Presente e futuro delle strategie di trattamento dell'infezione da HIV

Lucia Taramasso

Disclosures

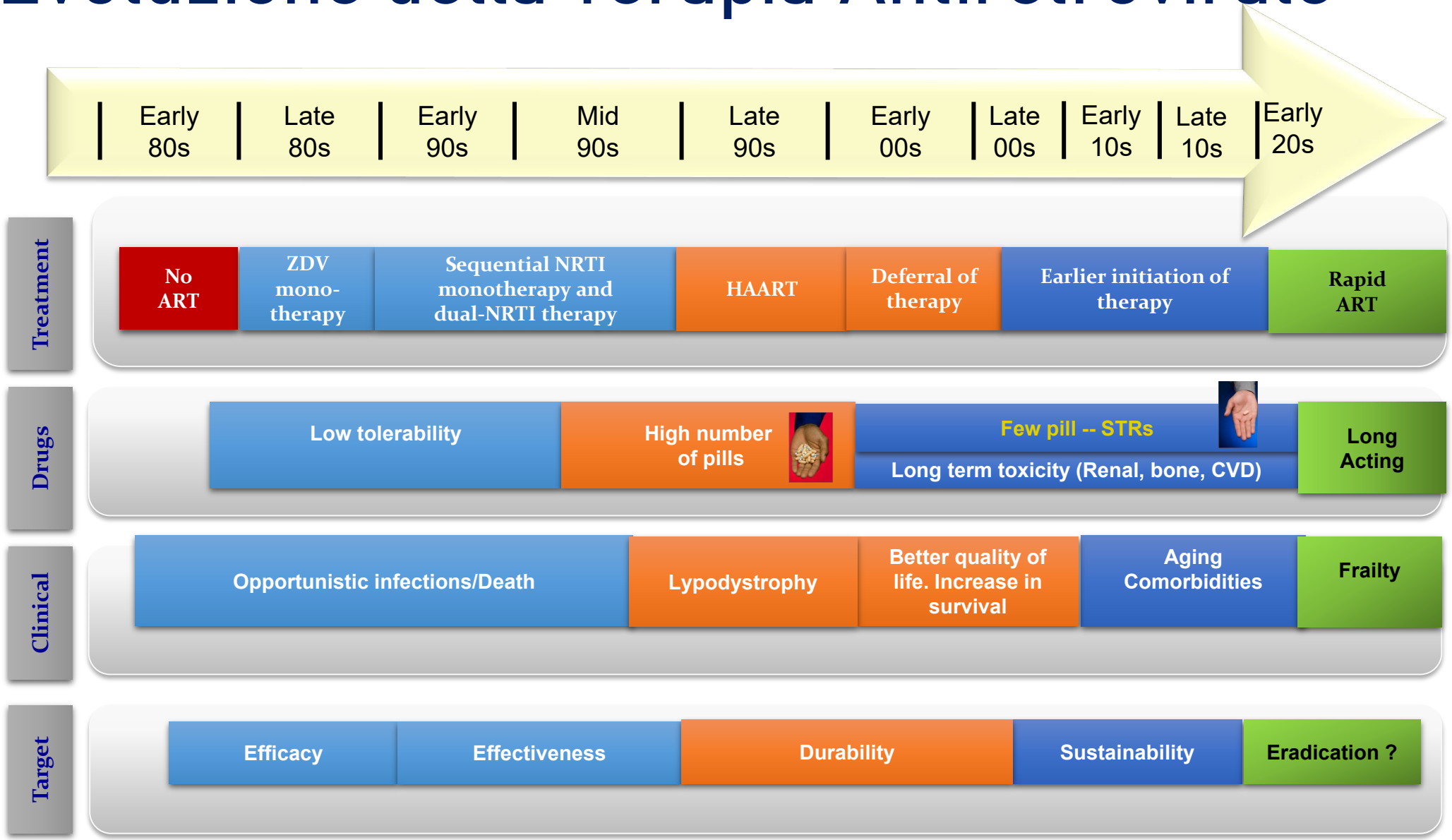
LT attended advisory boards or served as consultant or received grants for conferences participations from Gilead Sciences, ViiV Healthcare and

Janssen and research grant for her institution from Gilead Sciences

Presente delle strategie di trattamento dell'infezione da HIV

- **La prima ART**
- **Il cambio di terapia a viremia controllata**

Evoluzione della Terapia Antiretrovirale



Life Expectancy After HIV Diagnosis 2008–2018, US

Azfar-E-Alam Siddiqi, et al. Abstract 761

- During 2008–2018, overall, the life expectancy for people with diagnosed HIV increased by 4.22 years or 15%
- Yet, the life expectancy for people with diagnosed HIV remains lower than that for the general U.S. population

RESULTS

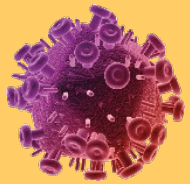
- In 2018, among persons with late-stage disease (HIV Stage 3 [AIDS]) at diagnosis, the LE was considerably lower (27.16 years, CI 27.02–27.31) compared to persons with disease not at stage 3 (34.39 years (CI 34.34–34.43).

Selecting an Optimal ARV Regimen

"The goal of antiretroviral therapy is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen in order to achieve sustained virologic control"

Select Features of an Optimal ARV Regimen[1]

- High Viral Suppression Rates



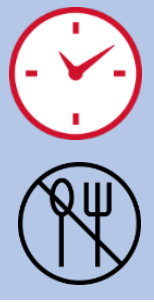
- Low Pill Burden

- Less Toxicity

- Better Tolerability

- Low Drug Interactions Potential

- Convenience



- High Barrier to Resistance

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

La prima ART

Recommended First-line ART Regimens 2020/21

ARV	EACS[1]	US DHHS[2]	IAS-USA[3]	WHO[4]
DTG	DTG + TAF/FTC or TDF/FTC or TDF/3TC	DTG + (TAF or TDF) + (FTC or 3TC)	DTG + TAF/FTC or TDF/FTC or TDF/3TC	DTG + TDF + 3TC (or FTC)
DTG	DTG + ABC/3TC† DTG/ABC/3TC†	DTG/ABC/3TC†	--	--
BIC	BIC/TAF/FTC	BIC/TAF/FTC	BIC/TAF/FTC	
RAL	RAL + TAF/FTC or TDF/FTC or TDF/3TC	--	--	--
DTG	DTG/3TC*	DTG/3TC*	DTG/3TC*	
DOR	DOR + TAF/FTC or TDF/FTC or TDF/3TC DOR/TDF/3TC	--	--	--

*DTG/3TC: Avoid in patients with HBV and HIV-1 RNA >500,000 c/mL; in some guidelines, avoid in those starting ART before results of GT resistance testing are available or with CD4+ cell count <200/µL. †If patient is HLA-B*5701 negative.

1. eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf
2. clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf
3. jamanetwork.com/journals/jama/fullarticle/2771873 4. who.int/publications/i/item/9789240031593

Our choice HAS been driven to avoid Toxicity Profile of Certain ARVs

Class	Agent	Select AEs
NRTI	ABC	Ischemic heart disease
	TDF	↓ BMD, osteomalacia, ↑ fracture risk, ↓ eGFR, Fanconi syndrome
NNRTI	EFV	Depression, sleep disturbance, headache, suicidal ideation
PI	ATV	↓ eGFR, nephrolithiasis
	DRV	Ischemic heart disease, nephrolithiasis
	LPV	Ischemic heart disease, ↓ eGFR

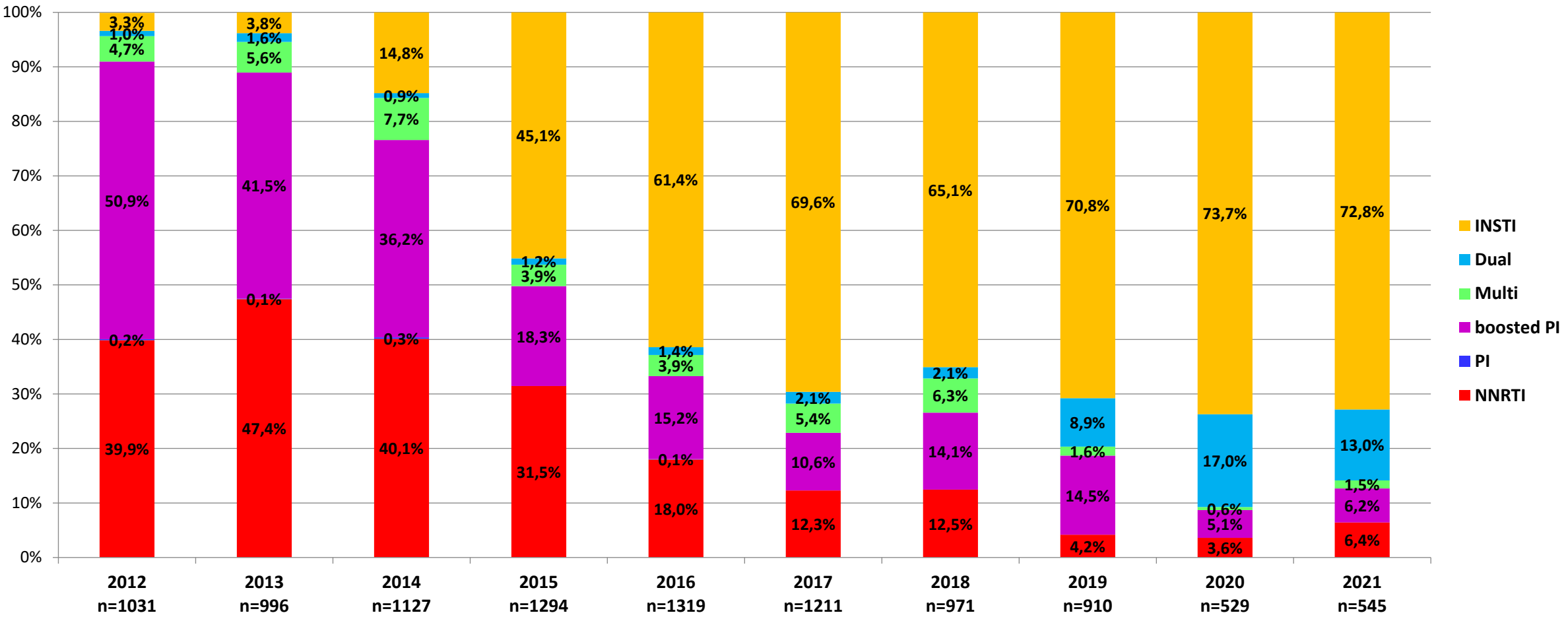
So we have moved towards using INSTIs and TAF

EACS Guidelines. October 2018.

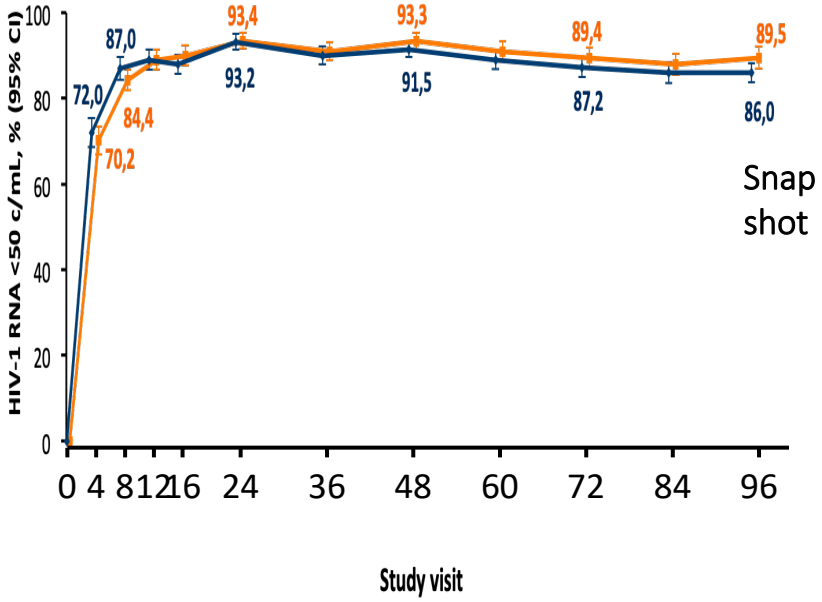
POZNIAK, ICAR 2020

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of usage of different ART classes as third drug in first line regimen according to calendar year of starting



GEMINI-1 AND GEMINI-2, PHASE III STUDY

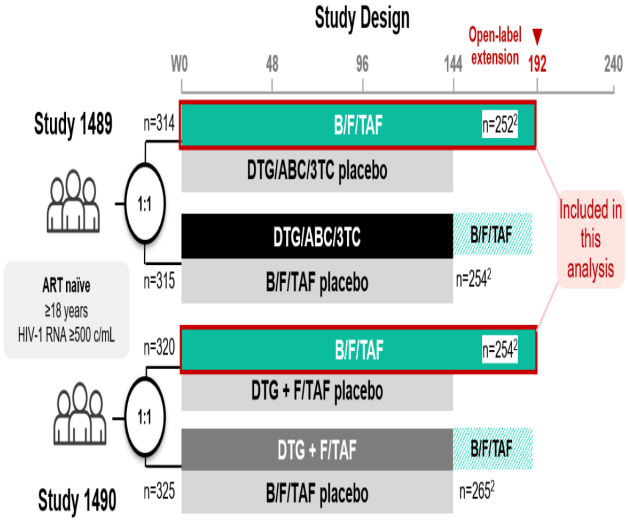


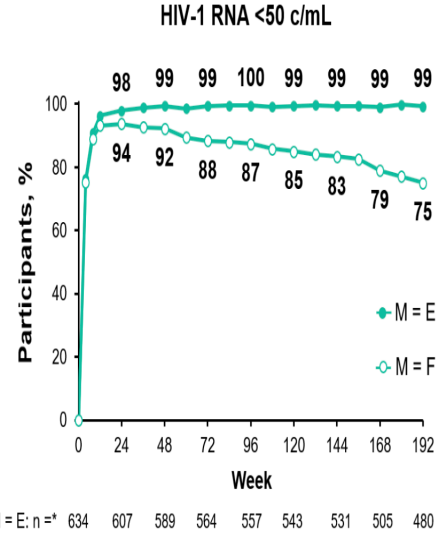
Snap shot

Cahn P, IAS 2019, Abs. WEAB0404LB

Pooled Analysis 1489/1490: B/F/TAF in **ART-Naïve**, W192

4-year Follow-up of B/F/TAF in Treatment-Naïve PLWH





*Participants with non-missing HIV-1 RNA value
M=E, missing=excluded; M=F, missing=failure

High rates of virologic suppression were achieved and maintained through 192W of follow-up

Arribas J, et al. vIAS 2021. PEB151

Il cambio di terapia a viremia controllata

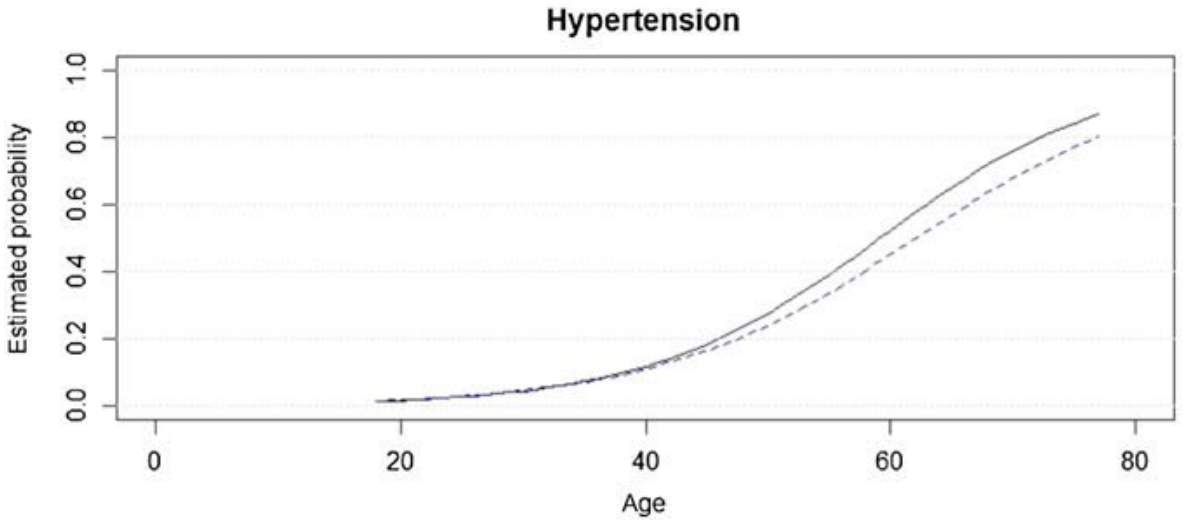
Attenzione

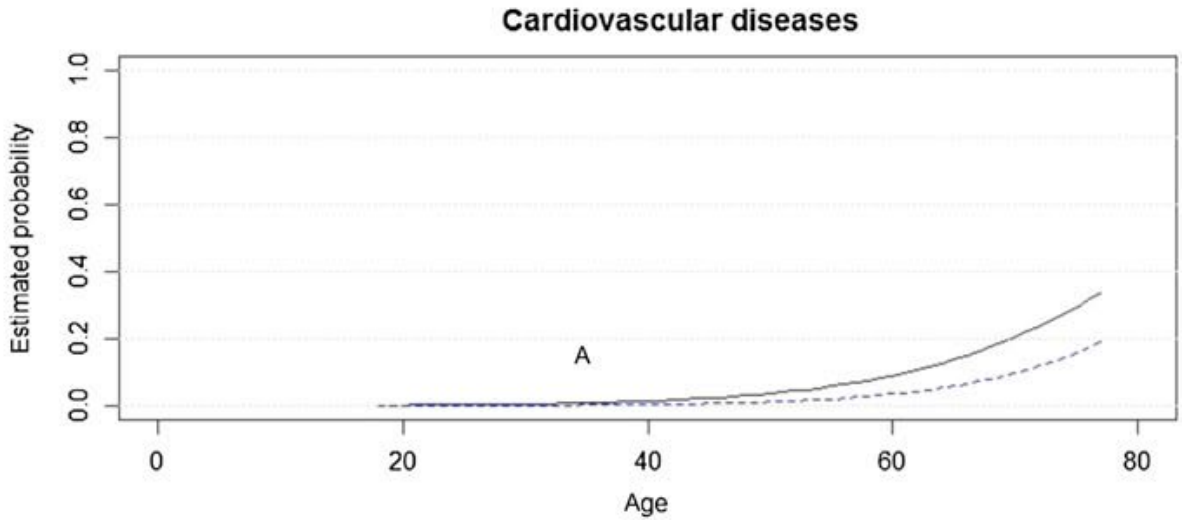
- **Effetti collaterali**
  - **One size does not fit all**
- **Riattivazione di HBV**
  - **TDF o TAF Sparing**
- **Genotipo storico**
  - **Semplificazioni**

CARDIOVASCULAR RISK

Cardiovascular risk

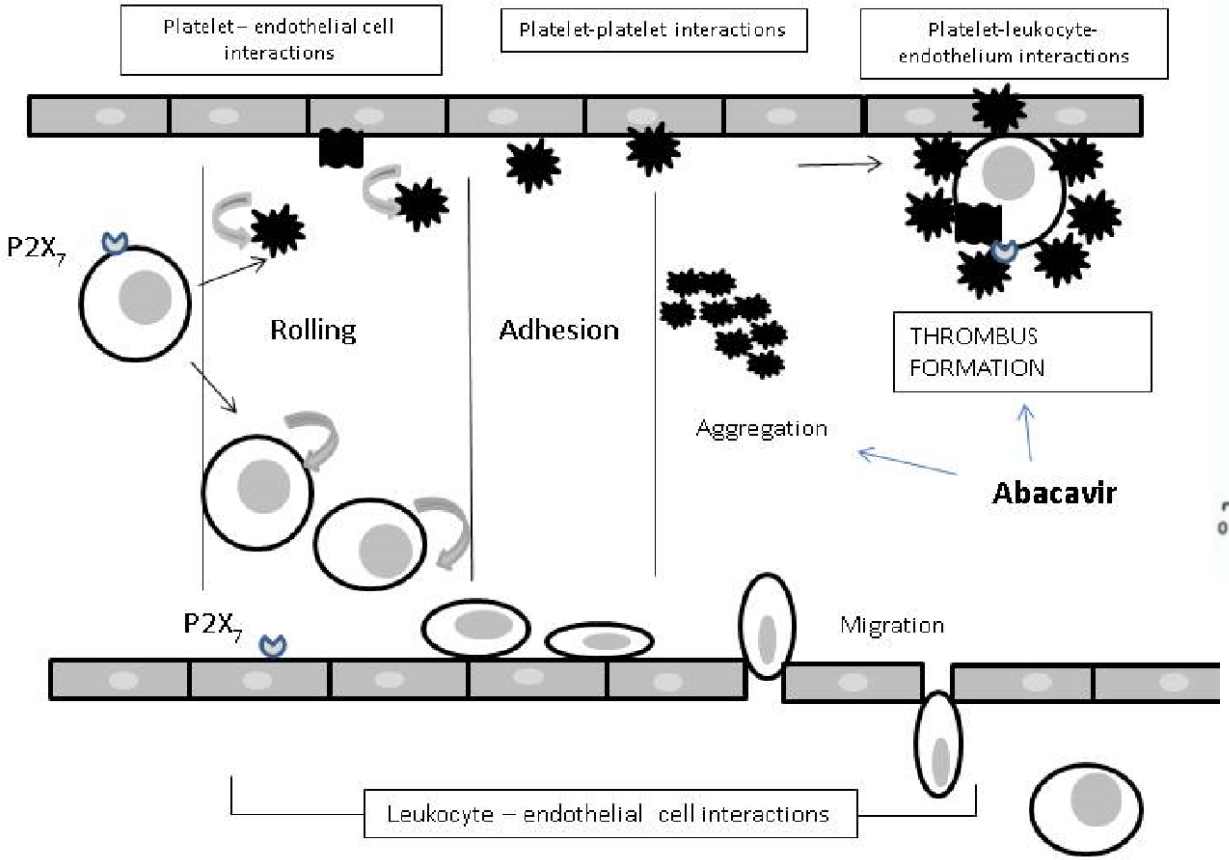
- The median age of people with HIV on ART will increase from 43.9 years in 2010 to 56.5 years in 2030, by which time 78% of people with HIV will have been diagnosed with CVD.
- The increase in RR of myocardial infarction among people with HIV ranges from 20% to 100% compared with people without HIV.
- Eart failure, sudden death and stroke are the CV events with the greatest incremental risk in PLWH.

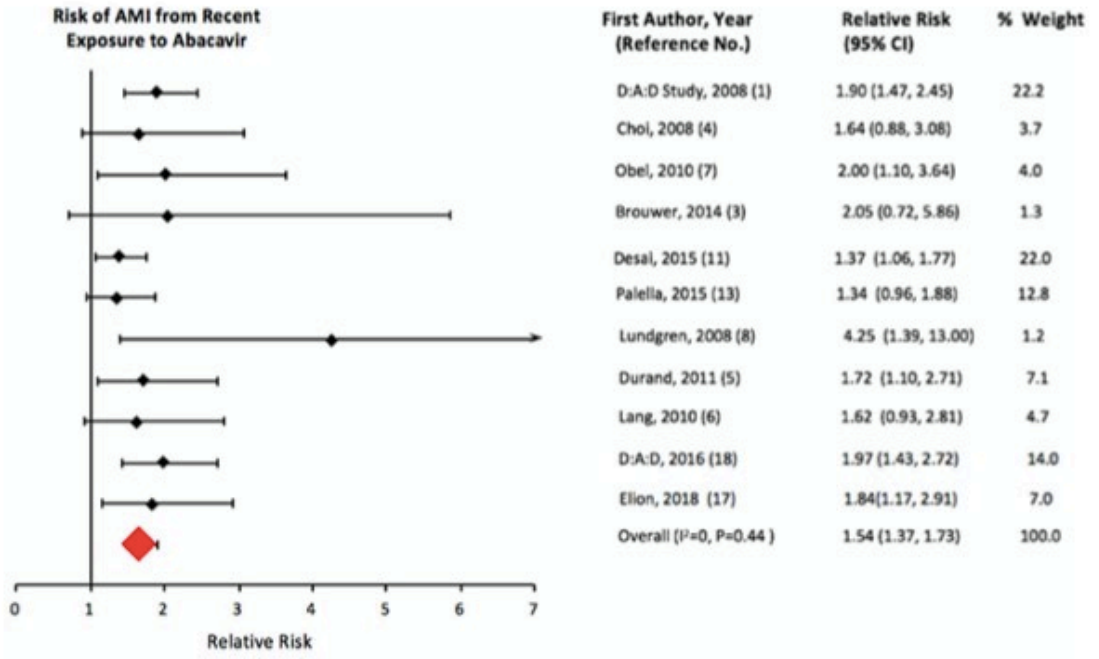


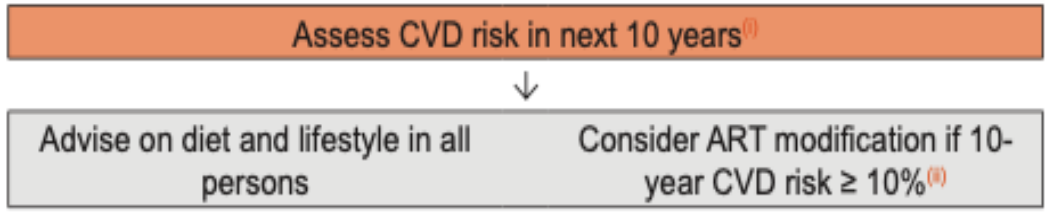


So-Armah K, et al., Lancet HIV 2020; 7: e279–e93. AlonsoA, et al.,J Am Heart Assoc 2019; 8: e012241. Guaraldi G. et al., CID. 2011; 53:1120–1126.

ABACAVIR





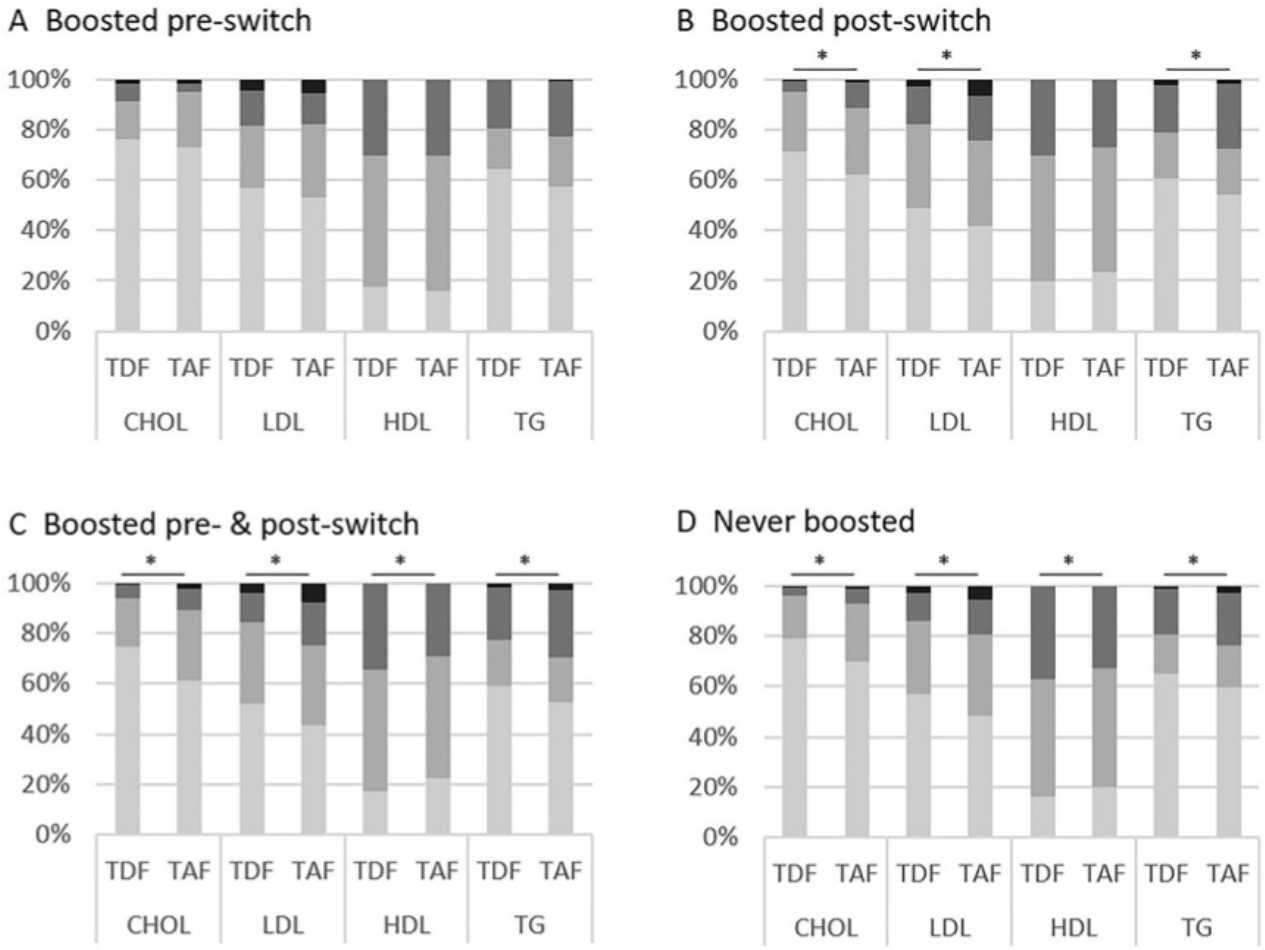


Consider replacing ZDV or ABC with TDF/TAF or use an NRTI- sparing regimen , consider 2DR

Alvarez A, et al., *AIDS.* 2017; 31: 1781-1795; EACS Guidelines 2020, Dorjee et al. J Antimicrob Agents. 2018;52(5):541-553.

TAF and TDF

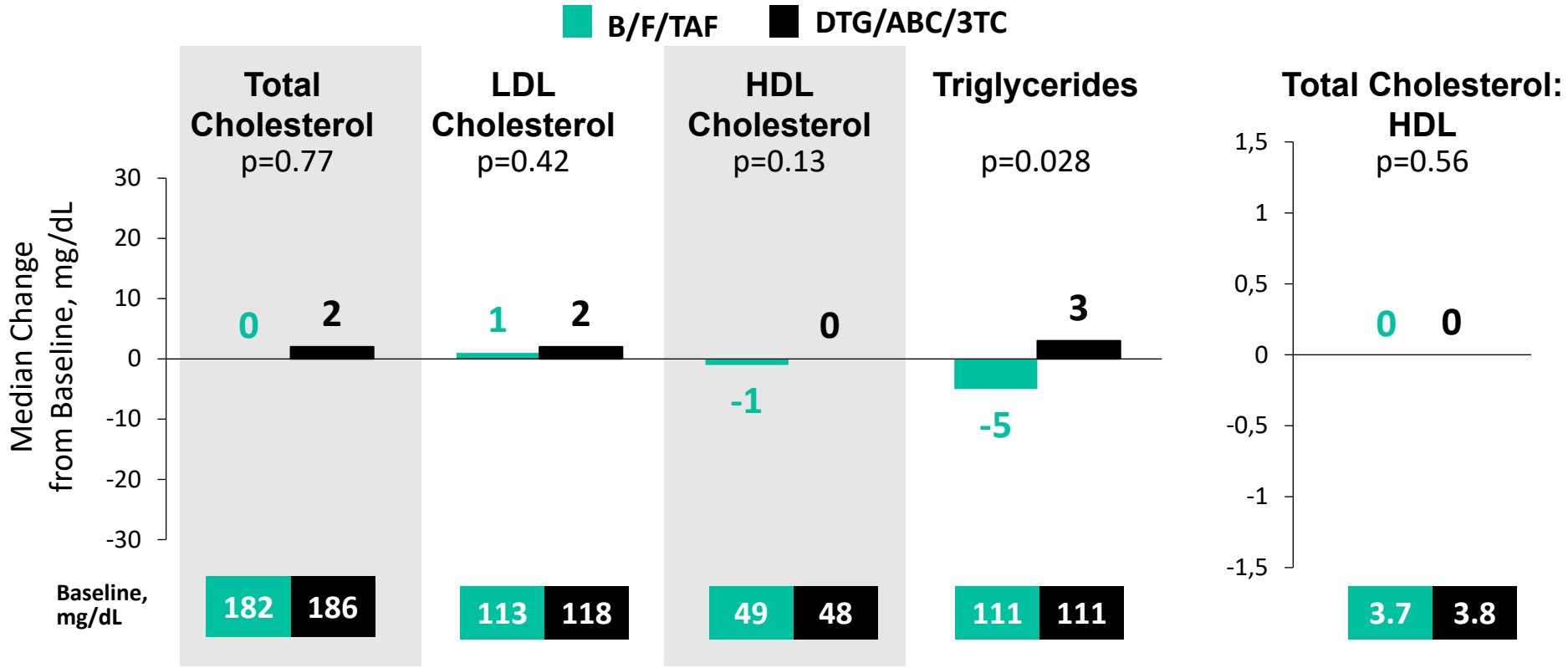
- TDF could have an independent lipid-lowering effect
- The switch from TDF to TAF is associated with less favorable lipid profiles, regardless of pharmaco-enhancers or third-agent use, however, less evident in people with higher lipid levels
- However, TAF per se does not seem to influence lipid profiles



Hemkens LG, et al., HIV Clin Trials. 2015;16(5):178–89; Brunet L , et al., Clinical Drug Investigation. 2021, Online ahead of print; Taramasso L, et al., PLoS One. 2019 Oct 11;14(10):e0223181; Study 1844, https://clinicaltrials.gov/ct2/show/NCT02603120

Study 1844: Suppressed Adults Switched from DTG/ABC/3TC

Changes in Fasting Lipids at Week 48*



No changes in fasting lipid parameters when switching from DTG/ABC/3TC to B/F/TAF

*p-values from 2-sided Wilcoxon rank sum test
HDL, high-density lipoprotein. LDL, low-density lipoprotein.

·Molina JM, et al. CROI 2018. Boston, MA. Oral 22.

Switches from PI or EFV

To BICTEGRAVIR
Study 1878 (N=577)[3]
vs. boosted DRV or ATV + 2 NRTIs

To DOR
Study DRIVE shift
vs. boosted DRV

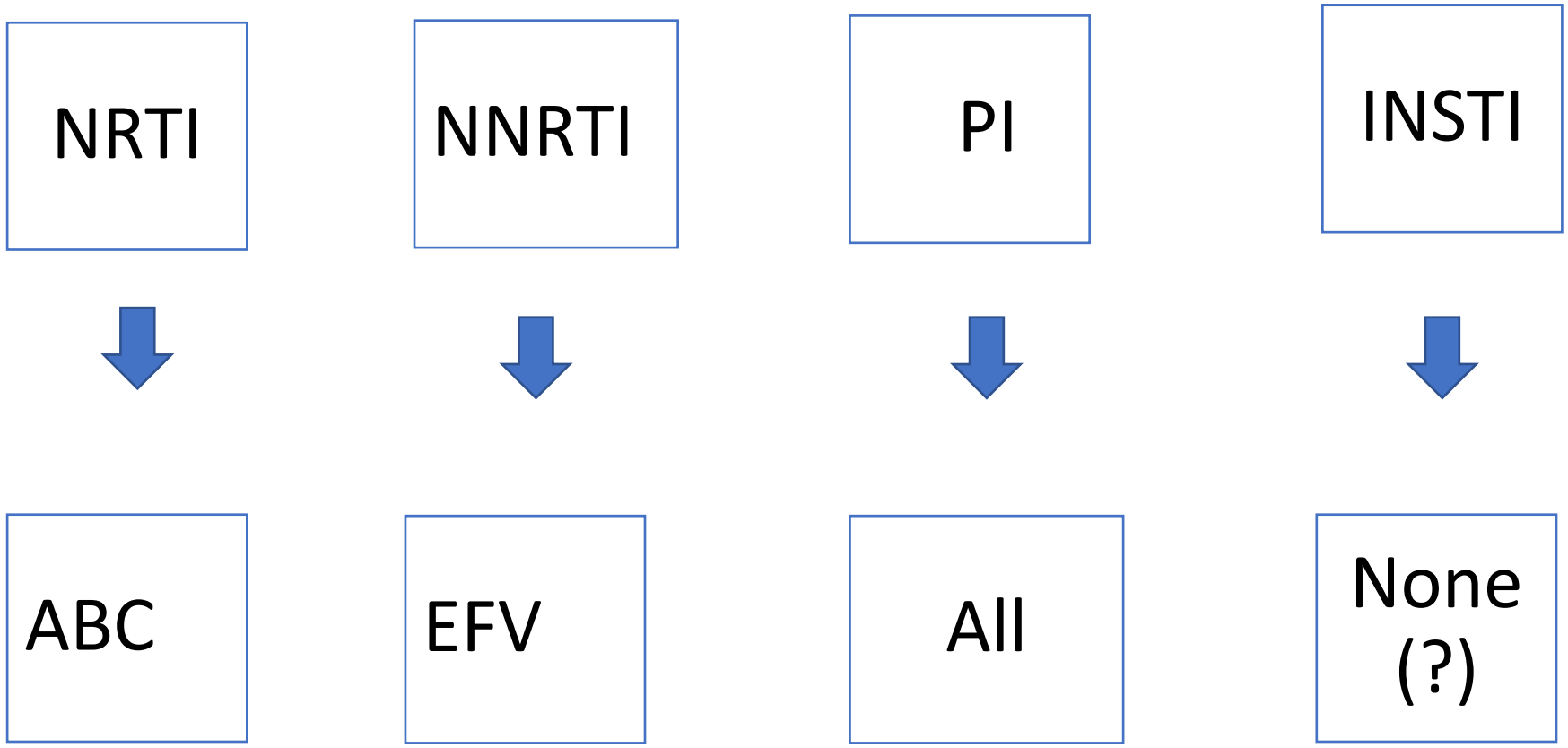
To RPV or INSTI
SCOLTA
Vs any boosted PI or EFV

To RAL
SPIRAL
Vs any boosted PI

To EVG
STRATEGY-PI and STRATEGY-NNRTI
Vs any boosted PI or NNRTI (80% EFV)

To DTG
NEAT022
Vs boosted DRV

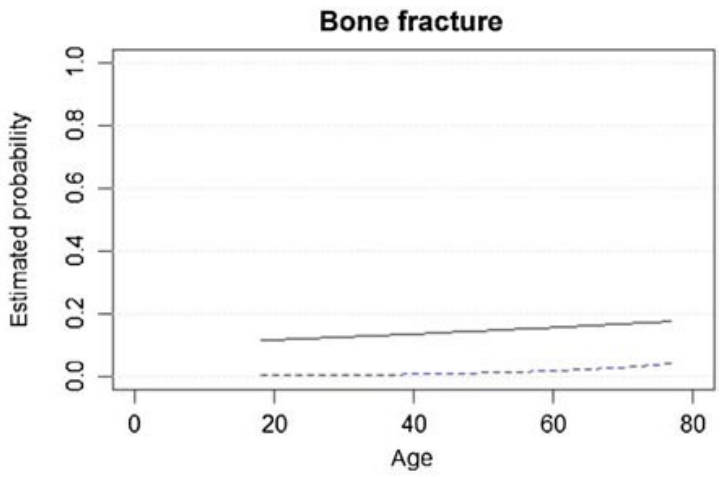
CARDIOVASCULAR

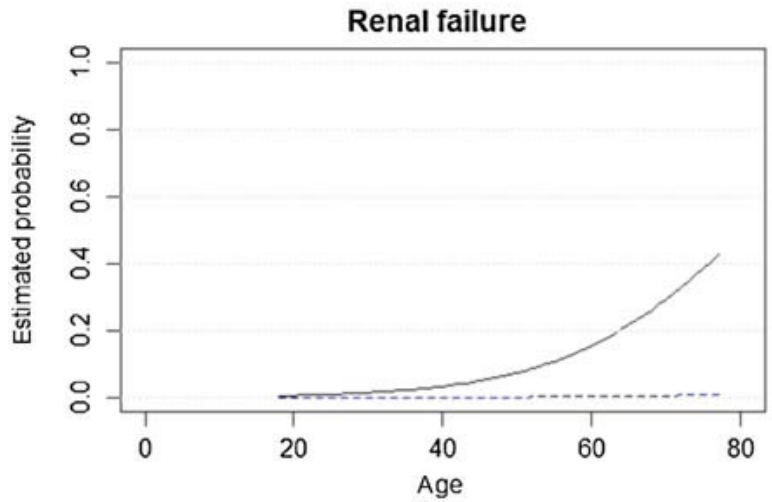


BONE AND KIDNEY

Bone and kidney

- In PLWH, the risks of any fracture and fragility fracture are increased 1.5-fold, whereas the risk of a hip fracture is increased 4-fold compared with uninfected controls.
- CKD is present in approximately 17% of HIV-positive individuals and its incidence increases by 11-fold among those aged 60–69 years old compared with those aged 40 years old.
- CKD is an important risk factor for cardiovascular events and death.





Starup-Linde J, et al., J Acquir Immune Defic Syndr 2020; 83: 1–8. Jotwani V, et al., J Am Soc Nephrol 2017; 28: 3142–54. Guaraldi G. et al., CID. 2011; 53:1120–1126. Yombi JC, et al .AIDS. 2014 Mar 13;28(5):621-32. Choi AI, et al., Circulation 2010; 121:651–658. George E, et al., AIDS 2010; 24:387–394. Campbell LJ, et al. HIV Clin Trials 2012; 13:343–349. Ibrahim F, et al.,Am J Kidney Dis 2012; 60:539–547.

Kidney

- Association of **cumulative** and **ever exposure** to tenofovir on kidney outcomes in 10,841 PLWH from the Veterans Health Administration (1997-2007)
- **Each year** of exposure to TDF was associated with:
  - 34% increased risk of proteinuria (95%CI 25-45, P < 0.0001)
  - 11% increased risk of rapid decline (3-18, P = 0.0033)
  - 33% increased risk of CKD (18-51, P < 0.0001)

Association of tenofovir exposure with risk * of kidney disease outcomes

	Demographic-Adjusted Model†		Time-Dependent Cox Model‡		Marginal Structural Model§	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Cumulative Exposure to Tenofovir (per year)						
Proteinuria *(n=3400 events)*	1.30 (1.22-1.37)	**<0.0001**	1.34 (1.25-1.45)	**<0.0001**	1.24 (1.17-1.32)	**<0.0001**
Rapid decline ** *(n = 3078 events)*	1.17 (1.11-1.24)	**<0.0001**	1.11 (1.03-1.18)	**0.0033**	1.16 (1.09-1.23)	**<0.0001**
CKD *(n=553 events)*	1.44 (1.30-1.60)	**<0.0001**	1.33 (1.18-1.51)	**<0.0001**	1.36 (1.22-1.51)	**<0.0001**
Ever Exposure to Tenofovir						
Proteinuria *(n=3400 events)*	1.70 (1.57-1.85)	**<0.0001**	1.68 (1.52-1.85)	**<0.0001**	1.51 (1.36-1.66)	**<0.0001**
Rapid decline *(n = 3078 events)*	1.51 (1.39-1.64)	**<0.0001**	1.36 (1.23-1.50)	**<0.0001**	1.50 (1.36-1.67)	**<0.0001**
CKD *(n=553 events)*	2.11 (1.76-2.54)	**<0.0001**	1.71 (1.38-2.12)	**<0.0001**	1.88 (1.50-2.36)	**<0.0001**

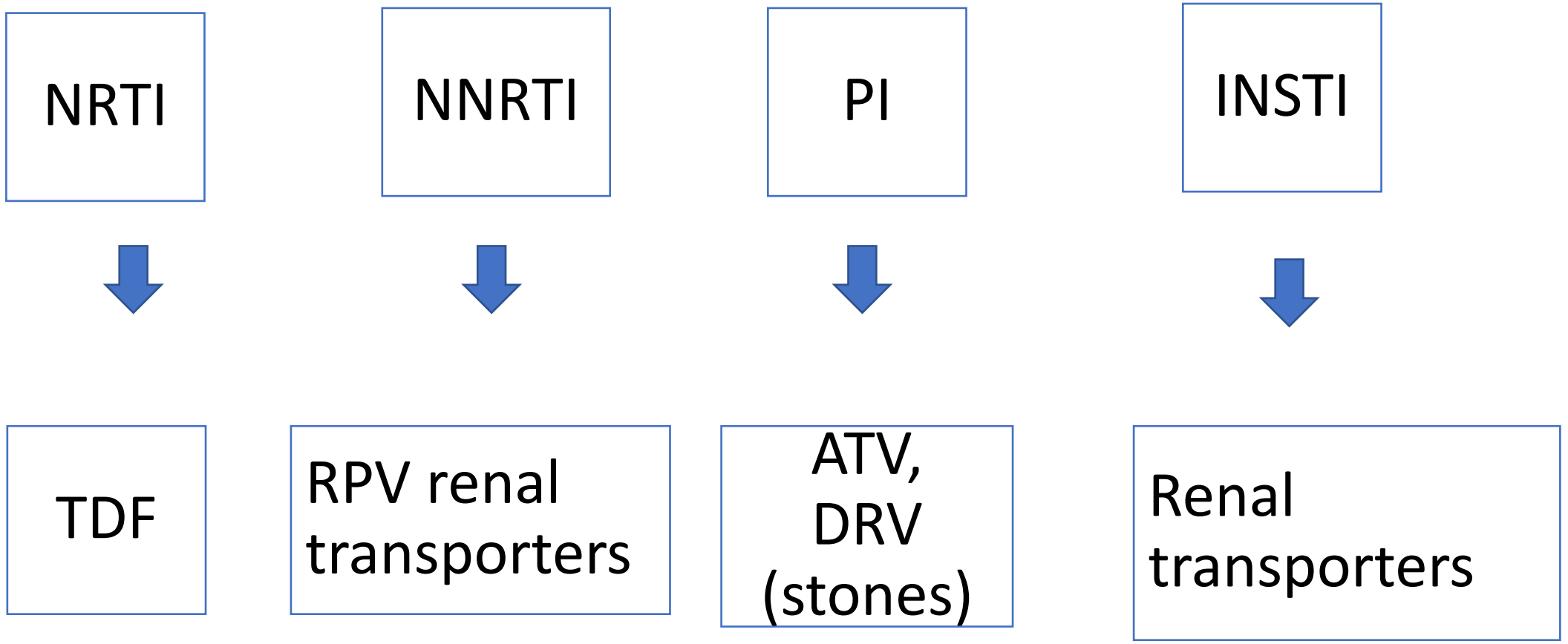
Scherzer R et al., AIDS. 2012;26(7):867-75.

Kidney

- In terms of severe renal toxicity, no differences have been demonstrated between tenofovir disoproxil fumarate and tenofovir alafenamide in unboosted regimens (without /cobicistat and / ritonavir).

PilkingtonV,HughesSL,PepperrellT,McCannK,GothamD, Pozniak AL, et al. Tenofovir alafenamide vs tenofovir disoproxil fumarate: an updated meta-analysis of 14894 patients across 14 trials. AIDS. 2020;34:2259–68.

KIDNEY


NRTI
NNRTI
PI
INSTI
TDF
RPV renal transporters
ATV, DRV (stones)
Renal transporters

Bone

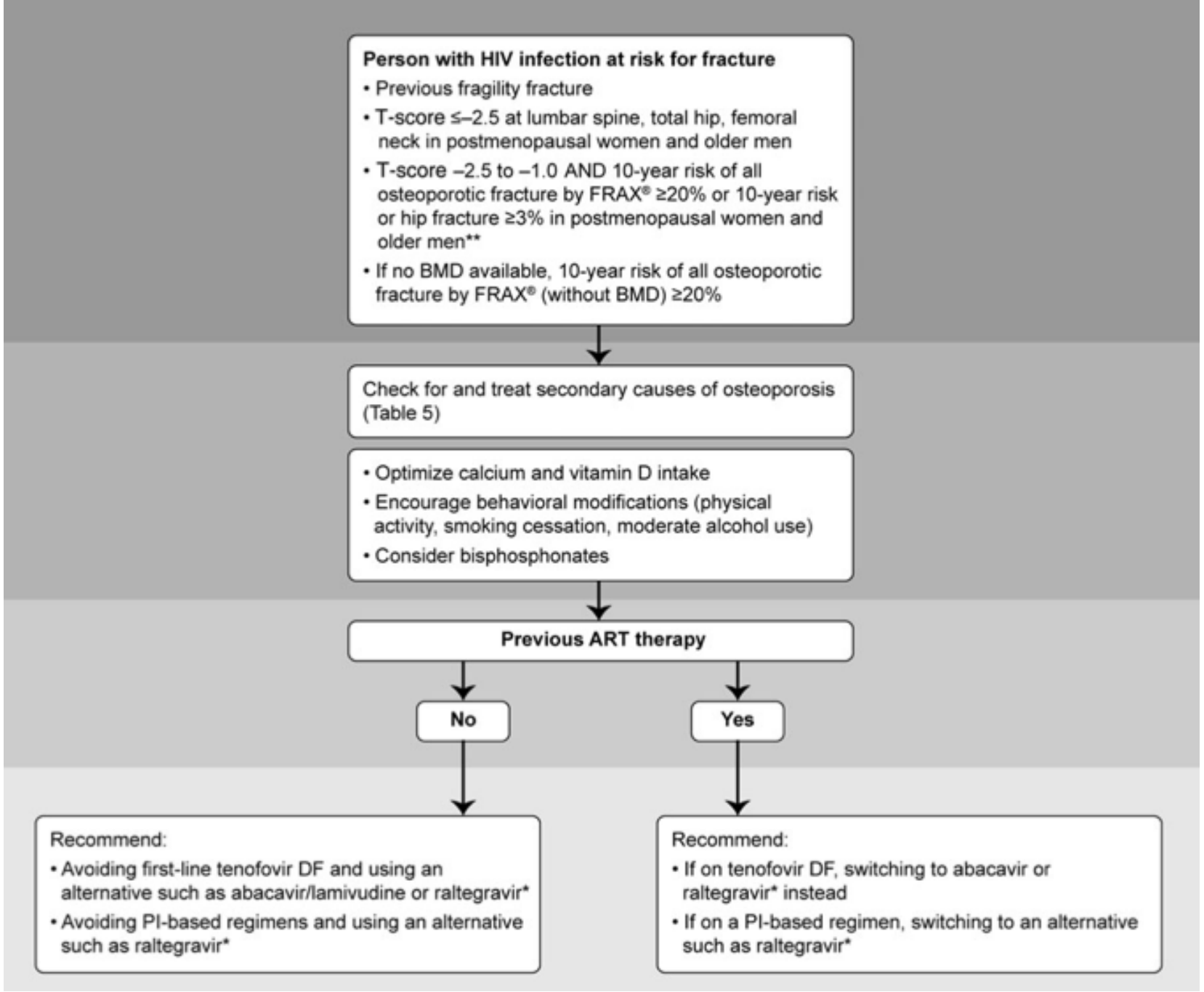
PLWH on TDF lose significantly more bone mineral density (BMD) than those treated with TAF or abacavir or regimens not containing any of them and have worse bone architecture and quality.

BMD losses 96 weeks after ART initiation were similar in magnitude among patients receiving PIs, ATV/r, or DRV/r but lowest among those receiving RAL

In general, PI associated with higher risk of osteopenia or osteoporosis compared to NNRTI and INSTIs

Efavirenz associated with the greatest risk of vitamin D deficiency

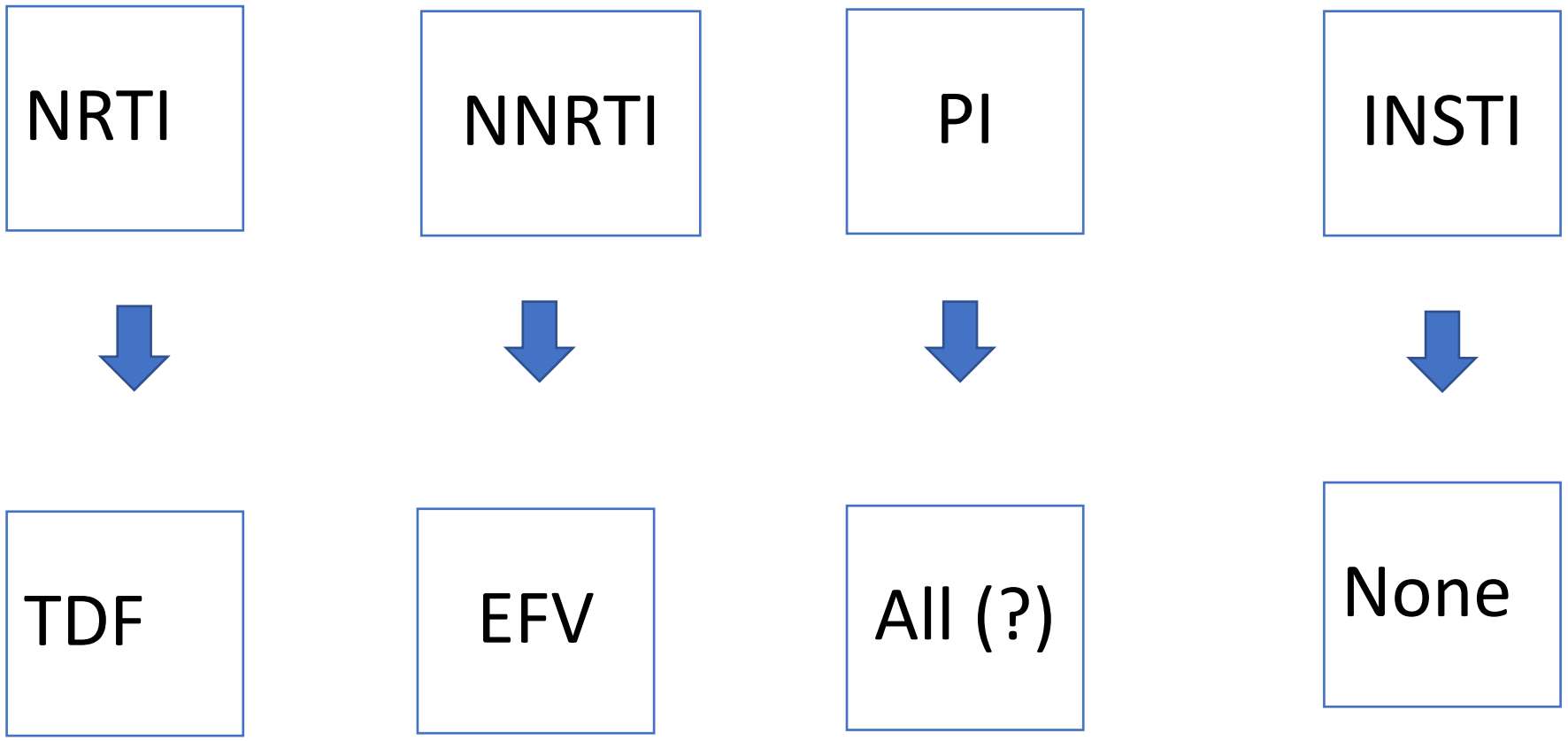
Pepperrell T, et al., HIV Med. 2019; 20: 92. Brown T. et al., J Infect Dis. 2015;212:1241-9.Brown T et al., AIDS. 2006 ;20(17):2165-74, Borderi, M, et al., AIDS, 2009. 23:1297-310. Orkin C. et al., AIDS Rev. 2014;16(2):59-74. Duvivier C, et al., AIDS. 2009;23(7):817-24



Brown TT et al., Clin Infect Dis. 2015. 60(8): 1242-51

Recommendations for Evaluation and Management of Bone Disease in HIV

BONE

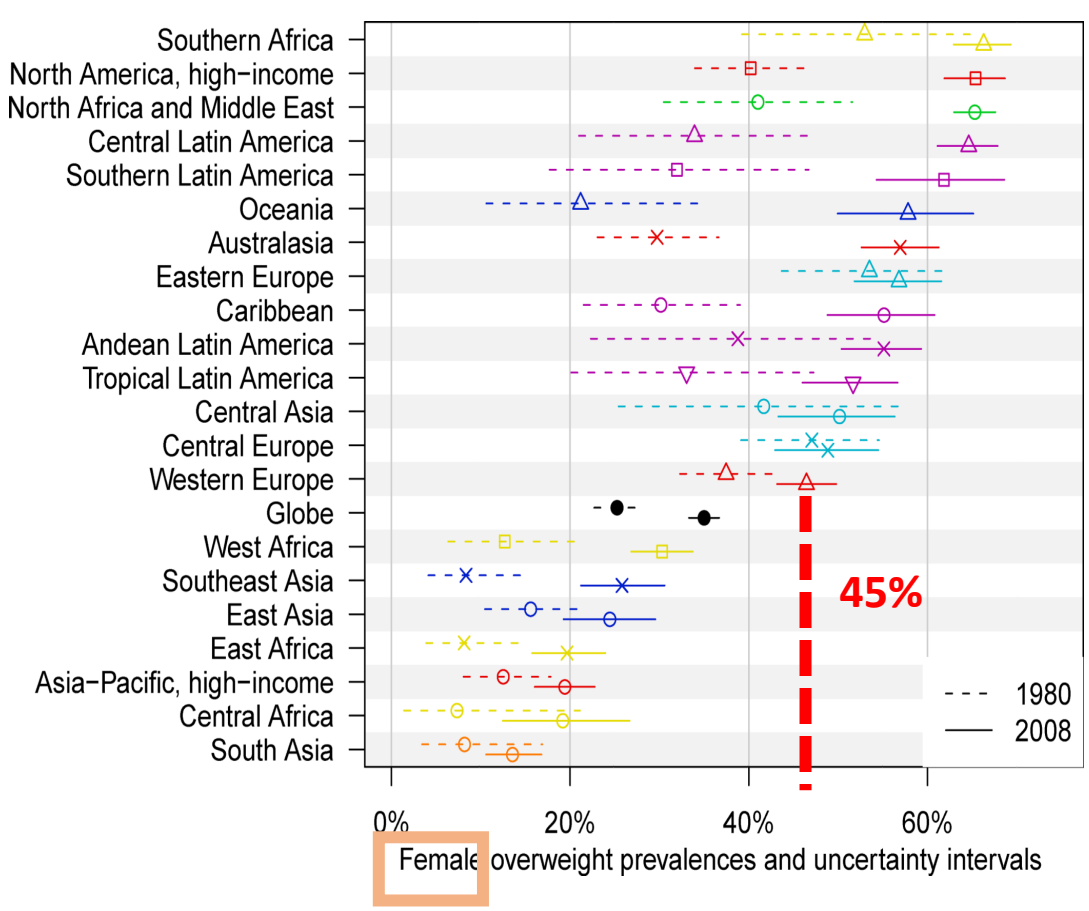


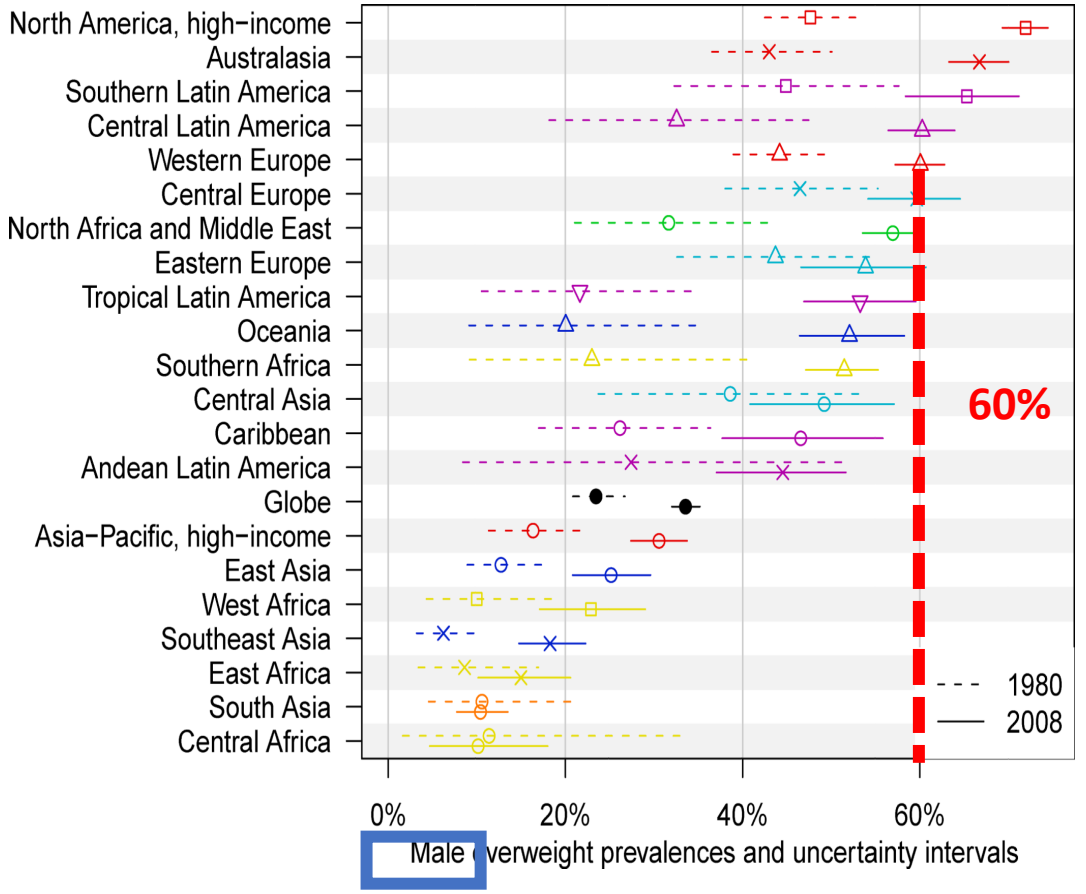
WEIGHT

Weight gain

- Obesity is a multifactorial disease that affects individuals the world over, regardless of sex, race, age, racial condition or geography
- In white subjects aged 35–50 years, the average weight gain in 1 year is about 0.5– 1 kg.

Hill A, J Virus Erad 2019; 5: 41–3. Sax PE, Clin Infect Dis 2019; 71: 1379–89.





The epidemiology is changing...

OVERWEIGHT

Finucane M, et al. Lancet 2011;377:557–567

Metabolic syndrome and body weight in people living with HIV infection: analysis of differences observed in three different cohort studies over a decade

Lucia Taramasso[1] | Paolo Bonfanti[2] | Elena Ricci[3] | Paolo Maggi[4] | Giancarlo Orofino[5] | Nicola Squillace[2] | Barbara Menzaghi[6] | Giordano Madeddu[7] | Chiara Molteni[8] | Francesca Vichi[9] | Erika Riguccini[10] | Annalisa Saracino[11] | Carmen Santoro[11] | Marta Guastavigna[5] | Daniela Francisci[10] | Antonio Di Biagio[12] | Giuseppe Vittorio De Socio[10] | for the CISAI study group†

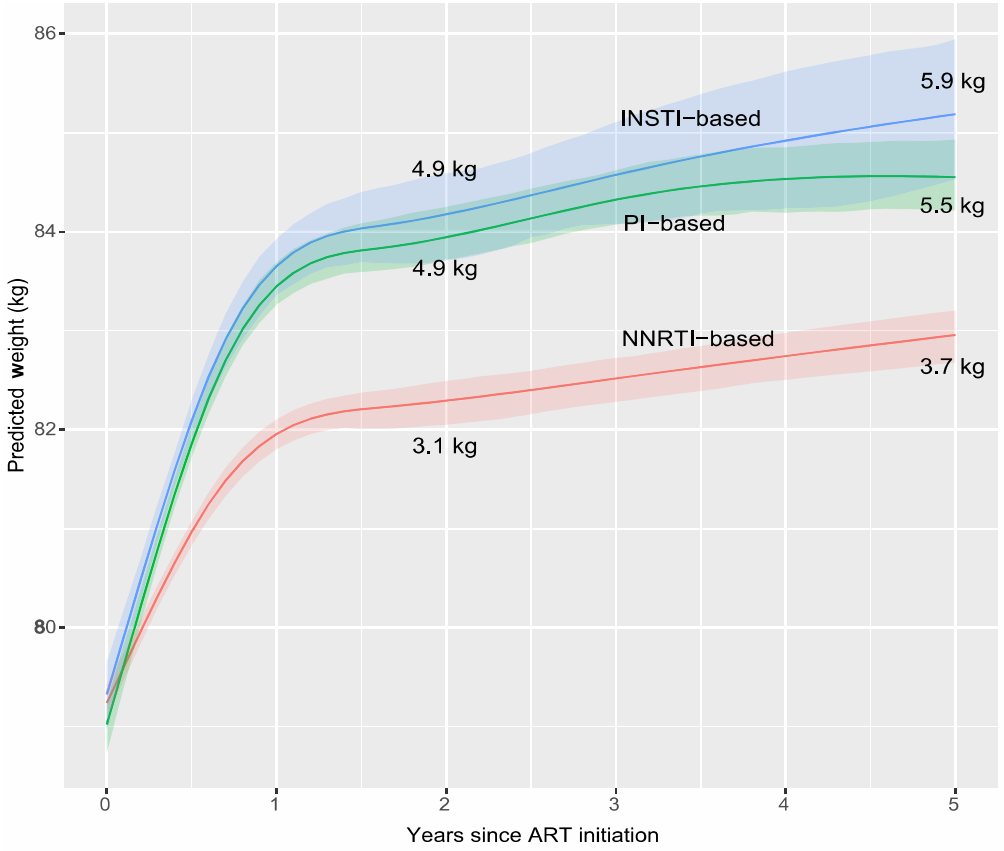
HIV Medicine. 2021;00:1–10.

TABLE 1 Clinical and laboratory features in HIV-infected patients enrolled in the SiMOne (2005), HIV-HY (2011) and STOPSHIV (2015) studies

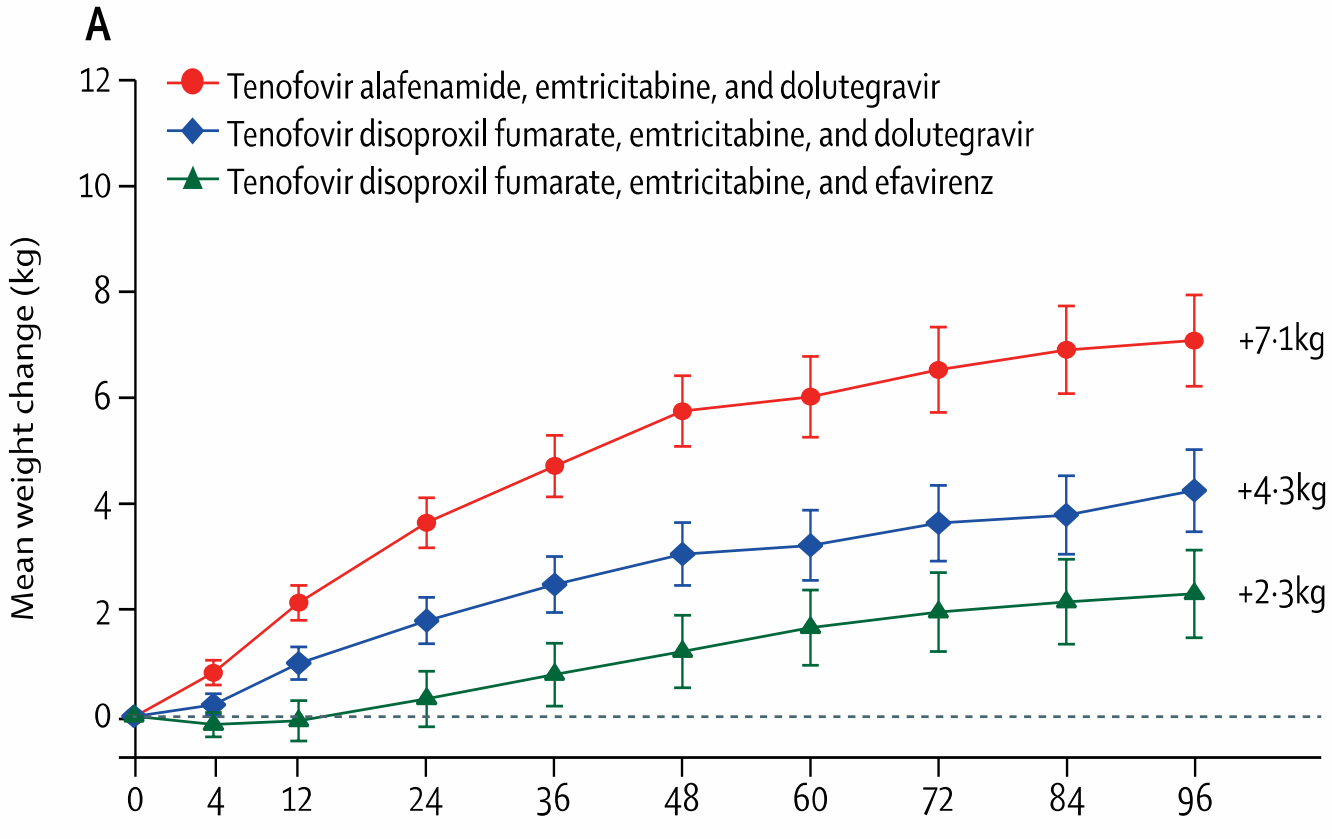
Variable	SiMOne 2005 ($n = 1243$)	HIV-HY 2011 ($n = 854$)	STOPSHIV, 2015 ($n = 917$)	p
Men [n (%)]	892 (71.8)	616 (72.1)	702 (76.6)	0.03
Age (years) (mean ± SD)	43.2 ± 9.2	50.3 ± 9.4	48.7 ± 10.6	< 0.0001
BMI (kg m^{-2}) (mean ± SD)	23.6 ± 3.4	24.5 ± 3.9	24.5 ± 4.0	< 0.0001
BMI (kg m^{-2}) [n (%)]				
≤ 18.5	67 (5.4)	32 (3.8)	47 (5.1)	
18.6–25.0	805 (65.2)	483 (56.7)	506 (55.2)	
25.1–30.0	303 (24.5)	266 (31.2)	287 (31.3)	
≥ 30.1	60 (4.9)	71 (8.3)	76 (8.3)	< 0.0001

Weight gain in naive PLWH

Weight over the first five-years of ART by regimen class (22,972 PLWH)

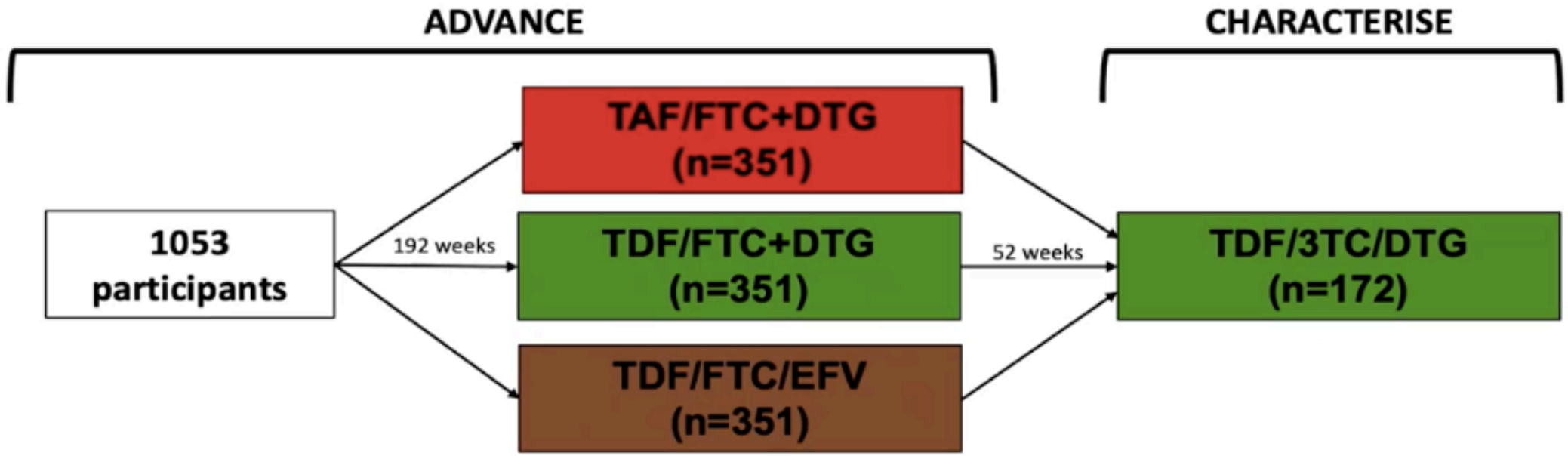


Mean change in bodyweight over time in all randomly assigned individuals (1,053 PLWH)



Bourgi K, et al., JIAS 2020, 23: e25484. Venter WDF, et al., Lancet HIV 2020; 7: e666–76.

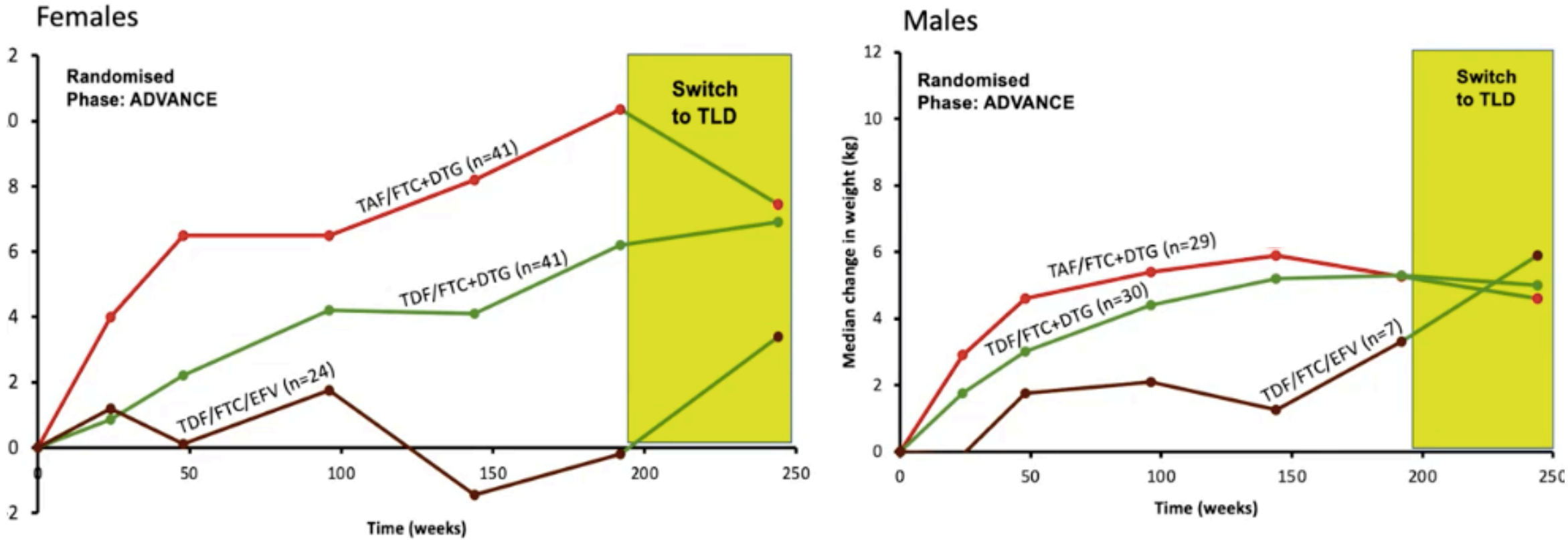
ADVANCE and CHARACTERISE trials



- At follow up, participants were assessed for weight, lipids, fasting glucose, HBA1C and HIV RNA

- Changes in weight and laboratory parameters during the first 192 weeks of randomized treatment and then after the switch to TDF/3TC/DTG were evaluated in each treatment arm using paired non-parametric tests

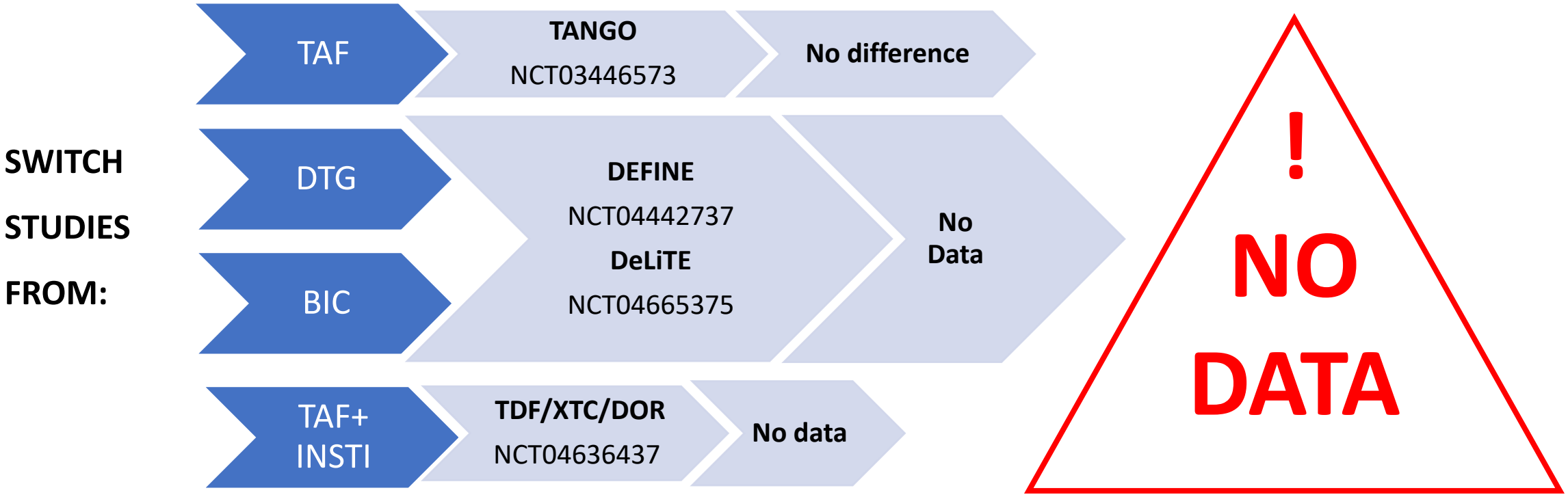
Change in weight after switch to TDF/3TC/DTG – Females and Males



Weight & Switch

Sufficient evidence is available from cohort studies and randomized clinical trials to conclude that bictegravir, dolutegravir and tenofovir alafenamide are associated with significantly higher increases in weight and obesity rates than efavirenz.

Rilpivirine, doravirine and darunavir appear to be associated with smaller increases in weight.



Sax PE, et al., Clin Infect Dis. 2020 Sep 12;71(6):1379-1389. Shah S et al. Drugs. 2021;81(3):299-315. van Wyk J, et al., Clin Infect Dis. 2020 Nov 5;71(8):1920-1929.

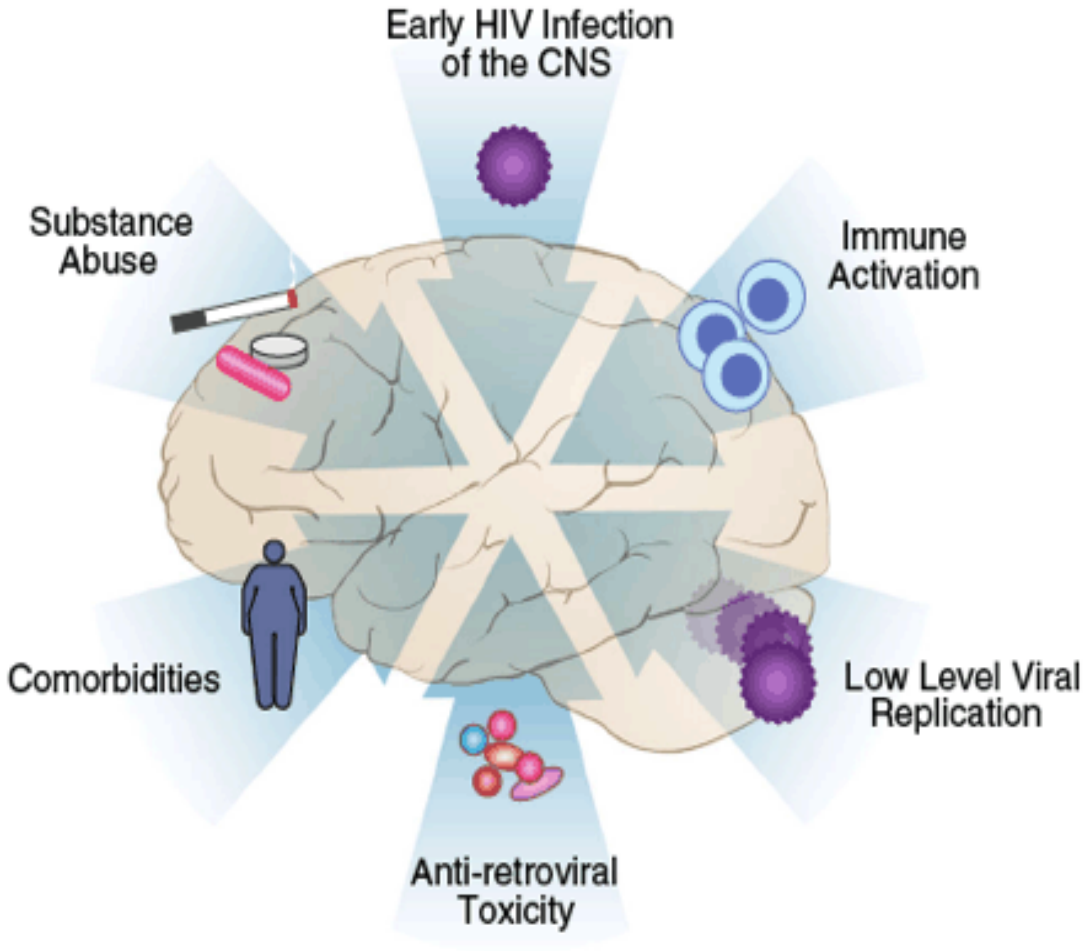
WEIGHT

NRTI	NNRTI	PI	INSTI
TAF, TDF protective	Low impact, EFV protective	All (< LPV)	All (<CAB?)

CNS

CNS

- Psychiatric disorders are common in subjects with HIV infection (20%–40%), especially in women, in whom the incidence (30%– 60%) is higher than in the general population (5%–10%).
- Depression and anxiety are the most frequent conditions..
- These disorders are often underdiagnosed, especially those of lower intensity, including low-degree ART-related neuropsychiatric AEs, which the patient may attribute to other causes.

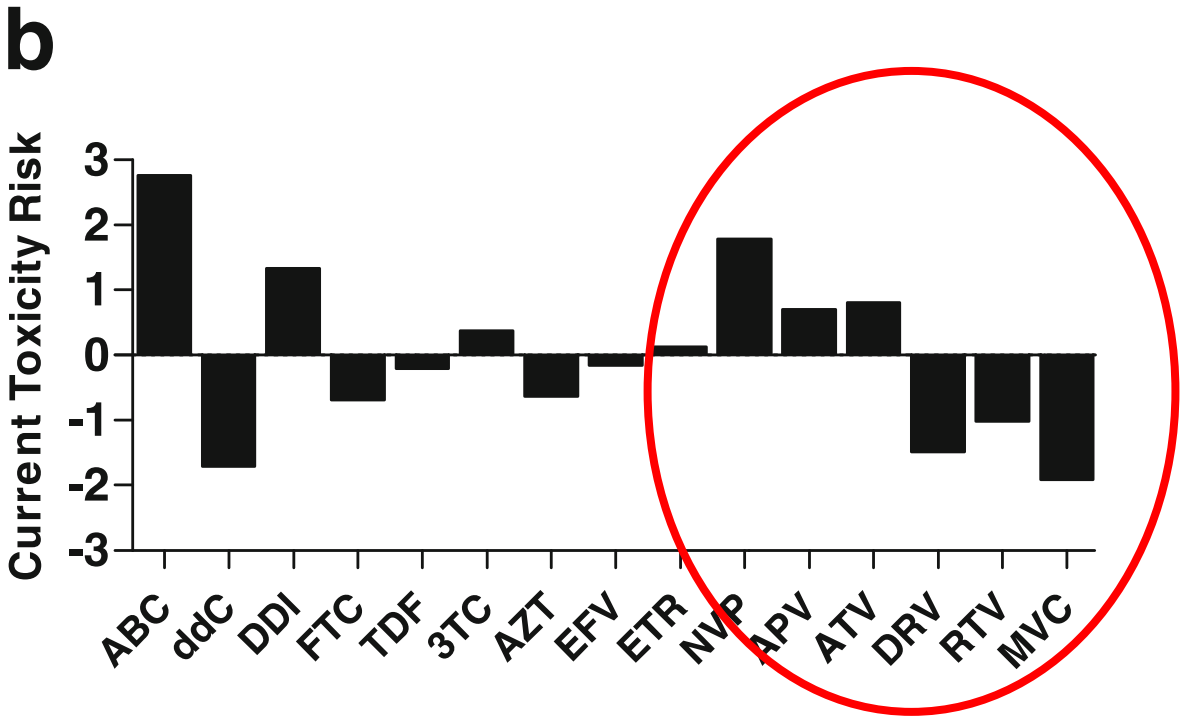


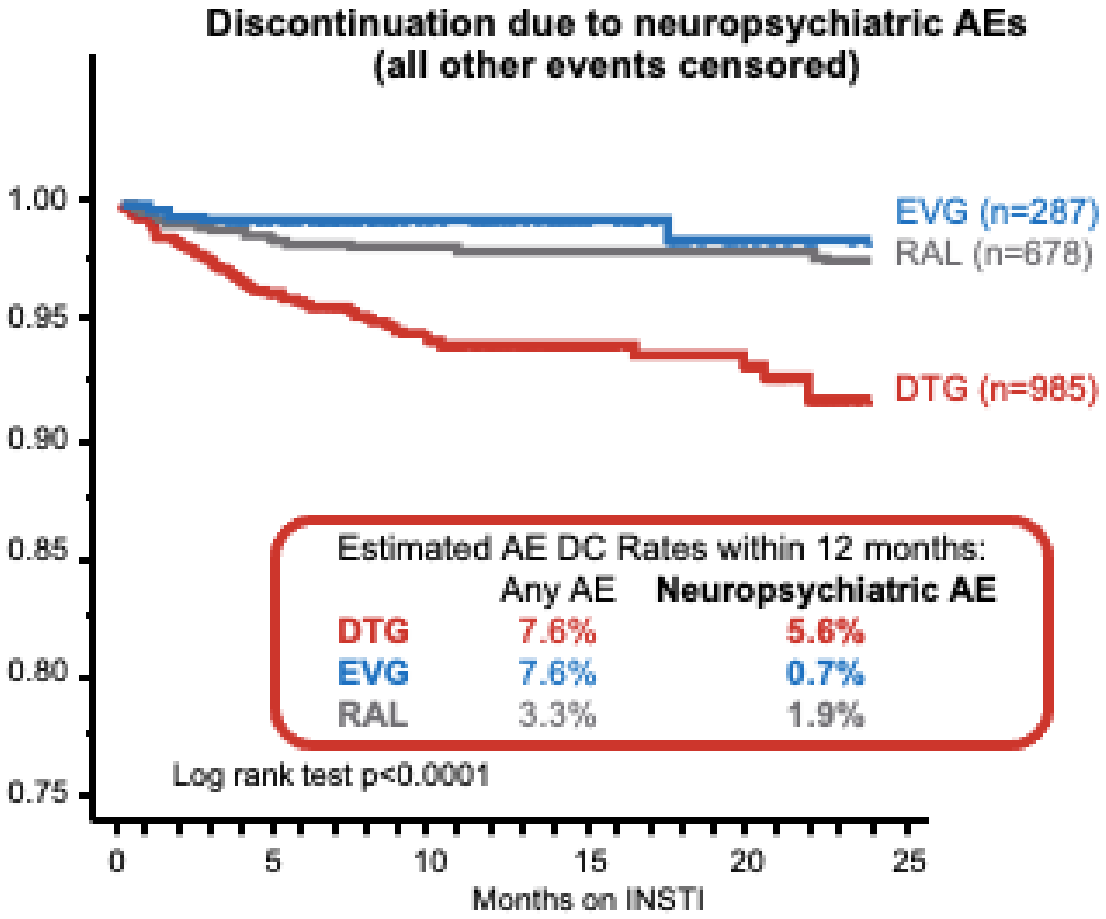
Hoffmann C, et al. AIDS Rev. 2019; 21: 4–10. Treisman GJ, et al., Drug Saf. 2016; 39: 945–57. Farhadian S et al., Curr Infect Dis Rep. 2017;19(12):50.

‡

PI and INSTI

APV (0.71) and ATV (0.81) had a low risk of toxicity, whereas al other compounds had negligible risk of toxicity based on this assessment





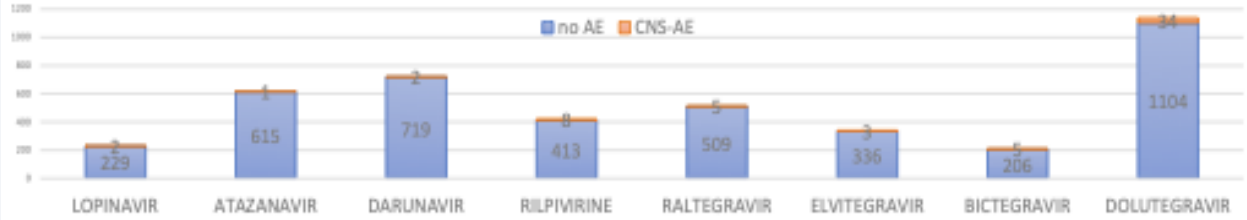
Robertson K et al., J. Neurovirol. 2012;18:388–399 . Sabranski M & al. HIV Drug Therapy 2016. #O214

Reversibility of Central Nervous System Adverse Events in Course of Art ‡

CNS ADVERSE EVENTS

- Sixty PLWH experienced at least one SNC-AE leading to ART discontinuation, 26/3613 (0.7%) in non DTG-cohorts and 34/1138 (3.1%) in DTG-cohort.

Figure 2. Central Nervous System- adverse events leading to drug discontinuations



The rate of discontinuations due to CNS-AE was higher in DTG (logrank p<0.0001), with a longer time between drug initiation and SNC-AE in DTG than non-DTG group, 10.0 (IQR 4-15) versus 4.0 (IQR 1-7) months (p=0.0160).

Four PLWH in non-DTG and six in DTG cohort reported more than one CNS-AE.
The reported CNS-AE were (frequency in non-DTG and in DTG cohorts, respectively):

- sleep disturbance (7 and 12);
- anxiety/agitation (4 and 6);
- depression (3 and 6);
- headache (6 and 5);
- vertigo (4 and 4);
- suicidal ideation (1 and 3);
- psychosis (1 and 1);
- other CNS disturbances (4 and 3).

TABLE 2: Factors associated to CNS-AE leading to drug discontinuation.

Variable	Crude HR	95% CI	P	Adjusted HR*	95% CI	P
Sex F (ref. M)	1.30	0.77-2.22	0.33			
Age (ref. <50 years)	**2.02**	**1.22-3.34**	**0.006**	**1.60**	**0.93-2.65**	**0.09**
Weight (by 5 Kgs)	1.01	0.92-1.10	0.89			
Ethnicity (ref. Caucasian)	1.34	0.58-3.11	0.49			
HCV-Ab+	1.12	0.66-1.92	0.67			
Naïve (ref. experienced)	**2.09**	**1.21-3.61**	**0.008**	**2.51**	**1.34-4.69**	**0.004**
CDC stage (ref. A)						
B	0.88	0.49-1.58	0.66			
C	0.74	0.40-1.37	0.33			
CD4 (ref. <250)						
250-499	1.26	0.62-2.58	0.52	1.32	0.63-2.78	
500-749	1.34	0.61-2.94	0.46	1.20	0.52-2.77	0.06
≥750	2.39	1.18-4.84	0.015	2.11	0.95-4.69	
Previous psychiatric disorder *	**2.56**	**1.26-5.20**	**0.009**	**2.27**	**1.10-4.68**	**0.027**
Cohort (ref. DTG)						
Non-DTG	**0.25**	**0.15-0.42**	**<0.0001**	**0.32**	**0.19-0.56**	**<0.0001**

* Major depressive disorder, anxiety, psychosis, bipolar disorder

Taramasso et al., Viruses. 2022;14(5):1028.

CNS

NRTI	NNRTI	PI	INSTI
None	Mainly EFV, but possible class effect	None	DTG>RAL>EVG BIC?

Possibili strategie per personalizzare ART

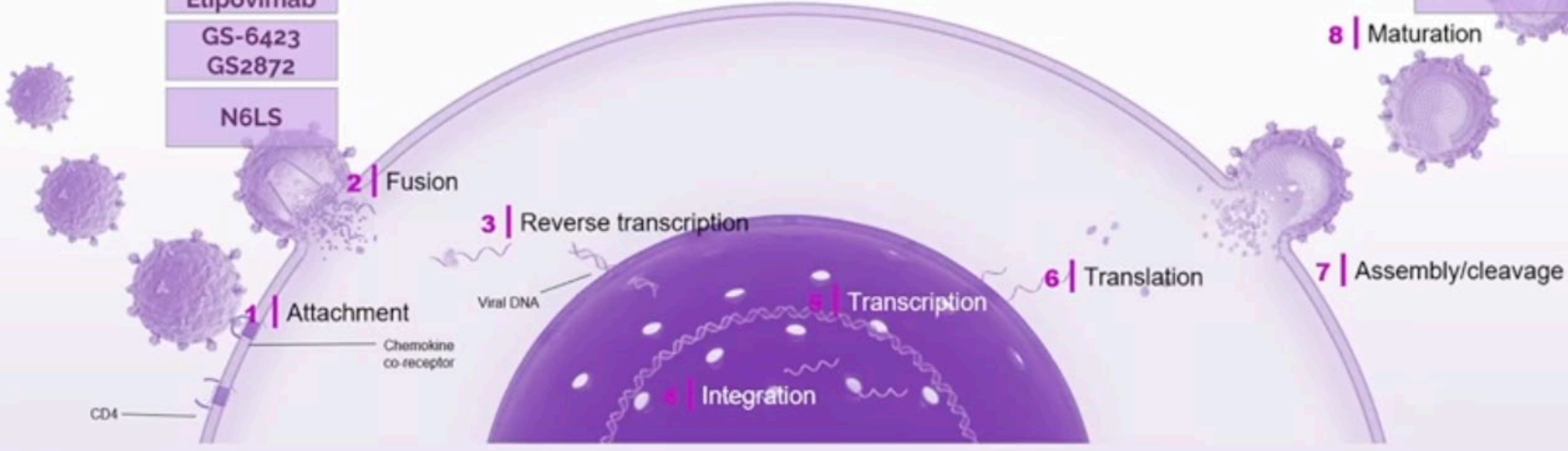
- Cardiovascular risk (Platelet aggregation and lipid control) → avoid abacavir and regimens associated with dyslipidemia; switching from EFV and boosted regimens improve lipids. Consider DOR, RPV or INSTIs as preferred anchor drugs.
- Bone –> switch from TDF to TAF o 2DR; avoid TDF + PIs
- Kidney–> switch from TDF to TAF o 2DR; avoid TDF + PIs
- Weight → exclude non pharmacological causes of weight gain, switch strategies not yet defined
- CNS → no advantage in switching asymtomatic PLWH, most AE are reversible after switch

Never forgive the revision of historical GRT and HBV serology before switch

Futuro delle strategie di trattamento dell'infezione da HIV

Compounds in clinical development for treatment and prevention

Entry inhibitor	bNAb	NRTI NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor	Topical IVR /MPT
Albuvirtide	UB-421	Islatravir	Elsulfavirine	Bictegravir	GS-1156	Lenacapavir	GSK254	Dapivirine
	Leronlimab (PRO-140)	TAF implant	ACC007	S-365598			GSK937	MIV 150 PC1005 gel
	VRC 01/LS VRC 07/LS							EVO-100 gel
	PG121 + Elipovimab							MB66 film
	GS-6423 GS2872							
	N6LS							



Compounds by modality and indication

Treatment

- Islatravir
- Lenacapavir
- MI 254

ORAL

INJECTABLE
IM, SC, IV

- Albuvirtide
- bNabs
- Lenacapavir
- Elsulfavirine
- Islatravir
- MI 934

Already available from now

VOCABRIA

cabotegravir sospensione per iniezione

18 maggio 2022

REKAMBYS

rilpivirina sospensione per iniezione

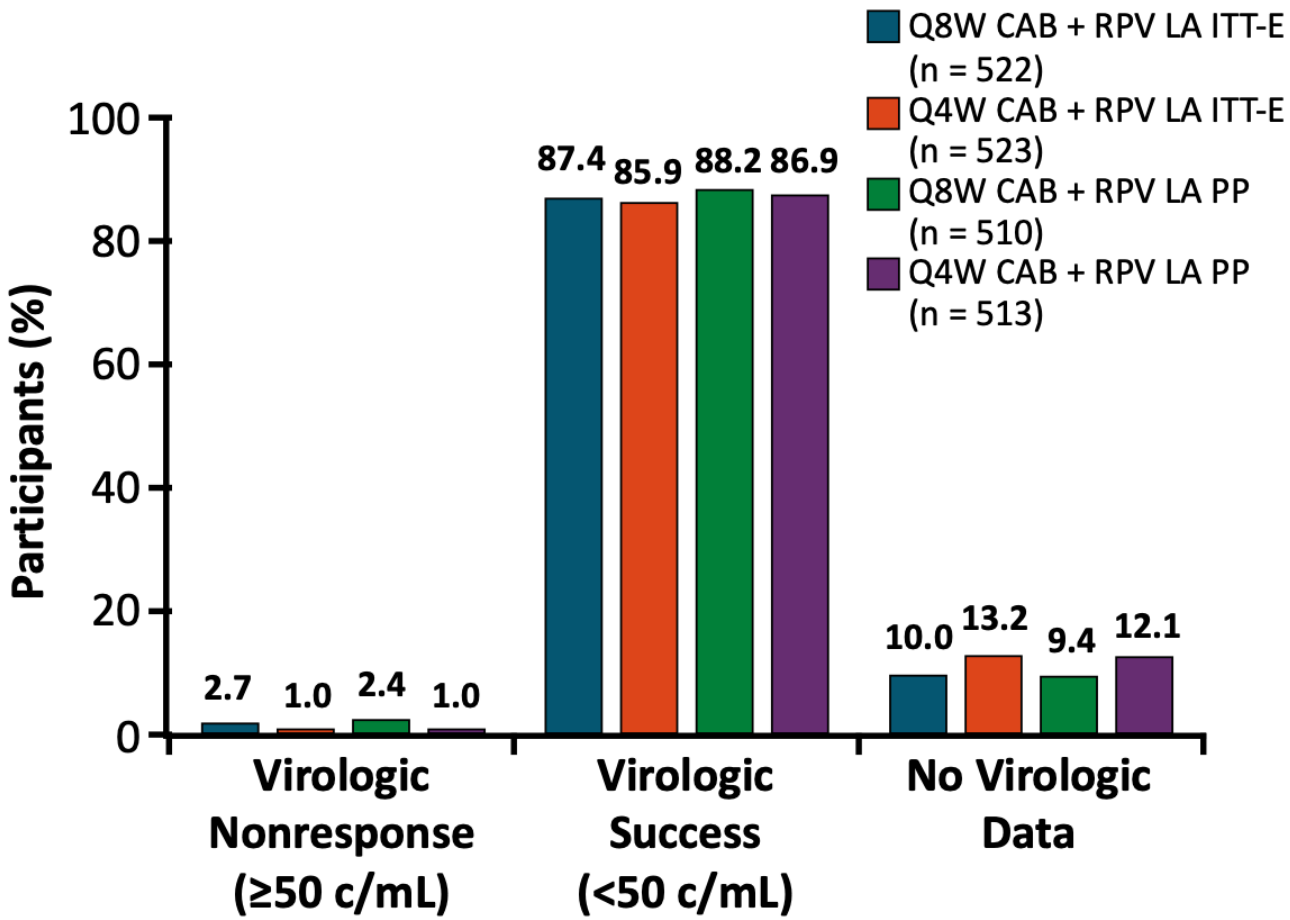
Riassunto delle caratteristiche del prodotto

18 maggio 2022

Indicazioni

- **Cabotegravir & Rilipvirina LA: Trattamento negli adulti in soppressione virologica, in regime stabile, senza evidenza presente o passata di resistenza virale e di precedente fallimento virologico a NNRTI e/o INSTI**

ATLAS-2M: Wk 152 Virologic Outcomes



- 2 additional participants (both male at birth, BMI <30 kg/m^2) in Q8W arm met CVF criteria between Wk 96 and 152 (Wk 112, 120)
  - At BL, neither had RAMs; participant with A6 subtype had L74I integrase polymorphism

Country	Baseline	At Failure		
	HIV-1 Subtype	HIV-1 RNA (c/mL)	RPV RAMs	INI RAMs
Germany	B	24,221	E138A+ M230M/L	Q148R
Russia	A6*	59,467	E138A+ Y181Y/C	Q148R

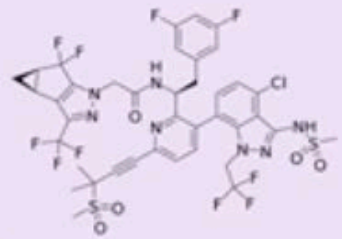
*Originally classified as A1; later reclassified as A6 upon reanalysis

- Through Wk 152, 13 participants had CVF: Q8W, n = 11 (2%); Q4W, n = 2 (<1%)
  - None with injection >7 days late

Overton. CROI 2022. Abstr 479.

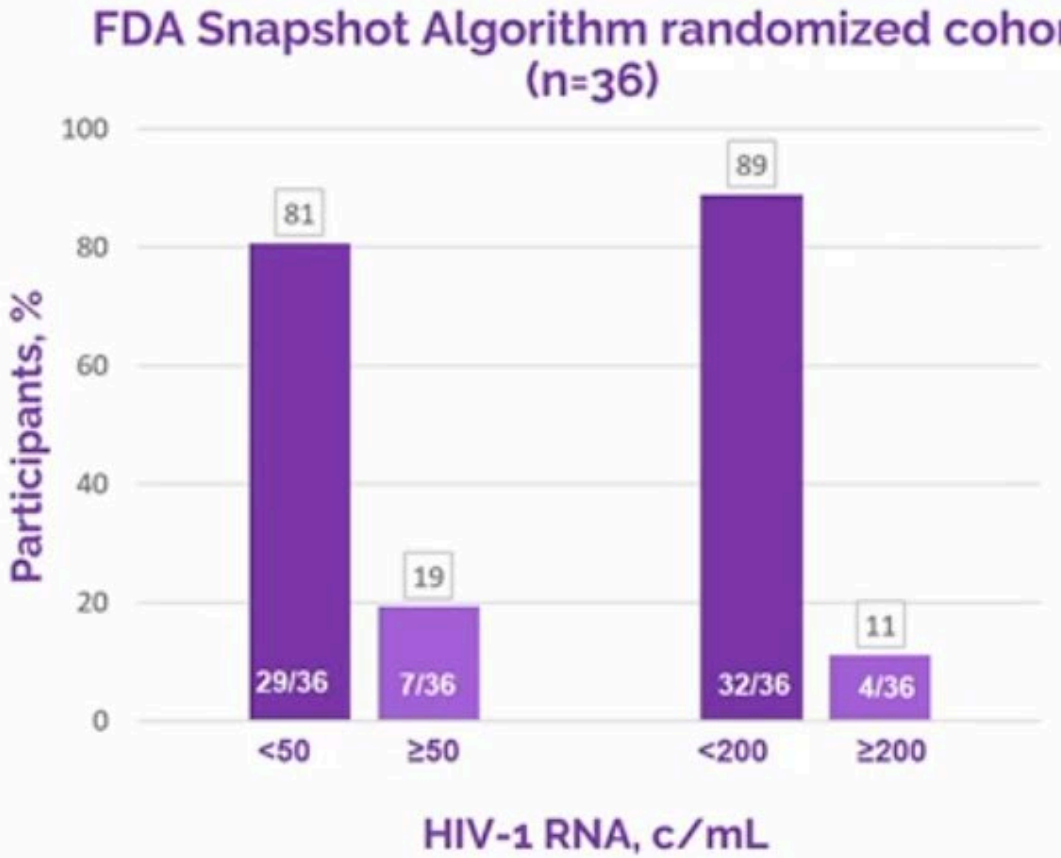
Lenacapavir (LEN)

- First in class capsid inhibitor, multi-stage activity in early and late lifecycle
- Small molecule active at picomolar doses
- No cross-resistance with approved drugs
- Oral or subcutaneous
- Supports 6 monthly dosing
- LEN SC n PrEP SHIV model significantly reduced acquisitions



* LEN studies under partial FDA hold while they change away from glass vials, participants stay on oral LEN

Efficacy at W26 in the LEN Arm



LEN + OBR led to high rates of virologic suppression in HTE

LEN resistance:

- 4 participants developed resistance: M66I
- 2 on functional monotherapy; 2 non adherent
- 3 resuppressed without resistance to OBR

Injection site reactions:

- 56% of participants reported ISRs
- 70% were grade 1 and resolved within days
- No discontinuations due to ISRs

LEN was well tolerated:

- No AEs that led to discontinuation
- No SAEs related to LEN

HTE, heavily treatment-experienced; OBR, optimized background regimen

Molina JM, et al. vIAS 2021. OALX01LB02; Ogbuagu et al. Abstract 491 CROI 2022

Conclusioni