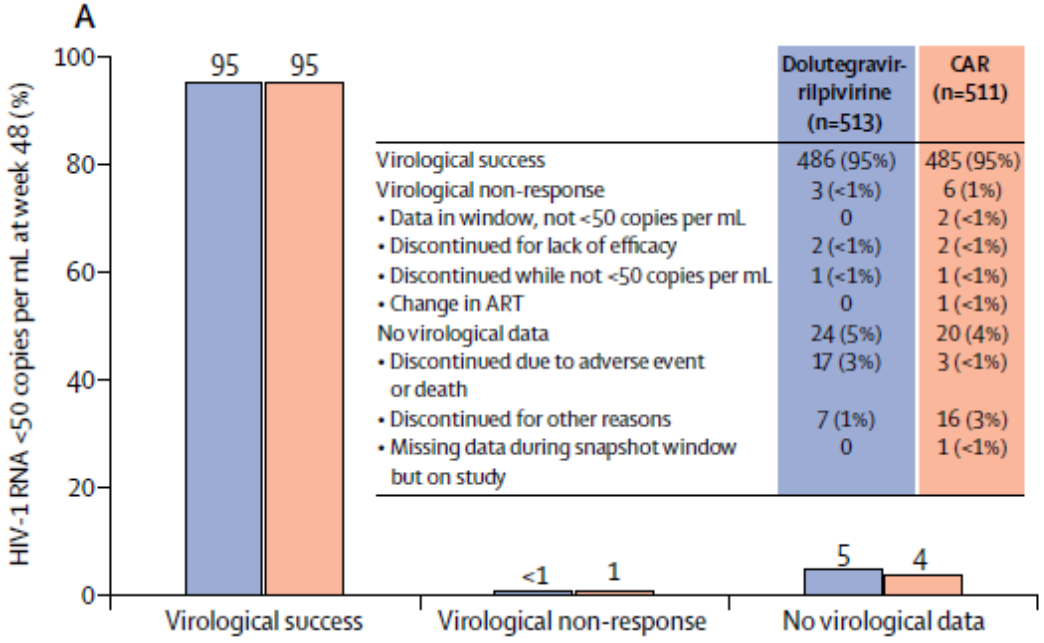
bPI + 3TC	Alternative	Recommended	Alternative ‡	‡ DRV is preferred over LPV and ATV
DTG + bDRV	Recommended	Alternative	Alternative	
bDRV + RPV	Not recommended	Alternative	Not recommended	

ART: anti-retroviral treatment; GeSIDA: Grupo de estudio del SIDA; EACS: European AIDS Clinical Society; DHHS: Department of Health and Human Services; HbS Ag: hepatitis B surface antigen; HIV VL: human immunodeficiency virus viral load; DTG: dolutegravir; 3TC: lamivudine; RAL: raltegravir; bDRV: boosted-darunavir; RPV: rilpivirine; bPI: boosted-protease inhibitor; DRV: davunavir; LPV: lopinavir; ATV: atazanavir. † If chronic kidney disease is present, and only DRV/r.

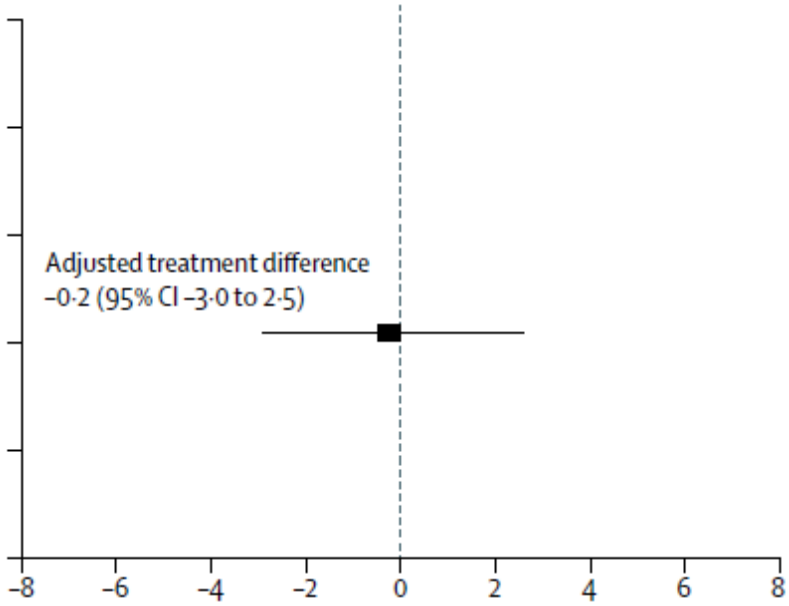
Pérez-González A et al. Microorganisms **2022**

DTG+RPV vs 3 Drugs: SWORD-1 and SWORD-2 studies

- Stable plasma HIV-1 RNA (viral load <50 copies/mL) for 6 months or longer at screening.



	Dolutegravir-rilpivirine (n=513)	CAR (n=511)
Virological success	486 (95%)	485 (95%)
Virological non-response	3 (<1%)	6 (1%)
• Data in window, not <50 copies per mL	0	2 (<1%)
• Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
• Discontinued while not <50 copies per mL	1 (<1%)	1 (<1%)
• Change in ART	0	1 (<1%)
No virological data	24 (5%)	20 (4%)
• Discontinued due to adverse event or death	17 (3%)	3 (<1%)
• Discontinued for other reasons	7 (1%)	16 (3%)
• Missing data during snapshot window but on study	0	1 (<1%)



DTG-RPV was non-inferior to current ART regimen (CAR) over 48 wk in participants with HIV suppression

Llibre JM et al. Lancet, 2018

RPV + DRV/c : PROBE 2 Study

Randomized, open-label, non-inferiority trial, participants had an HIV-RNA <50 copies/mL on a stable (>6 months) 3 drug regimen, N = 80/arm

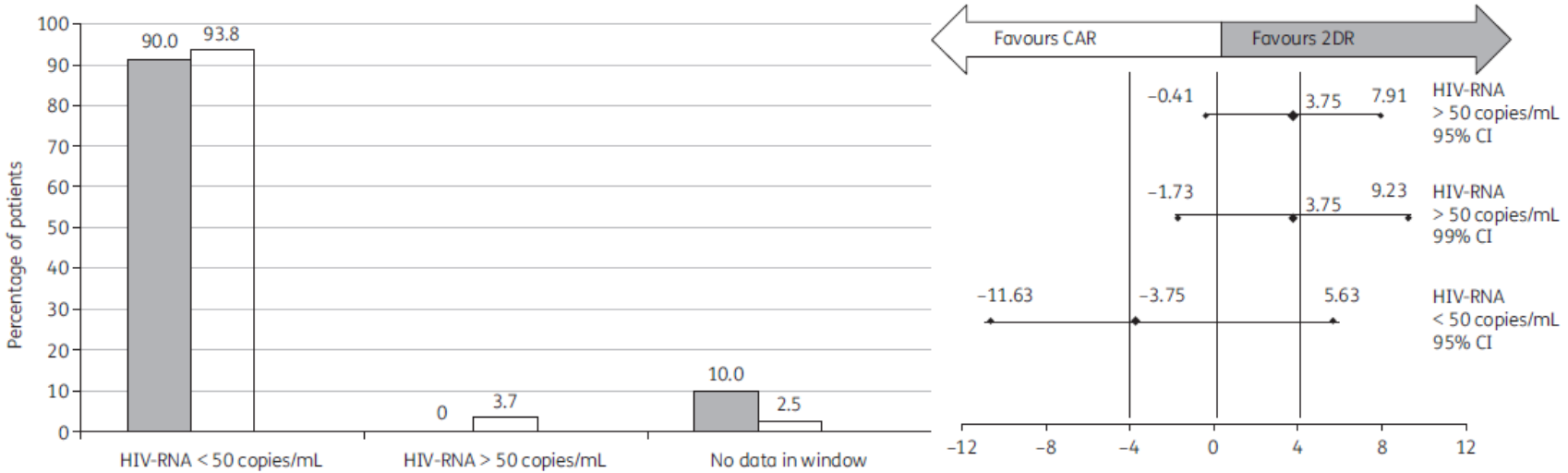


Figure 2. Virological outcomes at Week 24 (US FDA snapshot). 2DR, grey; CAR, white.

Once-daily RPV plus DRV/c is an effective 2DR that combines a high virological efficacy with a potential to avoid major NRTI toxicities

Maggiolo F et al. JAC, 2020

Main clinical trials comparing two- versus three-drug regimens for HIV infection

Clinical Trial	2DR Arm	Comparator	Subject Population	Sample Size	Follow-Up	HIV-RNA ≤ 50 cp/mL, Absolute Risk Difference (95% CI)	Virological Response in 2DR Arm vs. Comparator
GARDEL	LPV/r + 3TC	LPV/r + 2 NRTIs	Naive to ART	214 vs. 202	48 weeks	4.6 (–2.2 to 11.8) †	88.3% vs. 83.7% †
OLE	LPV/r + 3TC	LPV/r + 2 NRTIs	Virologically suppressed	118 vs. 121	48 weeks	1.19 (–7.10 to 9.50) †	88.0% vs. 87.0% †
SALT	ATV/r + 3TC	ATV/r + 2 NRTIs	Virologically suppressed	133 vs. 134	96 weeks	1.39 (–8.50 to 11.30) ‡	69.9% vs. 71.3% ‡
ATLAS-M	ATV/r + 3TC	ATV/r + 2 NRTIs	Virologically suppressed	133 vs. 133	48 weeks	6.77 (–2.20 to 15.70) *	89.5% vs. 79.7% *
DUAL-GESIDA 8014	DRV/r + 3TC	DRV/r + 2 NRTIs	Virologically suppressed	126 vs. 123	48 weeks	–3.79 (–10.90 to 3.30) *	88.9% vs. 92.7% *
SECOND-LINE	LPV/r + RAL	LPV/r + 2 or 3 NRTIs	First-line virological failure	270 vs. 271	48 weeks	1.8 (–4.7 to 8.3) ¶	80.8% vs. 82.6% ¶
SELECT	LPV/r + RAL	LPV/r + 2 or 3 NRTIs	First-line virological failure	260 vs. 255	48 weeks	3.4 (–8.4 to 1.5) ¶	89.7% vs. 87.6% ¶
EARNEST	LPV/r + RAL	LPV/r + 2 or 3 NRTIs	First-line virological failure	433 vs. 426	96 weeks	–0.1 (–5.0 to 4.8) §	64.0% vs. 60.0% §
GEMINI 1 and 2	DTG + 3TC	DTG + FTC/TDF	Naive to ART	719 vs. 722	48 weeks	–1.7 (–4.4 to 1.1) *	91.0% vs. 93.0% *
TANGO	DTG + 3TC	TAF-based 3DR	Virologically suppressed	369 vs. 372	48 weeks	–0.3 (–1.2 to 0.7) *	93.2% vs. 93.0% *
SWORD 1 and 2	DTG + RPV	3DR	Virologically suppressed	516 vs. 512	48 weeks	–0.2 (–3.0 to 2.5) *	95.0% vs. 95.0% *
DUALIS	DTG + bDRV	DRV-based 3DR	Virologically suppressed	131 vs. 132	48 weeks	–1.6 (–9.9 to 6.7) *	86.3% vs. 87.9% *
NEAT001/ANRS 143	RAL + DRV/r	DRV/r + FTC/TDF	Naive to ART	401 vs. 404	123 weeks	4.0 (–0.8 to 8.8) ††	87.6 % vs. 89.7% ††
PROBE-2	bDRV + RPV	3DR	Pre-treated	80 vs. 80	24 weeks	–3.75 (–11.63 to 5.63) *	90.0% vs. 93.8% *
FLAIR	CAB + RPV	DTG/3TC/ABC	Pre-treated	283 vs. 283	48 weeks	0.4 (–3.7 to 4.5) *	93.6% vs. 93.3% *

2DR: two-drug regimen; LPV/r: ritonavir-boosted lopinavir; 3TC: lamivudine; NRTIs: nucleoside/nucleotide reverse transcriptase inhibitors; ATV/r: ritonavir-boosted atazanavir; DRV/r: ritonavir-boosted darunavir; RAL: raltegravir; FTC/TDF: emtricitabine/tenofovir-disoproxil-fumarate; DTG: dolutegravir; TAF: tenofovir alafenamide; 3DR: three-drug regimen; RPV: rilpivirine; bDRV: boosted-darunavir; CAB: cabotegravir; DTG/3TC/ABC: dolutegravir/abacavir/lamivudine. † Intention-to-treat, exposed, snapshot; ‡ Time to loss of virological response (TLOVR); * US Food and Drug administration (FDA) snapshot algorithm; ¶ Custom analysis equivalent to FDA snapshot algorithm; § Custom composite end-point; †† Kaplan–Meier estimated proportions analysis.

Pérez-González A et al. Microorganisms **2022**

Points of Learning

- Case 1: Dolutegravir intolerance
- Case 2: Diagnosis and management of TDF-induced osteomalacia
- Case 3: Metabolis side effect of protease inhibitors
- Case 4: 2-drug regimens