10° WORKSHOP NAZIONALE CISAI

MILANO

PREVENZIONE E GESTIONE DELLE CO-MORBIDITÀ ASSOCIATE ALL'INFEZIONE DA HIV

PRESIDENTI
PAOLO BONFANTI
ANTONIO DI BIAGIO

30 SETTEMBRE
1 OTTOBRE
2021

CISAI

FONDAZIONE ASIA

Ottimizzazione della terapia antiretrovirale nei pazienti con sindrome metabolica

Giordano Madeddu

UNIVERSITÀ DEGLI STUDI DI SASSARI

CISAI
FONDAZIONE ASIA

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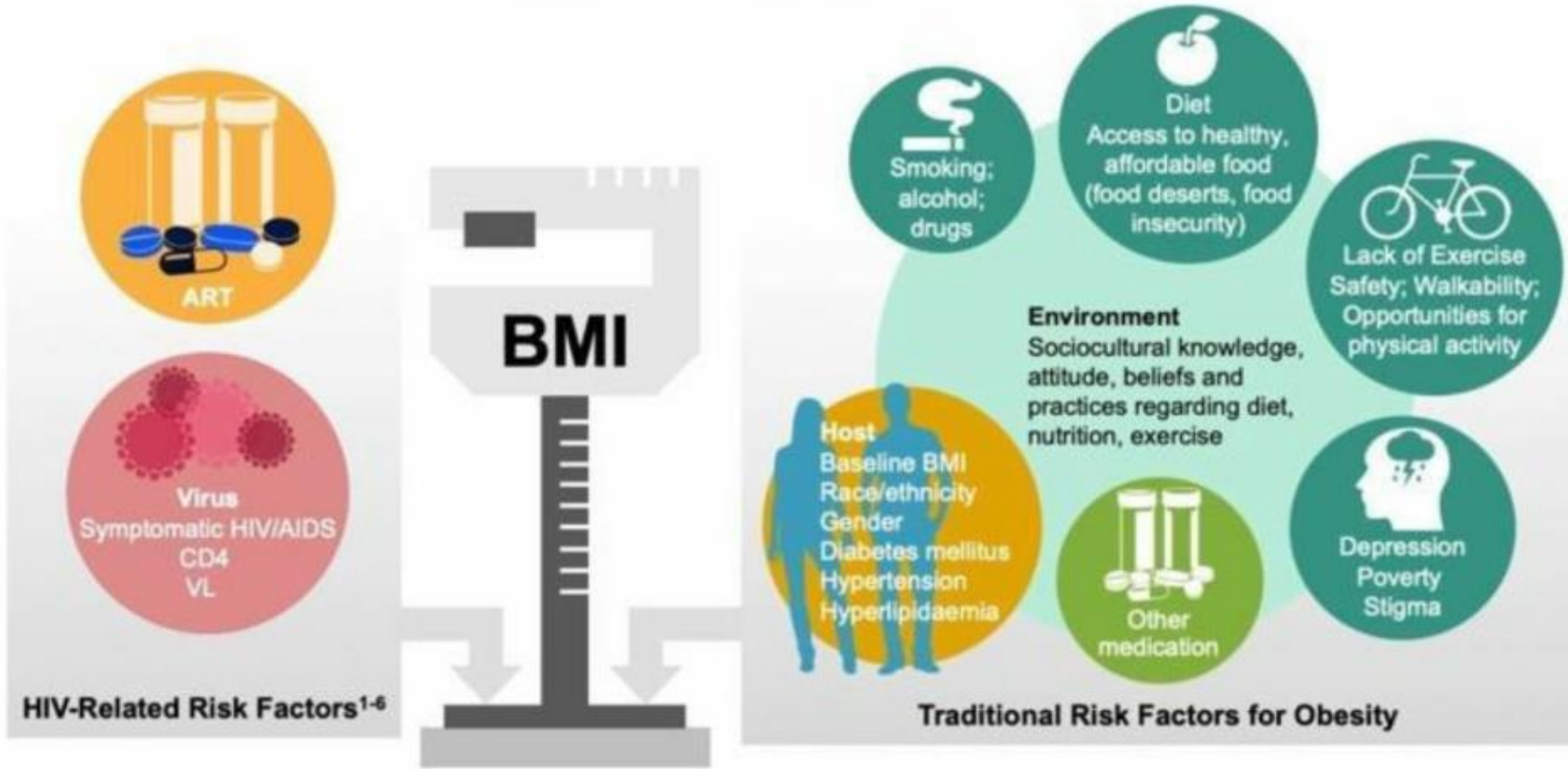
What is Metabolic Syndrome?

Weight gain in PLHIV is a multifactorial process driven by the interplay among virus, ART, host and environment-specific risk factors

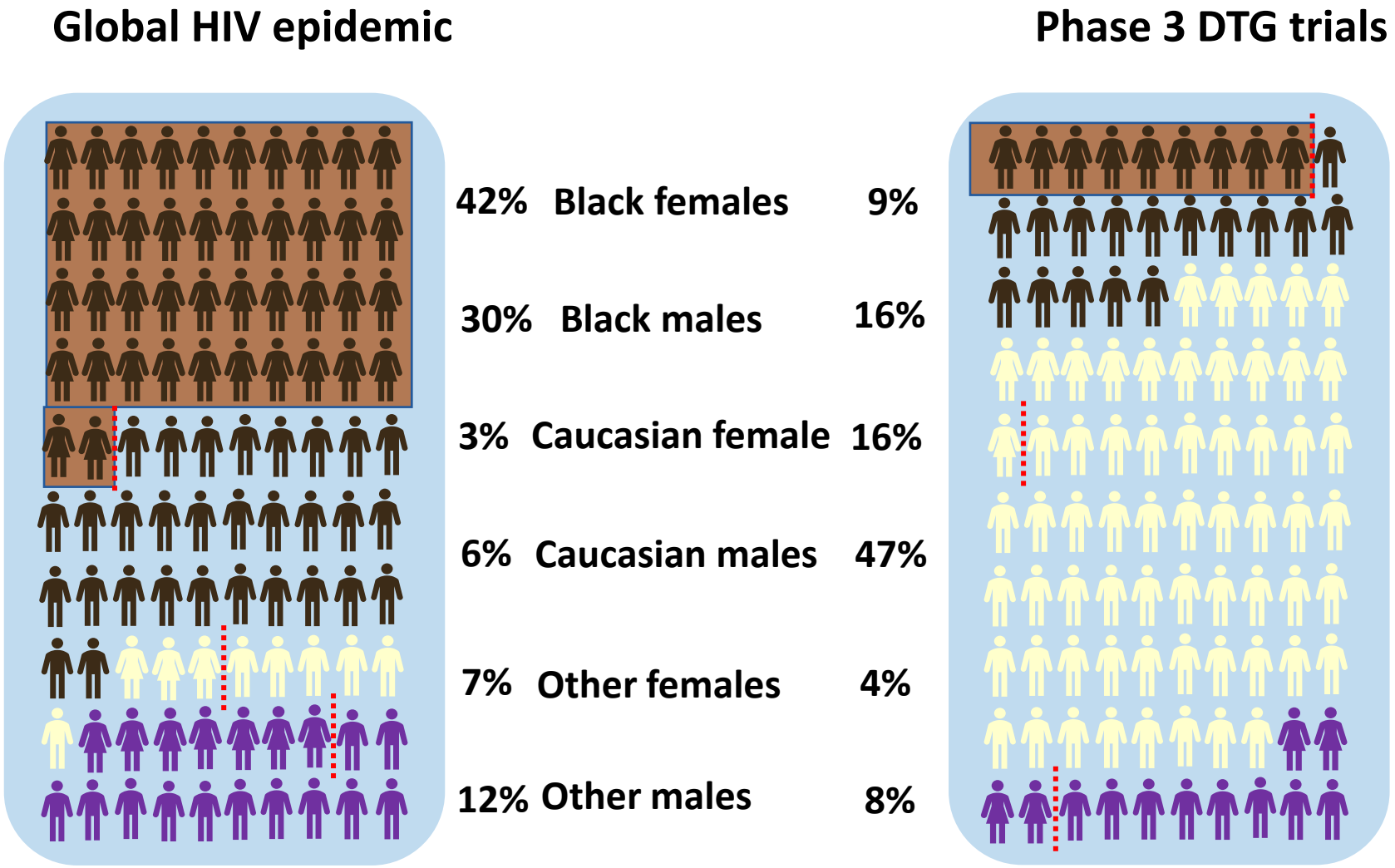


Antiretroviral therapy and body fat distribution

Year	HIV lipodystrophy
1996	ART is safe
1997	Features reported; largely ignored
1998	Syndrome recognised; attributed to PIs
1999-2001	Also attributed to tNRTIs PI and NRTI mechanisms proposed PI switching+++
2002	Partially reversible with tNRTI switch
2003	Prospective confirmation Prevented with initial TDF/ABC
2004	Treatment: glitazones not very effective
2005	Mitochondrial mechanism
2008	PI (LPVr) did not cause LD in RCT

Year	HIV weight gain
2014	Modern ART is safe
2017	Reports of generalised weight gain
2018	Larger cohorts – INSTI link
2019	"TAF / DTG cause fat gain" "TDF / EFV prevent fat gain"

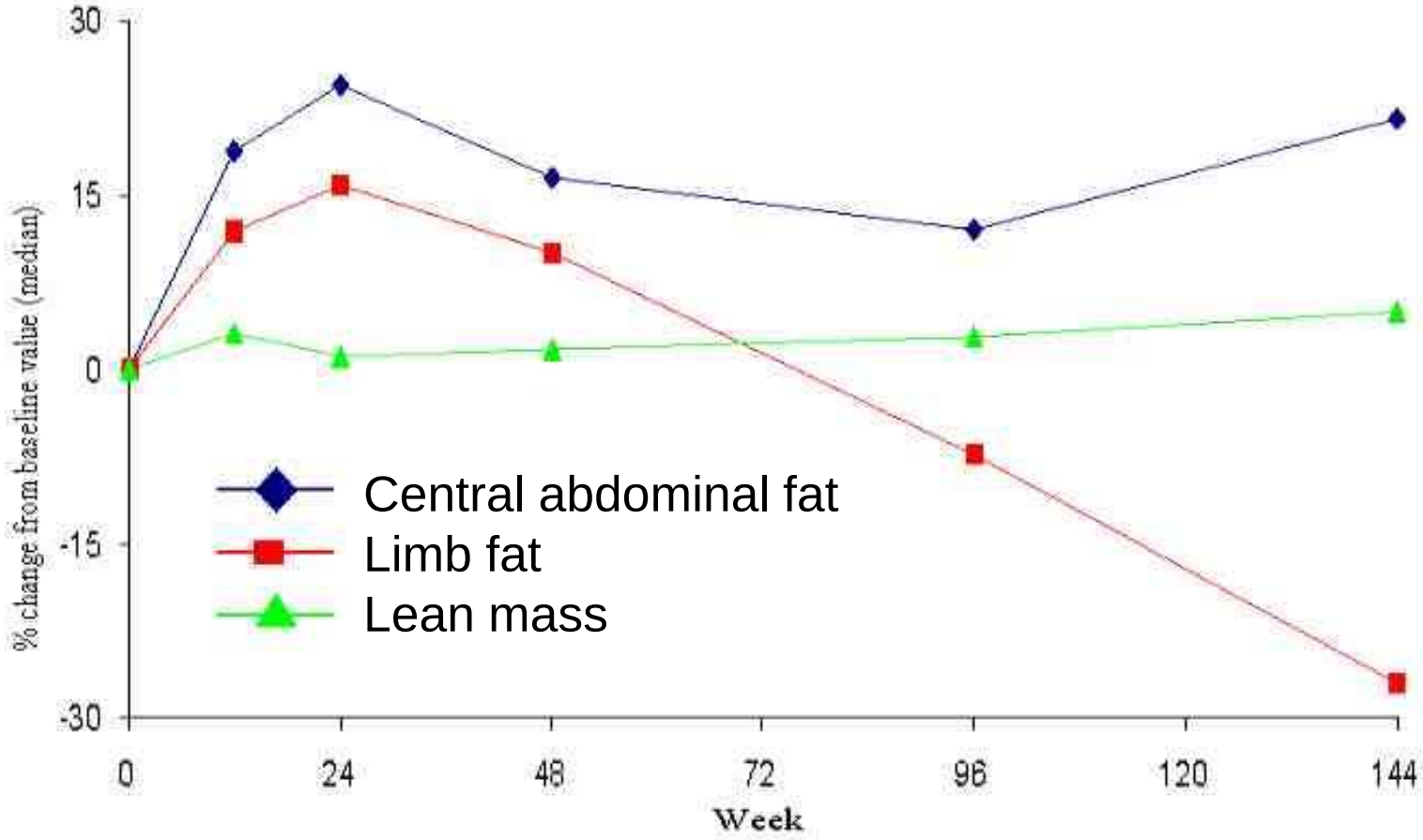
Phase 3 trials under-represent the people at highest risk of adverse events



Pepperrell et al EACS Nov 2019 [Abstr]

Changes in body composition with ART

Sydney. N=40 men. Median (IQR) BMI 22.5 (21.3 – 23.8) kg/m^2



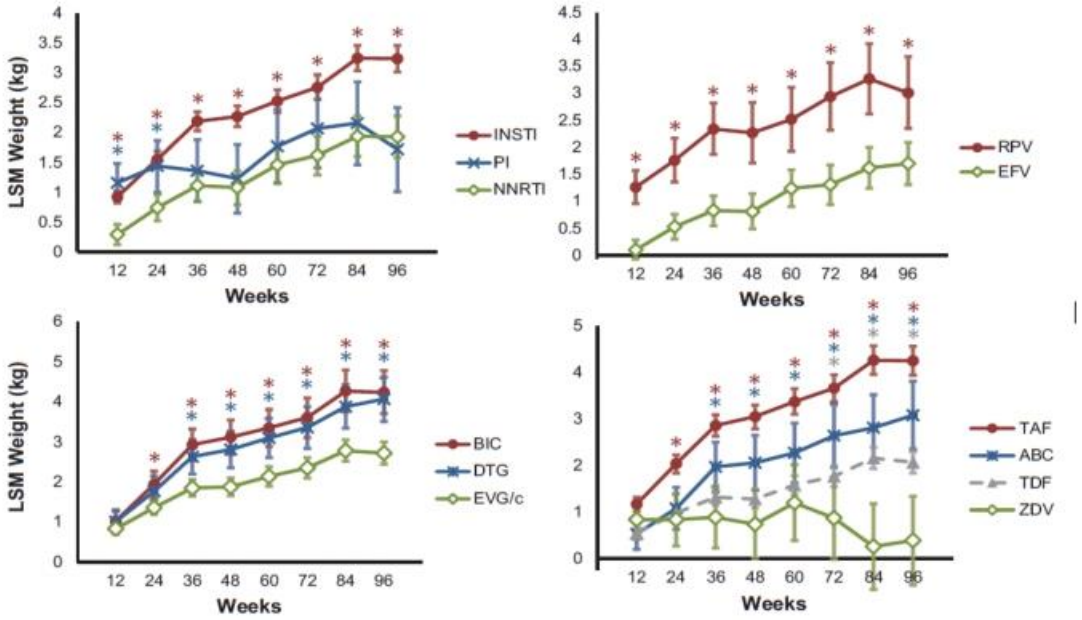
PI:
IDV, NFV, SQV
NNRTI:
EFV, NVP
NRTI:
ZDV/3TC
d4T/3TC

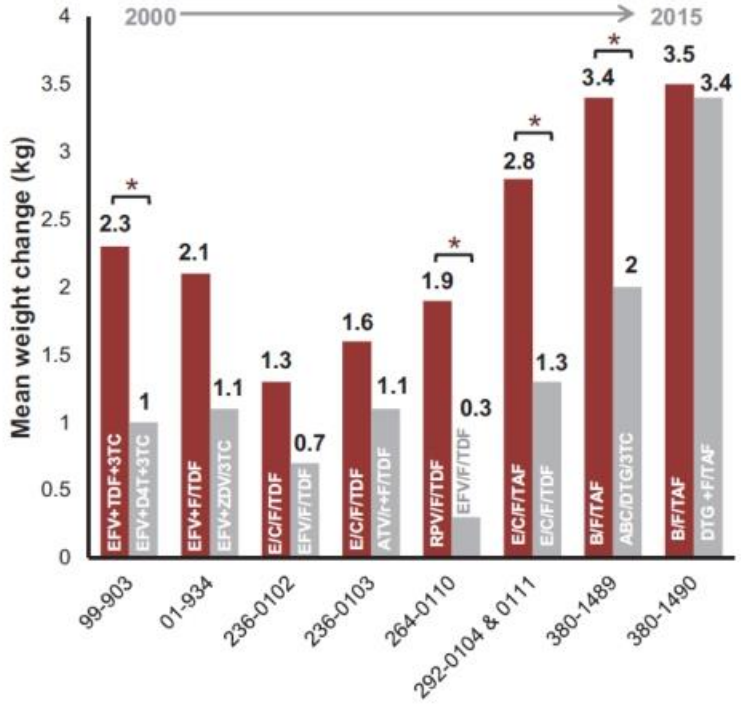
Median 20% increase in body fat to week 24

Mallon et al. *AIDS* 2003. May 2;17(7):971-

Antiretrovirals and weight gain

8 studies in naïve patients



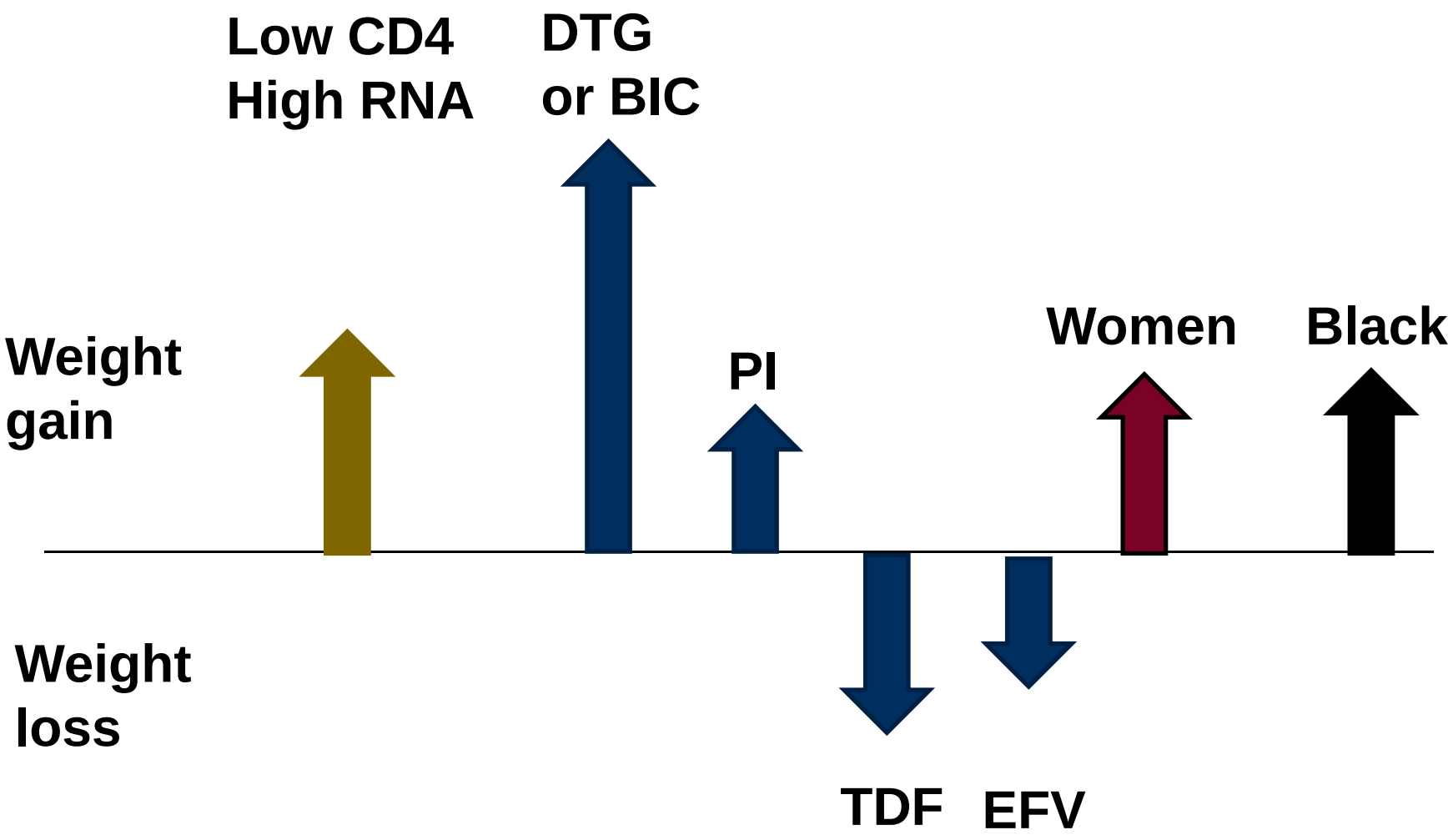


Risk factor	Odds ratio
CD4 <200	4.36
HIV RNA >100,000	1.98
BMI>25, >30	1.54, 1.66
Female	1.54
Black origin	1.32

Risk factor	Odds ratio
BIC / DTG vs. EFV	1.82
RPV vs. EFV	1.51
TAF vs. ABC	1.90
TAF vs. TDF	1.47

Sax et al, Clin Infect Dis 2020

Drivers of weight gain / loss



Antiretrovirals and weight gain

Randomised trial	Study	TDF/F-3TC	TAF/FTC	INSTI	ABC/3TC	Cont/Pbo
ART-naïve: INSTI	NEAT-001	+1.4				DRVr: +3.1
	Spring-1			+2.1		EFV: 0
	1489		+3.6		+2.4	
	1490		+3.5, +3.9			
	ADVANCE	+5.0	+8.0			EFV: +2.0
	FLAIR			+1.3	+1.5	
	GEMINI	+2.1		+3.1		
ART-naïve: NNRTI	DRIVE	+2.4, +1.6				DRVc: +1.8
ART switch	STEAL	+0.7			+1.9	
	TANGO		+0.8			+0.8
	NEAT-022			(+0.8)		(PIr: +0.3)
	ATLAS			+1.8		+0.3
	BRAAVE			+0.9		+0.2
PrEP	HPTN-077			+1.1		Pbo: +1.0
	iPrEx	(+0.1)				(Pbo: +1.6)
	HPTN-083	+0.3		+1.3		
	DISCOVER	+0.5	+1.7			

TDF/EFV: less than comparator

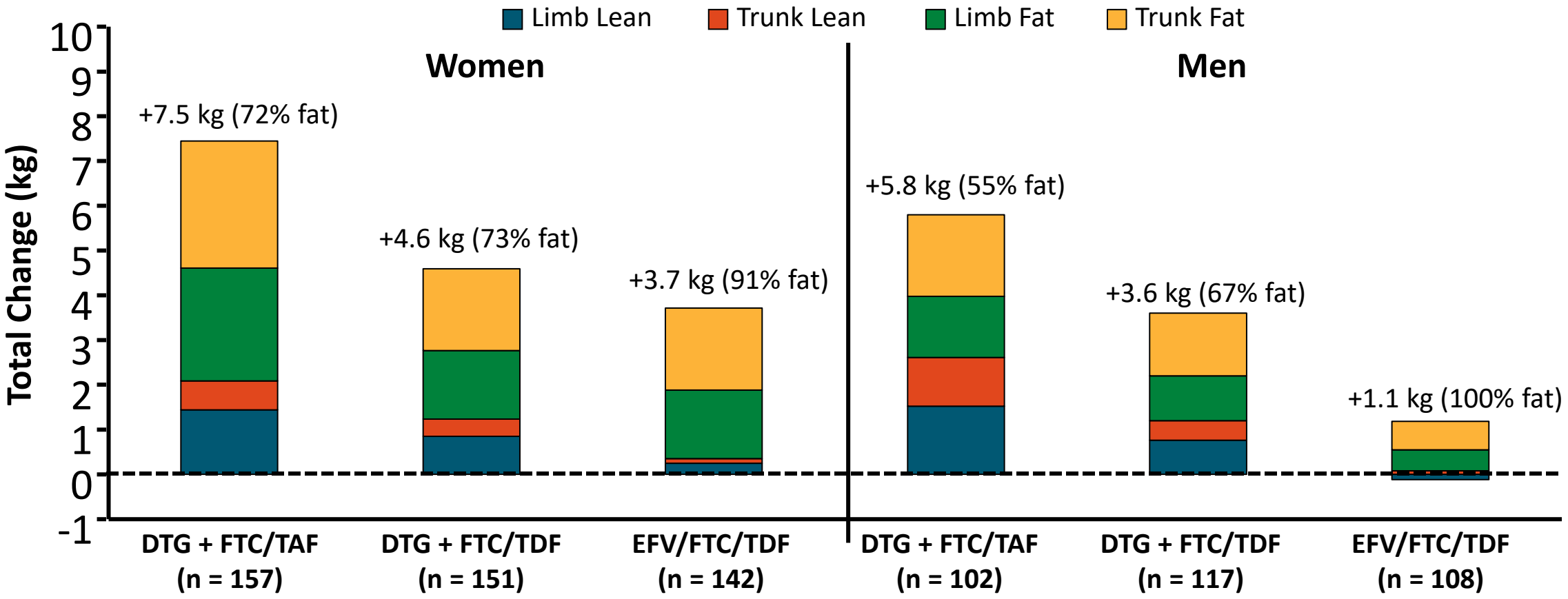
TAF: greater than comparator

INSTI: greater than comparator

Martinez et al, Glasgow 2018
Carr et al, IAS 2019

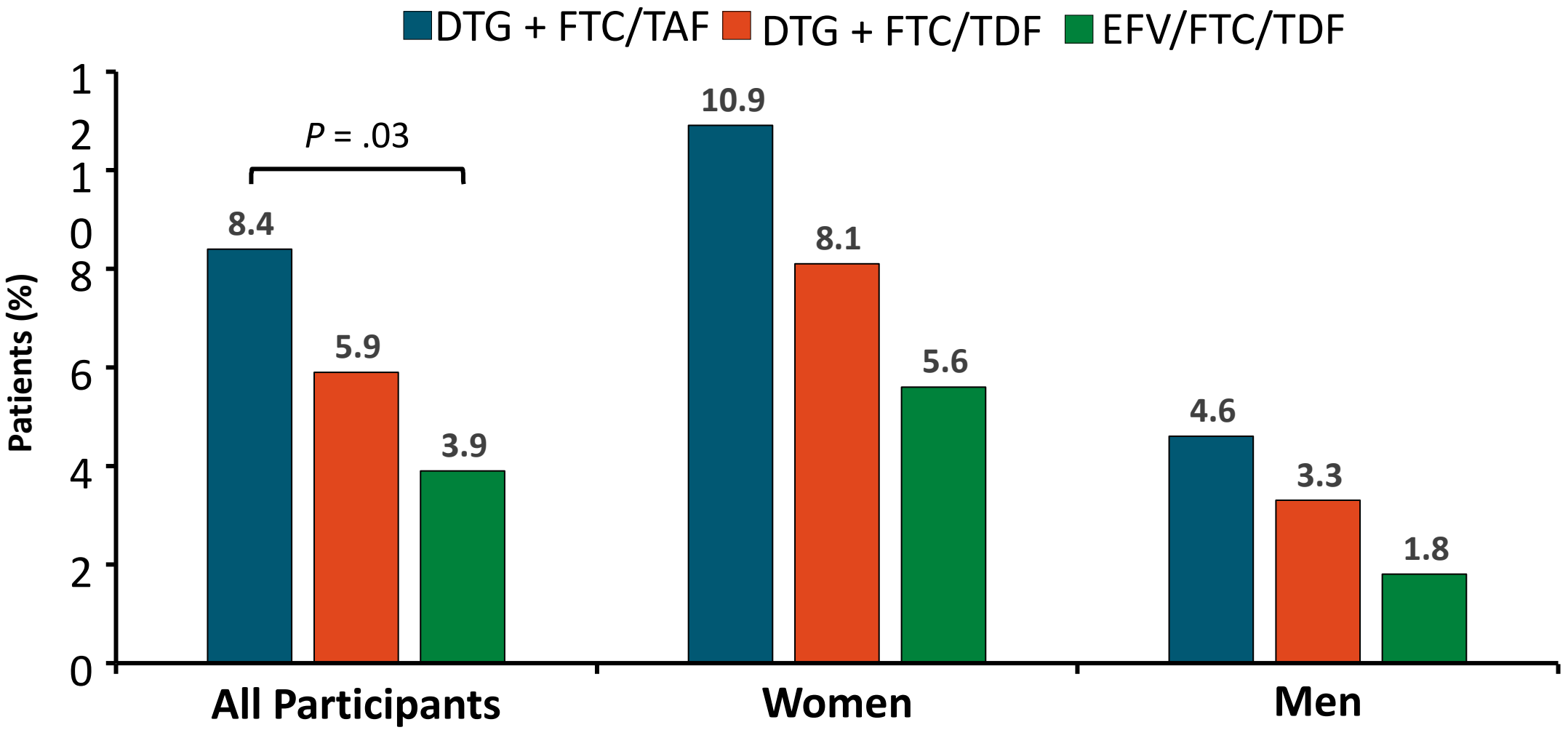
ADVANCE 96-Wk Analysis: Body Composition Changes to Wk 96

- Mass increases predominantly driven by fat gain and distributed between limbs and trunk across all study arms; women gained significantly more fat mass vs men ($P < .001$)



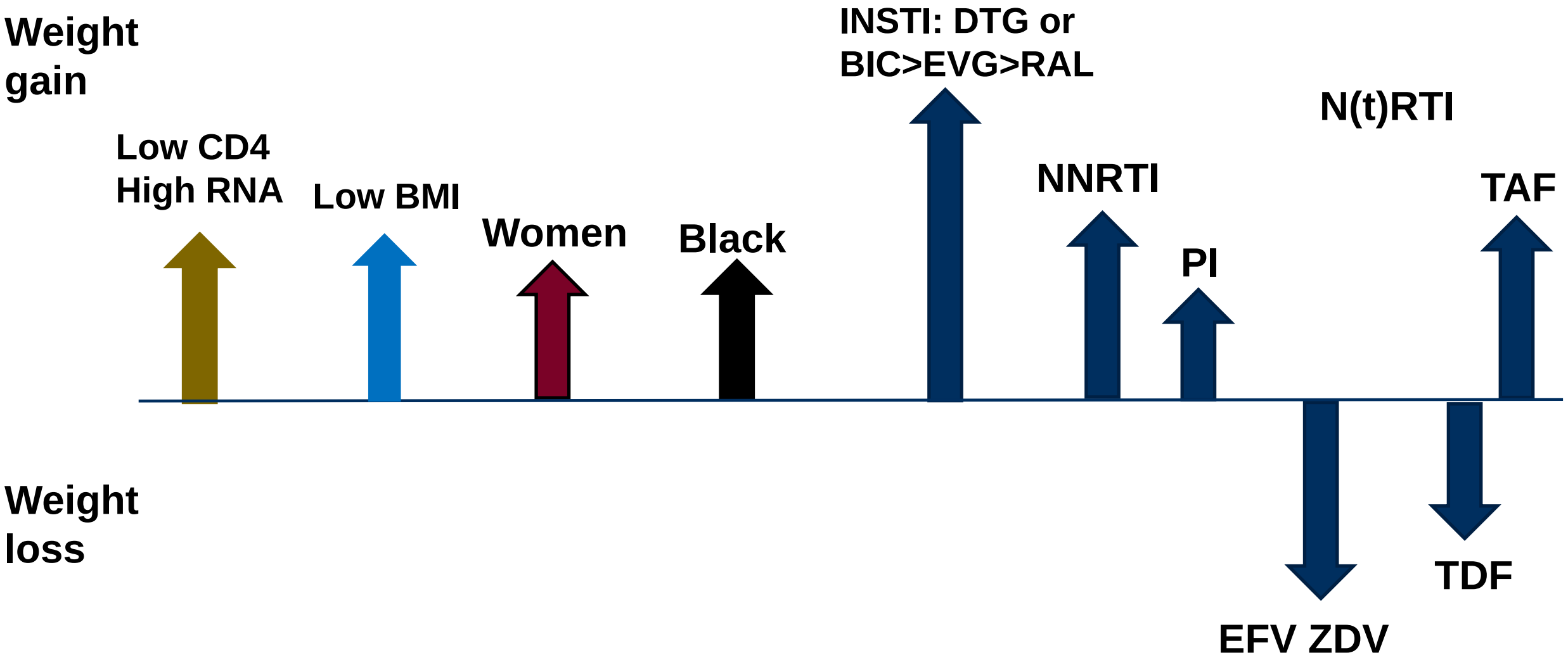
Sokhela. AIDS 2020. Abstr OAXLB0104.

ADVANCE 96-Wk Analysis: Treatment-Emergent Metabolic Syndrome (Wk 96)



Sokhela. AIDS 2020. Abstr OAXLB0104..

Clinical and treatment-related drivers of weight change in PLWH



AIDS. 2021 May 1;35(6):939-945. doi: 10.1097/QAD.0000000000002853.

Dolutegravir is not associated with weight gain in antiretroviral therapy experienced geriatric patients living with HIV

Giovanni Guaraldi [1], Stefano Calza [2], Jovana Milic [1], Andrea Calcagno [3], Emanuele Focà [4], Matteo Rota [2], Stefano Renzetti [2], Anna Celotti [4], Matteo Siano [5], Benedetto Maurizio Celesia [6], Stefania Piconi [7], Giuseppe Vittorio de Socio [8], Anna Maria Cattelan [9], Giancarlo Orofino [10], Agostino Riva [5], Silvia Nozza [11], Giovanni di Perri [3]

ORIGINAL RESEARCH

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.

Methods

Metabolic syndrome was diagnosed, according to the 2009 harmonized definition [30], if three or more of the following five criteria were met:

- waist circumference ≥ 94 cm (men) or ≥ 80 cm (women),
- blood pressure ≥ 130/85 mmHg (or pharmacological treatment for hypertension),
- fasting TG level ≥ 150 mg/dl (or pharmacological treatment for hypertriglyceridaemia),
- fasting HDL cholesterol < 40 mg/dL in men or < 50 mg/ dL in women (or pharmacological treatment for hypercholesterolaemia)
- and fasting glucose ≥ 100 mg/dL (or pharmacological treatment for hyperglycaemia).

Taramasso et al. 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
Diabetes [n (%)]	68 (5.5)	40 (4.7)	54 (5.9)	0.73
Hypertension on therapy [n (%)]	117 (9.4)	145 (17.0)	164 (17.9)	< 0.0001
Systolic blood pressure (mmHg)	123.1 ± 16.0	123.0 ± 14.1	123.4 ± 15.3	0.83
Diastolic blood pressure (mmHg)	78.6 ± 10.0	77.4 ± 8.8	77.9 ± 9.0	0.01
Naïve to antiretroviral therapy [n (%)]	186 (15.0)	9 (1.1)	34 (3.7)	< 0.0001
Smoking habits				
Never	358 (20.4)	305 (35.7)	226 (24.6)	
Current	748 (61.4)	418 (49.0)	503 (54.8)	
Former	113 (9.3)	131 (15.3)	188 (20.5)	< 0.0001
ART (2781 experienced) [n (%)]				
NRTI	924 (87.8)	709 (83.9)	709 (80.3)	< 0.0001
PI	453 (43.0)	411 (48.6)	361 (40.9)	0.004
NNRTI	371 (35.2)	400 (47.3)	359 (40.7)	< 0.0001
INSTI	0	152 (18.0)	246 (27.9)	< 0.0001
Other[a]	11 (1.0)	37 (4.4)	1 (0.1)	< 0.0001
Interrupted/unknown	120 (11.4)	10 (1.2)	36 (4.1)	< 0.0001

Metabolic syndrome (MS) [*n* (%)]	431 (34.7)	286 (33.5)	298 (32.5)	0.57
MS, controlling by sex [*n* (%)]				
Male	333 (37.3)	211 (34.2)	248 (35.3)	
Female	98 (27.9)	75 (31.5)	50 (23.3)	0.46
MS, controlling by age class [*n* (%)]				
< 30–39 years	100 (22.5)	19 (17.6)	21 (12.1)	
40–49 years	211 (38.2)	94 (30.3)	77 (27.2)	
50–59 years	69 (42.6)	114 (36.7)	139 (39.8)	
≥ 60 years	51 (61.4)	59 (47.2)	61 (54.5)	< 0.0001
MS, controlling by BMI class [*n* (%)]				
≤ 18.5 kg/m^2	13 (19.4)	2 (6.2)	3 (6.4)	
18.6–25.0 kg/m^2	206 (25.6)	110 (22.8)	87 (17.2)	
25.1–30.0 kg/m^2	165 (54.5)	122 (45.9)	155 (54.0)	
≥ 30.1 kg/m^2	45 (75.0)	51 (72.8)	52 (68.4)	0.002
Total cholesterol (mg/dL) (mean ± SD)	191 ± 48	202 ± 42	186 ± 42	< 0.0001
HDL cholesterol (mg/dL) (mean ± SD)	47 ± 16	48 ± 16	47 ± 15	0.57
Triglycerides (mg/dL) [median (IQR)]	151 (98–126)	132 (94–197)	119 (84–178)	< 0.0001
Blood glucose (mg/dL) (mean ± SD)	95 ± 27	93 ± 21	93 ± 21	0.02
CD4 count (cells/μL) [median (IQR)]	440 (286–636)	638 (470–857)	640 (442–830)	< 0.0001
HIV-RNA < 50 copies/mL	Not available	93.2	90.8	0.07
AIP [median (IQR)]	0.16 (−0.07, −0.42)	0.12 (−0.10, 0.35)	0.06 (−0.15, 0.30)	< 0.0001

Abbreviations: AIP, atherogenic index of plasma; ART, Antiretroviral therapy; BMI, body mass index; HDL, high-density lipoprotein; INSTI, integrase inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

[a]Maraviroc, enfuvirtide.

Taramasso et al. HIV Medicine. 2021;00:1–10.

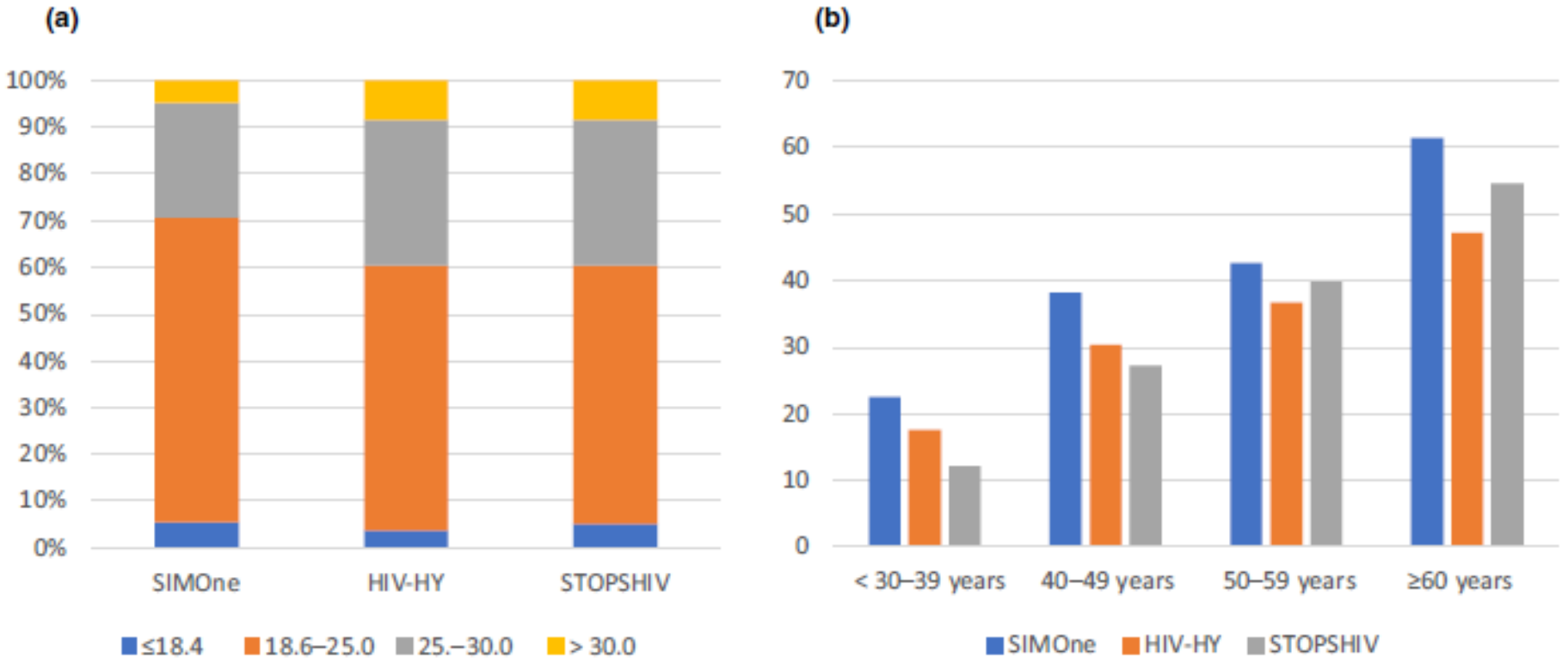


FIGURE 1 Body mass index categories (a) and metabolic syndrome by age (b) in study periods 2005, 2011 and 2015

Taramasso et al. HIV Medicine. 2021;00:1–10.

TABLE 2 Metabolic syndrome criteria in HIV-infected patients with metabolic syndrome (MS), enrolled in the SiMOne (2005), HIV-HY (2011) and STOPSHIV (2015) studies

Variable	SiMOne, 2005 ($n = 431$)	HIV-HY, 2011 ($n = 286$)	STOPSHIV, 2015 ($n = 298$)	p
MS criteria				
WC > 94 (male) or 80 (female) cm	282 (65.4)	222 (77.6)	243 (81.5)	<0.0001
Blood pressure ≥ 130/85 mmHg	336 (78.0)	214 (74.8)	226 (75.8)	0.46
Triglycerides ≥150 mg/dL	359 (83.3)	231 (80.8)	214 (71.8)	0.0003
HDL-cholesterol < 40 (male) or < 50 (female) mg/dL	275 (63.8)	187 (63.4)	205 (68.8)	0.17
Blood glucose ≥100 mg/dL	232 (53.8)	136 (47.6)	151 (50.7)	0.33

Abbreviations: HDL, high-density lipoprotein; WC, waist circumference.

Taramasso et al. HIV Medicine. 2021;00:1–10.

TABLE 3 Odds ratio for metabolic syndrome (MS) and MS features in HIV-infected patients enrolled in HIV-HY (2011) and STOPSHIV (2015) studies as compared with SiMOne study (2005)

	Crude OR (95% CI)		Adjusted OR (95% CI)[a]	
Reference category: SIMOne, 2005	**HIV-HY, 2011**	**STOPSHIV, 2015**	**HIV-HY, 2011**	**STOPSHIV, 2015**
MS	0.95 (0.79–1.14)	0.91 (0.76–1.09)	0.56 (0.44–0.70)	0.57 (0.46–0.71)
MS (sensitivity analysis)[b]	0.94 (0.78–1.14)	0.92 (0.75–1.14)	0.59 (0.46–0.75)	0.58 (0.46–0.74)
WC > 94 (male) or 80 (female) cm	1.58 (1.32–1.88)	1.35 (1.14–1.61)	1.15 (0.92–1.43)	1.11 (0.90–1.36)
WC > 94 (male) or 80 (female) cm (sensitivity analysis)[b]	1.61 (1.34–1.92)	1.41 (1.56–1.72)	1.16 (0.92–1.46)	1.18 (0.94–1.49)
Blood pressure ≥ 130/85 mmHg	0.91 (0.76–1.08)	0.92 (0.78–1.10)	0.46 (0.37–0.58)	0.52 (0.42–0.54)
Triglycerides ≥ 150 mg/dL	0.72 (0.61–0.86)	0.53 (0.44–0.63)	0.48 (0.39–0.60)	0.37 (0.30–0.46)
HDL-cholesterol < 40 (male) or < 50 (female) mg/dL	0.96 (0.80–1.14)	1.00 (0.84–1.18)	0.96 (0.77–1.19)	0.96 (0.78–1.18)
Blood glucose ≥ 100 mg/dL	0.78 (0.64–0.96)	0.84 (0.69–1.02)	0.47 (0.36–0.61)	0.55 (0.44–0.70)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]The logistic equation included age, sex, geographical area, current use of nonnucleoside reverse transcriptase inhibitors, current use of protease inhibitor, naïve status, current CD4 count (≤ 350, 351–500, 501–750, ≥ 751 copies/mL).

[b]Analysis performed using the complete cases.

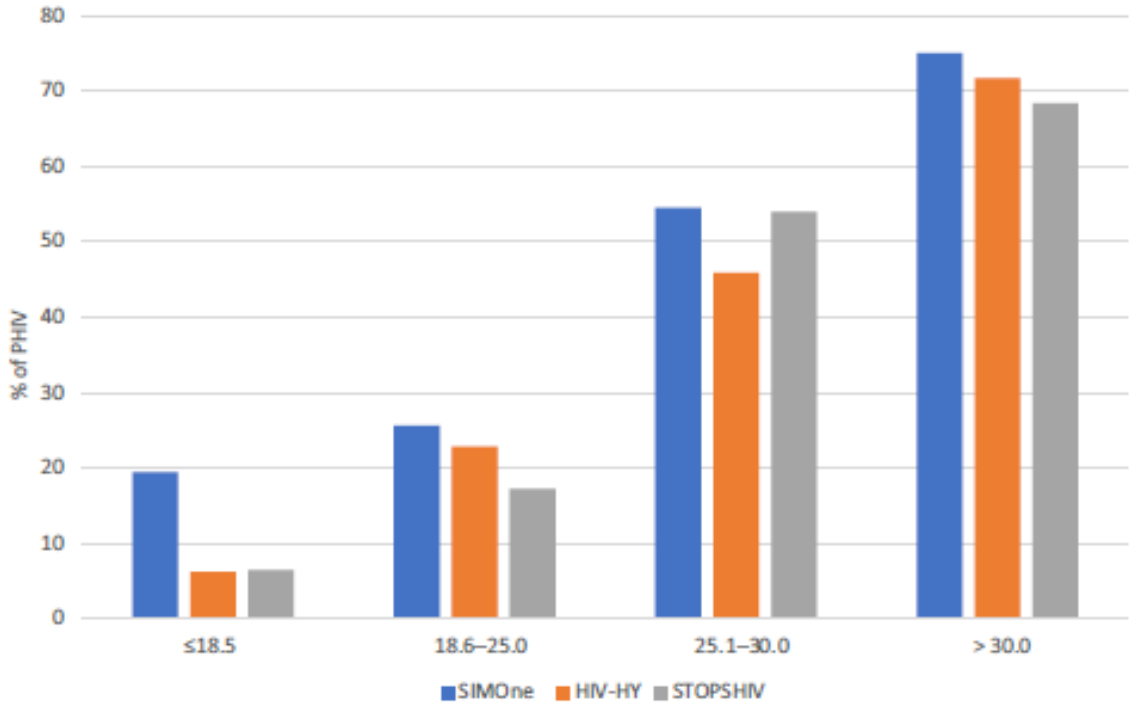


FIGURE 2 Prevalence of Metabolic Syndrome in underweight (body mass index, BMI, ≤ 18.5 kg/m^2), normal weight (BMI 18.6-25.0 kg/m^2), overweight (BMI 25.1-30 kg/m^2) and obese (BMI >30 kg/m^2) study participants

Taramasso et al. HIV Medicine. 2021;00:1–10.

“Our study offers a punctual description of the prevalence of MS and being overweight in a large population enrolled in multiple centres in Italy and probably reflects the real-life population followed in this country over the period 2005–2015.
In recent years, PHIV have clearly improved their metabolic profile, in parallel with the increasing use of modern ART and with growing attention to educational interventions. No increase in MS was observed with increasing patient weight in more recent years of the study.»

Taramasso et al. HIV Medicine. 2021;00:1–10.

Antiretroviral therapy and body fat distribution

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1996	ART is safe
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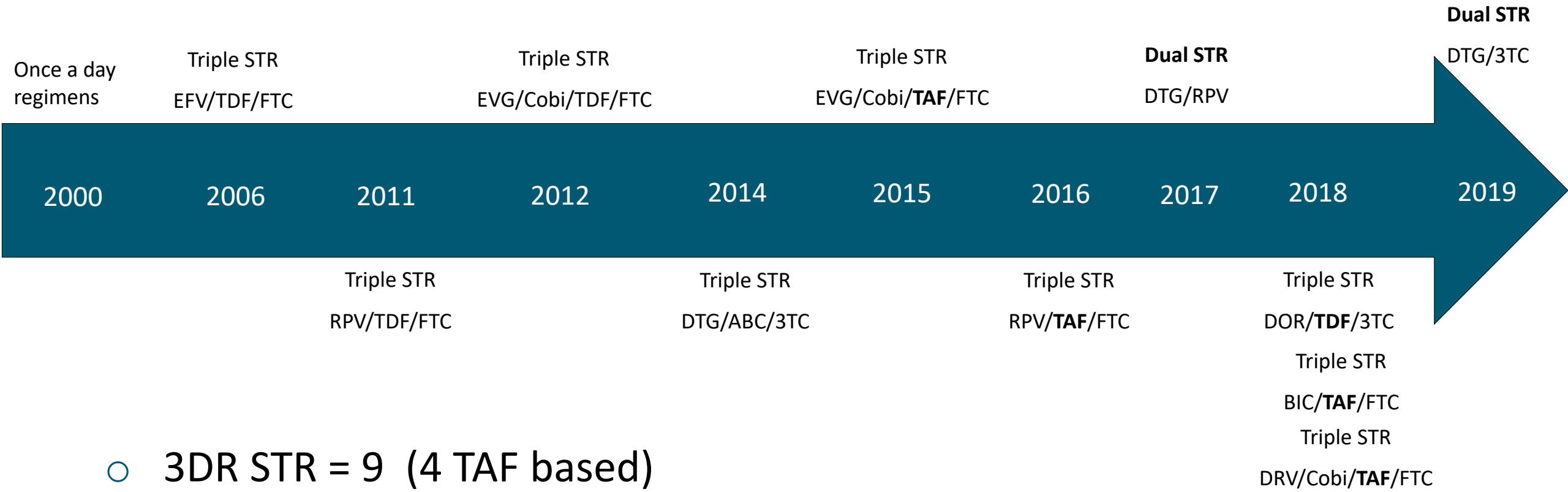
2003	Prospective confirmation Prevented with initial TDF/ABC
2004	Treatment: glitazones not very effective
2005	Mitochondrial mechanism
2008	PI (LPVr) did not cause LD in RCT

Year	HIV weight gain
2014	Modern ART is safe
2017	Reports of generalised weight gain
2018	Larger cohorts – INSTI link RCT of DTG switching
2019	"TAF / DTG cause fat gain" "TDF / EFV prevent fat gain"
2020+	3 DR vs 2 DR? Mechanism(s)? Biology of risk factors? Hierarchy in drug classes? Does weight gain stabilise? Reversibility / treatment? Clinical consequences?

ART simplification over the years: what to switch to?



- 3DR STR = 9 (4 TAF based)
- 2DR STR = 2 (DTG + RPV o 3TC)

Switch Strategies for Virologically Suppressed Persons

Definition of virologically suppressed

Clinical trials exploring switching strategies have generally defined suppression as an HIV-VL < 50 copies/mL for at least 6 months

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipoatrophy (d4T, AZT), central nervous system adverse events (EFV, DTG), diarrhoea (PI/r) and jaundice (ATV), proximal renal tubulopathy and low bone mineral density (TDF), see Adverse Effects of ARVs and Drug Classes
2. **Prevention of long-term toxicity**. Example of this proactive switch: prevention of lipoatrophy in persons receiving d4T or AZT and prevention of proximal renal tubulopathy with TDF, see Adverse Effects of ARVs and Drug Classes. This may include person's concerns about safety
3. **Avoidance of drug-drug interactions**, page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see Drug-drug Interactions between DAAs and ARVs
4. **Planned pregnancy or women wishing to conceive**, see Antiretroviral Drugs Not Recommended in Women who Wish to Conceive or Become Pregnant while on ART
5. **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification**: to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification**: Increasing the genetic barrier of a regimen in order to prevent resistance (e.g. in persons with reduced adherence)
9. **Cost reduction**: switching to the generic form of their current regimen, if available

Principles

Clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. Just because the viremia is suppressed it should not be assumed that the PLWH is well adapted and tolerating the current regimen

1. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of comorbid conditions, and improve quality of life. The primary concern when switching should be to sustain and not to jeopardize virological suppression. In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy. The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures and historical resistance
2. The complete ARV history with HIV-VL, tolerability issue, cumulative genotypic resistance history and/or phases of viremia on previous regimens with the potential of resistance development should be evaluated prior to any drug switch
3. Switches within the same drug class (e.g. TDF/FTC -> TAF/FTC, EFV -> RPV) are usually virologically safe if equal potency and in the absence of resistance
4. Cross-class switches of single drugs with the same genetic resistance barrier (for example EFV to RAL) are usually virologically safe in the absence of resistance to the new compound
5. In case of prior virologic failures, with or without evidence of resistance, switches have to be planned especially carefully when they result in a lower genetic resistance barrier of the regimen. A PI/b may only be switched to unboosted ATV, an NNRTI, INSTIs RAL and EVG if full activity of the 2 NRTIs in the new regimen can be assumed based on resistance data, ARV history and HIV-VL results before switching (see 2.) Due to the higher genetic barrier of DTG and BIC, it is currently unclear if a switch to DTG- or BIC-based regimens also requires full activity of 2 NRTIs in the combination

Switch Strategies for Virologically Suppressed Persons

6. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. This requires knowledge about the resistance selection profile of the switch regimen. For example, some mutations (e.g. K65R or M184I/V) might affect the activity of most currently available STRs and preclude their future use. Especially, when reducing the number of drugs in a regimen or its genetic barrier to resistance, the chances of composing a fully suppressive regimen after potential failure following switch should be considered
7. Proviral DNA genotyping may be useful in persons with multiple virological failures, unavailable resistance history or low-level viremia at the time of switch. Results ought to be taken cautiously as proviral DNA genotype may not detect previous resistance mutations and can also detect clinically irrelevant mutations. Therefore, routine proviral DNA genotyping is currently not recommended
8. When selecting a new regimen, clinicians should carefully review the possibility of new drug-drug interactions with antiretroviral and concomitant medication leading to suboptimal drug exposure or toxicity, as well as the lag time for hepatic enzyme induction or blockade following discontinuation of the offending drug. Examples are: increased TDF toxicity with a PI/b or an increase in metformin exposure with DTG
9. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV and HBV vaccination status. TDF or TAF should not be discontinued in persons with chronic HBV
10. PLWH should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity or tolerability issues of the new regimen
11. If a PLWH receives and tolerates a regimen that is no longer a preferred option, and none of the other reasons for change applies, there is no need to change. Example: persons tolerating EFV-containing regimens
12. See online video lecture How to Change ART from the EACS online course Clinical Management of HIV

Dual therapies

Dual therapies supported by large randomized clinical trials or meta-analyses

DTG + RPV
3TC + DTG
3TC + DRV/b
3TC + ATV/b

In clinical trials, these strategies have not been associated with more virological rebounds than triple therapy. There were a few cases of resistance development on DTG + RPV.

Dual therapy options supported only by small trials:

DRV/b+ RPV

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is
a) no historical resistance and
b) absence of chronic HBV co-infection

Strategies not recommended

a. Monotherapy with a PI/b
b. Monotherapy with DTG
c. Dual or triple NRTIs combinations
d. Specific two-drug combination, i.e. 1 NRTI + 1 NNRTI or 1 NRTI + 1 unboosted PI, 1 NRTI + RAL, MVC + RAL, PI/b + MVC, ATV/b + RAL
e. Intermittent therapy, sequential or prolonged treatment interruptions

Switching From Suppressive ART to an STR: Key Studies With Contemporary Regimens

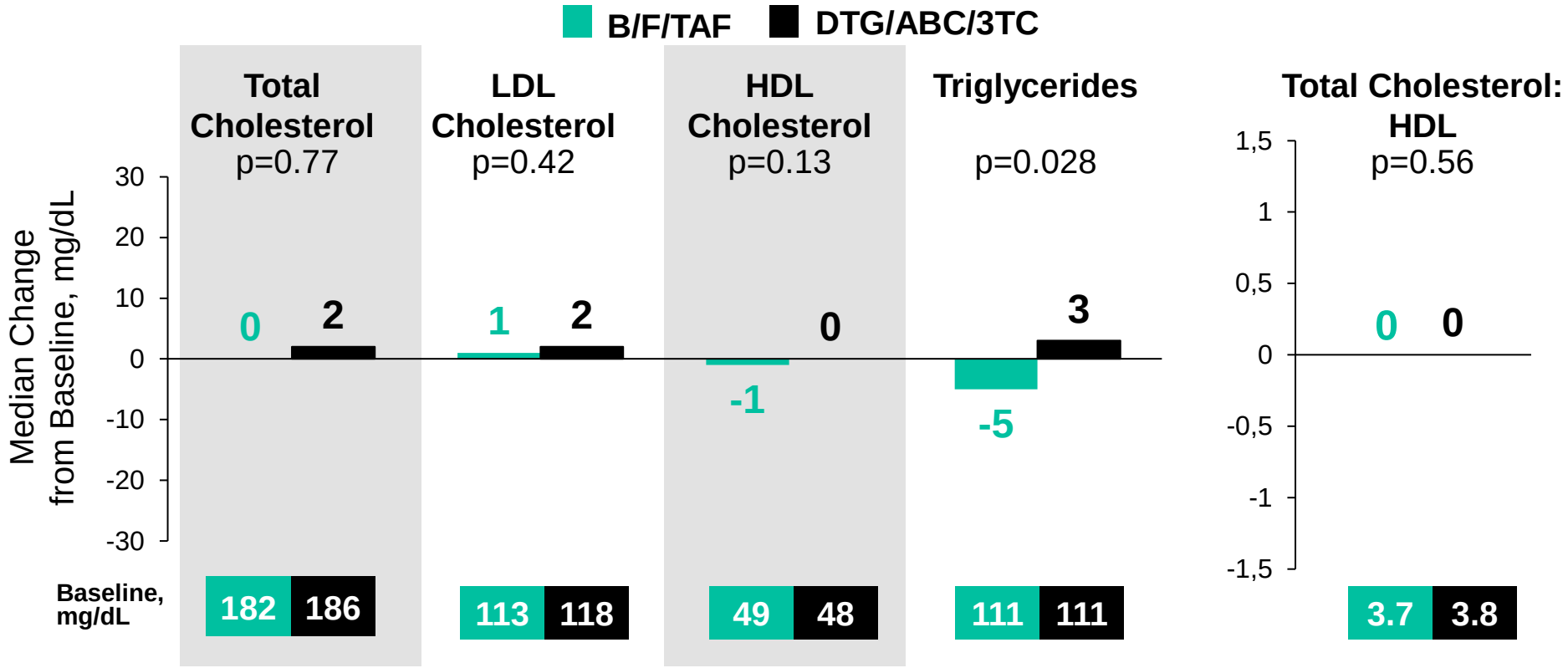
- Noninferior efficacy for all switch regimens vs baseline regimen; all FDA approved to treat virologically suppressed patients

Key Studies	Switch From	Switch to
380-1878[1] or 380-1844[2] or 380-4030[3]	Boosted PI + 2 NRTIs or DTG/ABC/3TC or DTG + FTC/(TAF or TDF)	BIC/FTC/TAF
DRIVE-SHIFT[4]	Third agent + 2 NRTIs	DOR/3TC/TDF
SWORD 1 & 2[5]	Third agent + 2 NRTIs	DTG/RPV
TANGO[6]	Third agent + 2 NRTIs	DTG/3TC
EMERALD[7]	Boosted PI + FTC/TDF	DRV/COBI/FTC/TAF
GS-1216[8] or GS-1160[9]	RPV/FTC/TDF or EFV/FTC/TDF	RPV/FTC/TAF

Most recent FDA approvals: for BIC/FTC/TAF and DTG/RPV, must have no history of treatment failure and no resistance to regimen components; for DRV/COBI/FTC/TAF, must have no resistance to DRV, TFV.

1. Daar. Lancet HIV. 2018;5:e347. 2. Molina. Lancet HIV. 2018;5:e357. 3. Sax. IAS 2019. Abstr MOAB0105.
4. Johnson. JAIDS. 2019;81:463-472. 5. Llibre. Lancet. 2018;391:839. 6. van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB
8. Mills. Lancet Infect Dis. 2016;16:43. 8. Orkin. Lancet HIV. 2017;4:e195. 9. DeJesus. Lancet HIV. 2017;4:e205.

Changes in Fasting Lipids at Week 48*

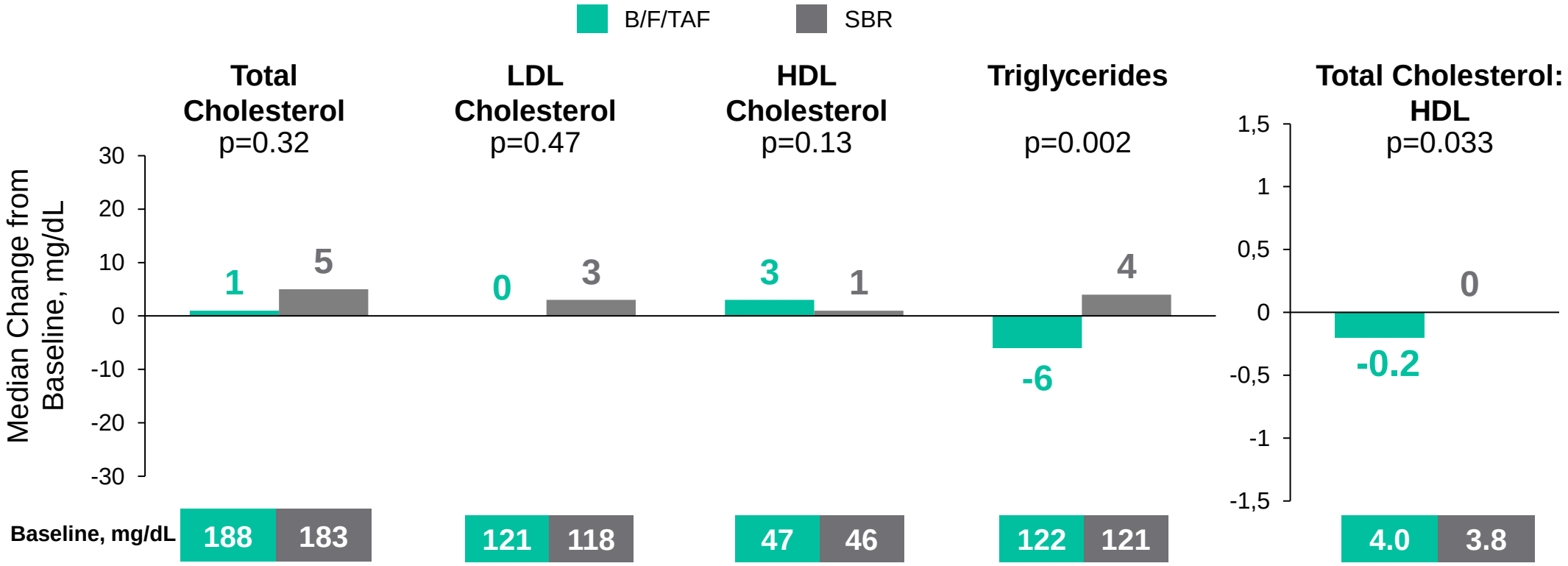


No changes in fasting lipid parameters when switching from DTG/ABC/3TC to B/F/TAF

*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.

Changes in Fasting Lipids at Week 48*

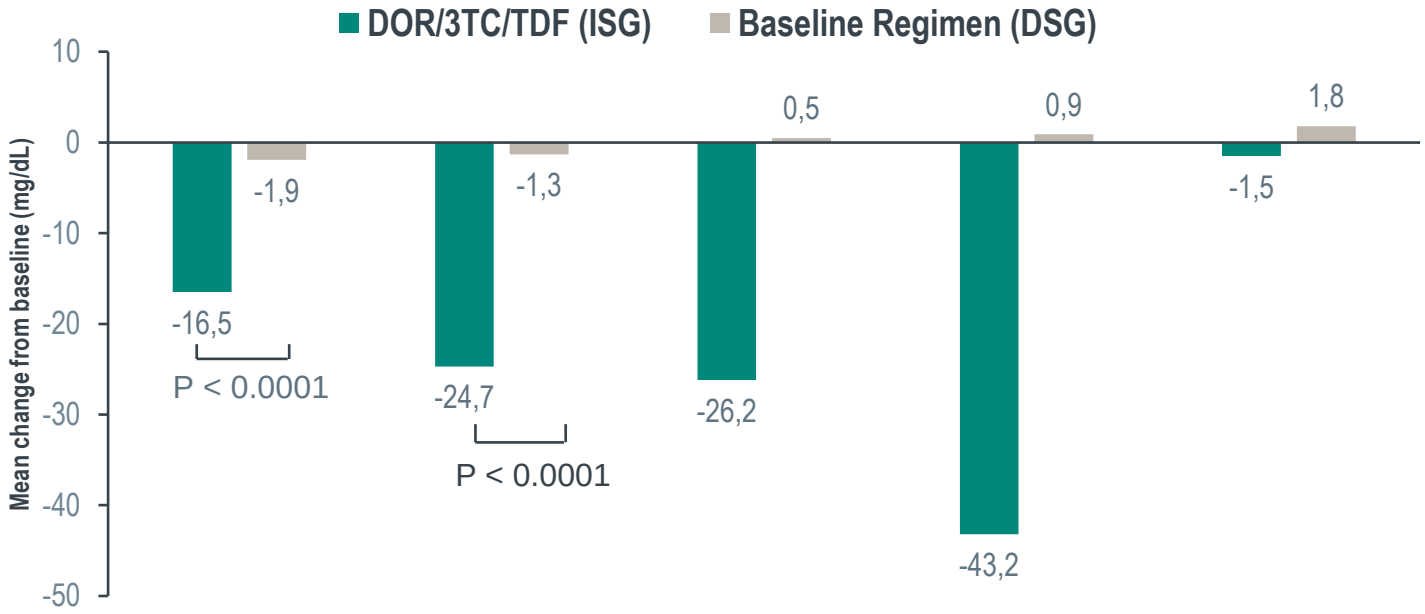


Initiated lipid lowering agents during the study: B/F/TAF 2.8%, SBR 3.5%, p=0.64
*P-values from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Switch to B/F/TAF is associated with small, significant decreases in triglycerides and TC:HDL ratio

DRIVE-SHIFT Week 48

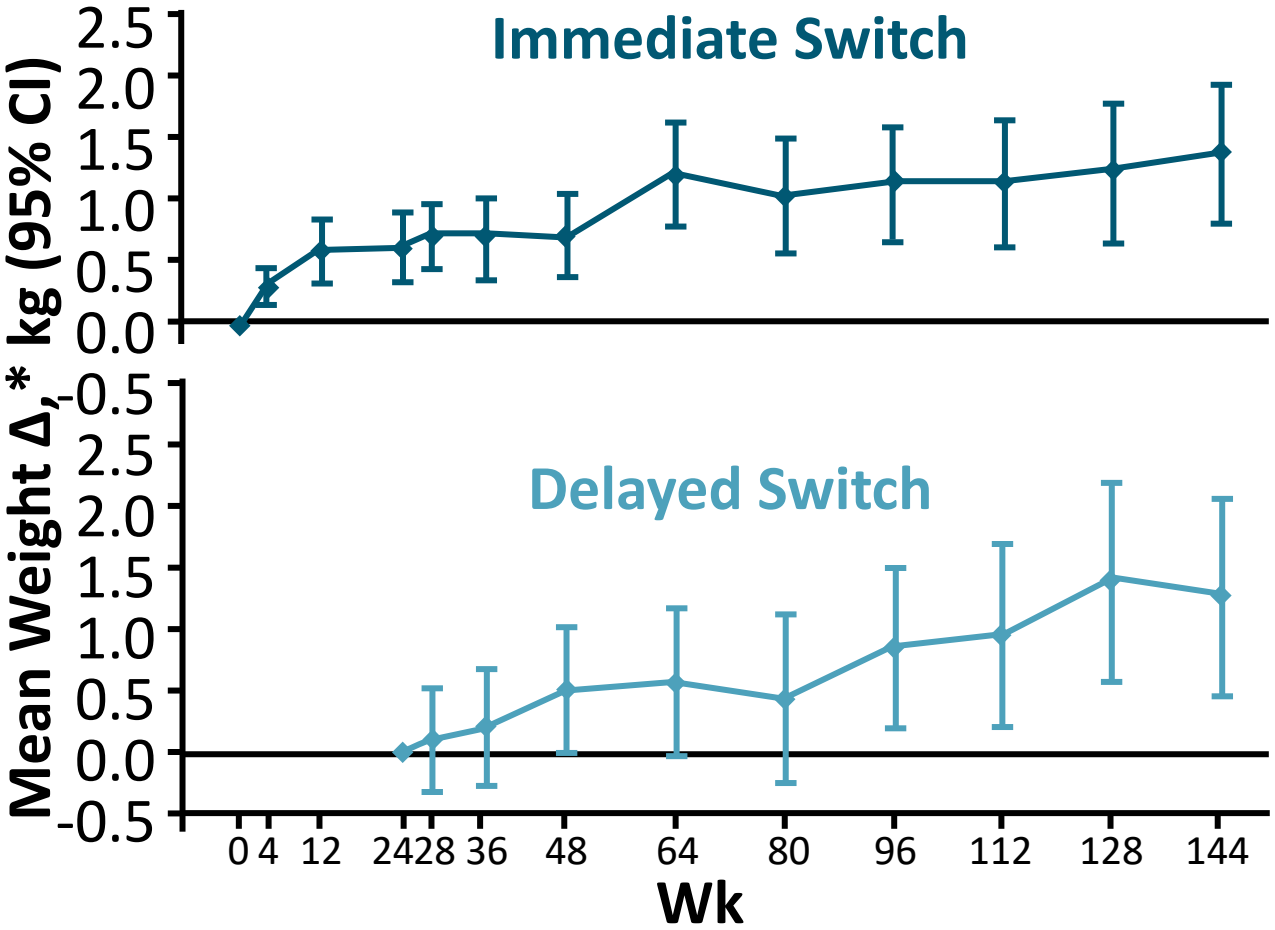
Change from Baseline in Fasting Lipids at Week 24, in Participants Receiving a Ritonavir-boosted PI Regimen



	LDL-C	Non-HDL-C	Cholesterol	Triglycerides	HDL-C
Difference (95% CI)	-14.7 (-18.9, -10.4)	-23.0 (-28.0, -18.1)	-25.8 (-30.9, -20.7)	-42.9 (-59.1, -26.7)	-3.0 (-4.8. -1.2)

Johnson M, Kumar P, Molina JM, et al. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr. 2019;81(4):463-472. https://www.ncbi.nlm.nih.gov/pubmed/30985556

DRIVE-SHIFT: Post-Switch Mean Weight Change

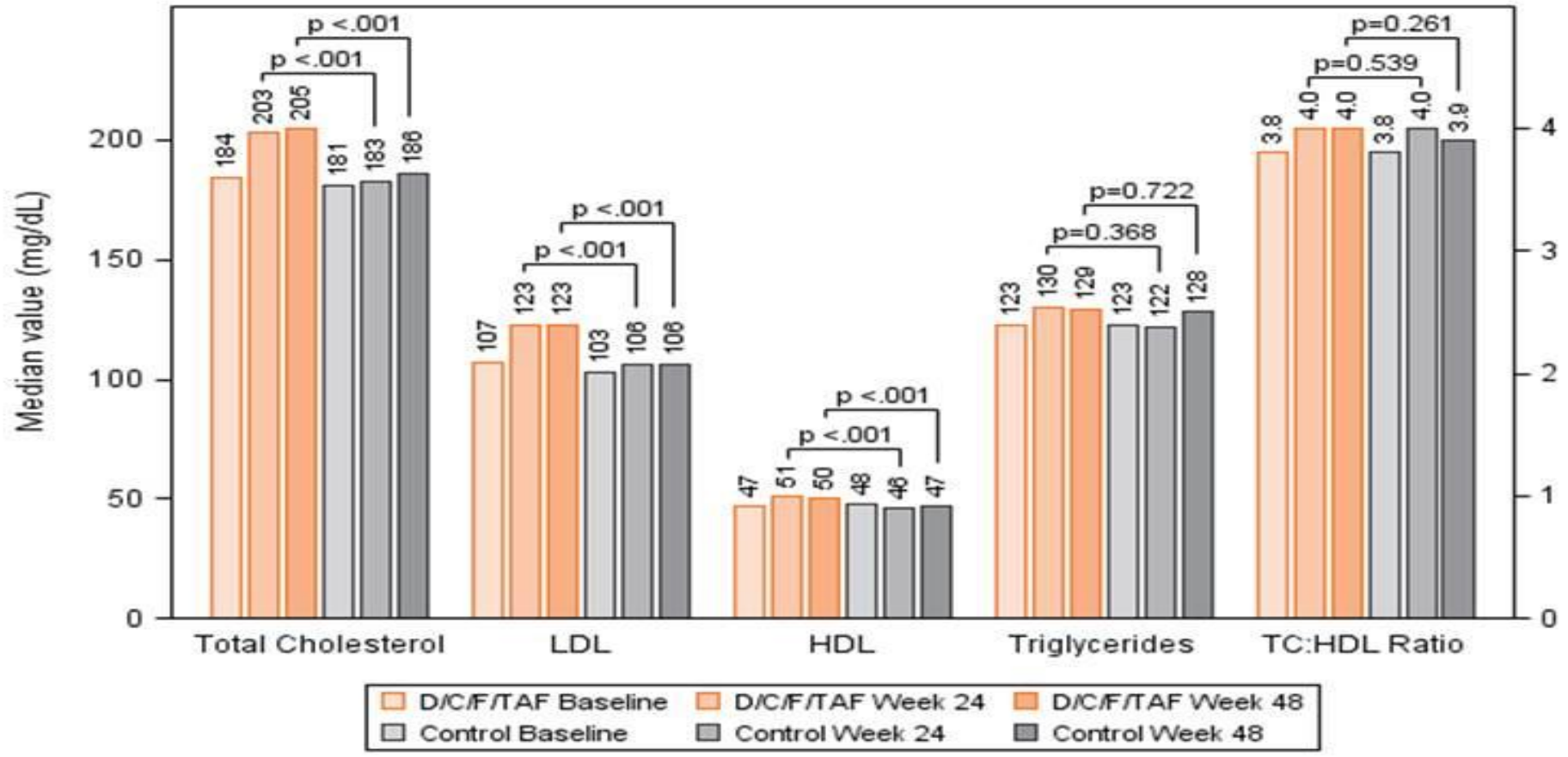


Mean Weight Δ,* kg (95% CI)	Immediate Switch	Delayed Switch
Wk 24	0.7 (0.4 to 0.9)	NA
Wk 48	0.7 (0.4 to 1.1)	0.5 (0 to 1.0)
Wk 96	1.1 (0.7 to 1.6)	0.8 (0.2 to 1.5)
Wk 144	1.4 (0.8 to 1.9)	1.2 (0.4 to 2.0)

*Adjusted for weight at switch, race (black vs nonblack), ethnicity (Hispanic vs other), sex, age, BL CD4+ cell count, and HIV-1 RNA.

Kumar. AIDS 2020. Abstr OAB0605.

EMERALD: Median fasting Lipids at Baseline, Week 24 and Week 48



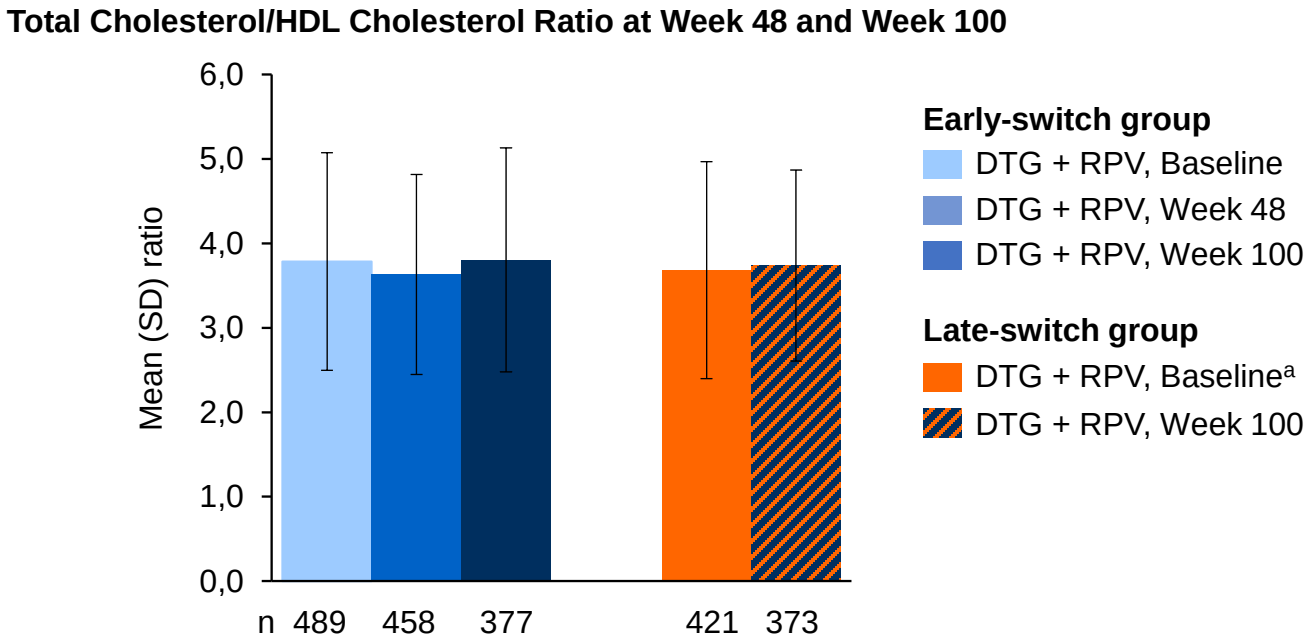
Source: GSFLAB03

Subjects starting any lipid-lowering drug during treatment	D/C/F/TAF	Control
	32/763 (4.2%)	11/378 (2.9%)

- More subjects in DCFTAF group had increases from BL at W48 of Total and HDL cholesterol
- There was no difference in TC/HDL between groups

SWORD STUDY: Lipids

- No discernable pattern of changes from baseline in mean serum concentration of lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides) was noted in the early- or late-switch groups



[a]Last pre-switch data (usually Week 48) used for late-switch baseline.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

Baseline TDF use >70%

TANGO: Lipid Changes at Wk 48

- In analysis excluding those with BL lipid-modifying agent use, lipid changes favored switch to **DTG/3TC** (n = 275) vs continued **TAF-based ART** (n = 263) in overall population
  - When stratified by previous use of boosting agents, statistically favorable changes with **DTG/3TC** vs **TAF-based ART** persisted in boosted subgroup

Change From BL to Wk 48, %	Overall			Boosted Subgroup			Unboosted Subgroup		
	DTG/3TC (n = 275)	TAF-Based ART (n = 263)	*P* Value	DTG/3TC (n = 202)	TAF-Based ART (n = 203)	*P* Value	DTG/3TC (n = 97)	TAF-Based ART (n = 94)	*P* Value
Total cholesterol	-4.5	2.3	< .001	-5.7	2.2	< .001	-0.8	2.0	--
HDL	-1.2	1.7	--	-0.8	1.02	--	-2.3	0.1	--
LDL	-5.5	2.2	< .001	-6.6	2.9	< .001	-2.0	-0.3	--
Triglycerides	-11.2	6.0	< .001	-14.1	4.0	< .001	-1.6	12.2	--
TC:HDL ratio	-3.3	0.5	.017	-4.8	0.1	.007	1.4	1.8	--

van Wyk. Clin Infect Dis. 2020;[Epub]. van Wyk. AIDS 2020. Abstr OAB0606.

TANGO: Weight Change at Wk 48

- Overall weight gains minimal, comparable between treatment arms

Weight Parameter	DTG/3TC (n = 343)	TAF-Based ART (n = 343)
Adjusted mean weight change from BL, kg (SE)	0.81 (0.23)	0.76 (0.22)
▪ Prior TAF duration < 1 yr*	1.45 (0.46)	1.35 (0.47)
▪ Prior TAF duration ≥ 1 yr†	0.60 (0.26)	0.60 (0.25)
▪ Boosted baseline regimen	0.81 (0.27)	0.88 (0.25)
▪ Unboosted baseline regimen	0.81 (0.45)	0.40 (0.44)
Weight increase ≥ 10% from BL, n (%)	11 (3)	13 (4)

*DTG/3TC, n = 83; TAF-based ART, n = 76. †DTG/3TC, n = 260; TAF-based ART, n = 267.

van Wyk. AIDS 2020. Abstr OAB0606.

How to Beat Inflammation: A Patient's Guide

- Continue your HIV medications. Stay undetectable
- Stop smoking
- Maintain normal weight
- If overweight, lose at least 5-10% of body weight
- Exercise
- Have a healthy diet
- Cut down on alcohol, avoid drugs
- Get your hepatitis C cured
- Maintain dental health

Conclusioni

L’ottimizzazione della terapia nel paziente con syndrome metabolica passa per un’attenta valutazione dei singoli fattori contribuenti

Alcuni regimi ART “lipid friendly” sono certamente utili nel ridurre l’impatto metabolico della terapia

La gestione della sindrome metabolica deve prevedere un approccio multidisciplinare che preveda un attenta valutazione dei fattori di rischio e degli stili di vita nelle persone con HIV.

GRAZIE PER L'ATTENZIONE!