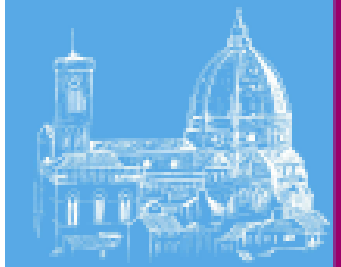
28 Febbraio
1 Marzo 2022

HYBRID EDITION



INNOVAZIONE E RICERCA PER LA PRATICA CLINICA

XIV Workshop Nazionale

TERAPIA E PREVENZIONE DELL'INFEZIONE DA HIV E MICRORGANISMI EMERGENTI

Sindrome metabolica e ART

Giordano Madeddu

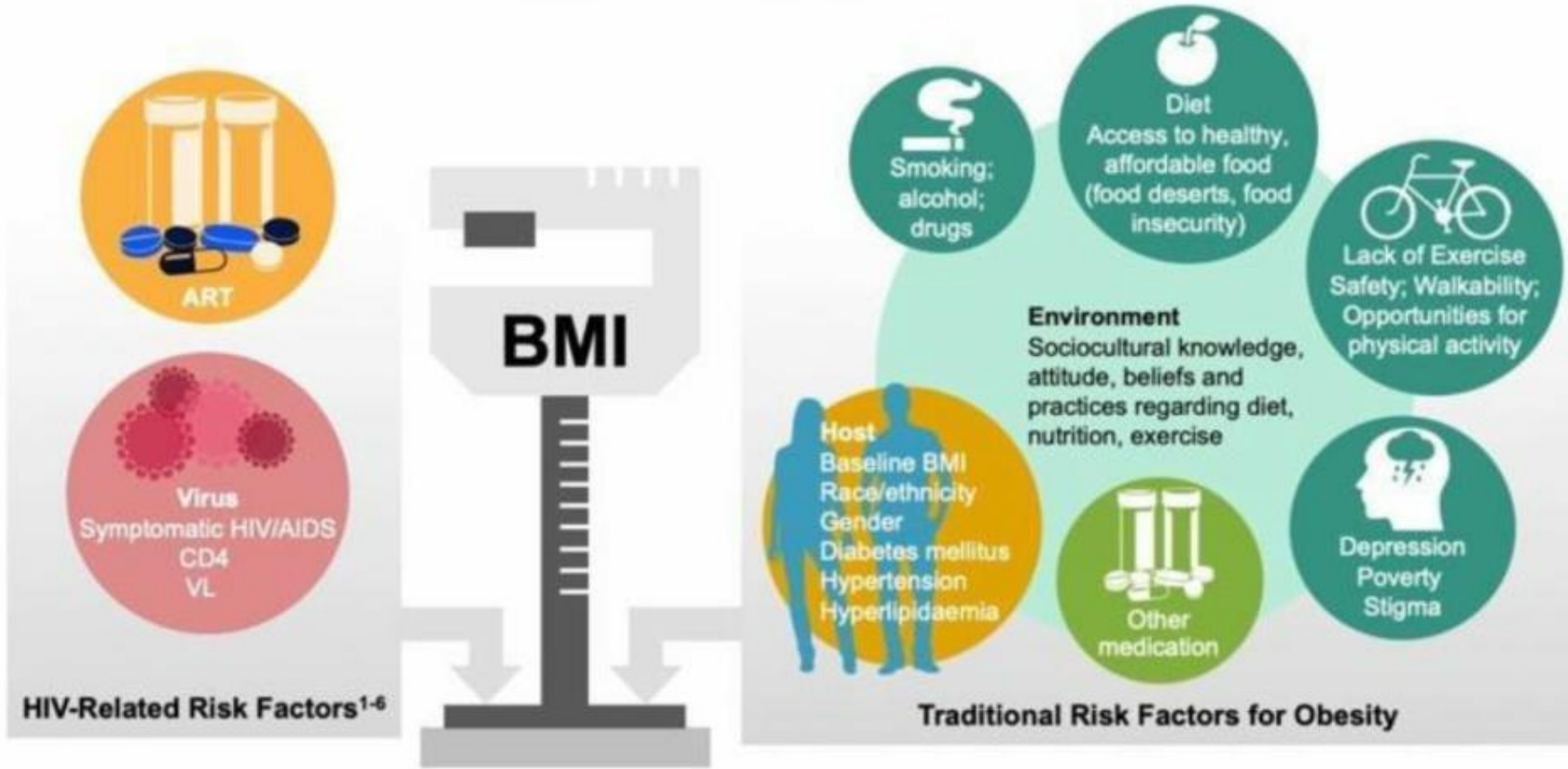
UNIVERSITÀ DEGLI STUDI DI SASSARI

Financial disclosure

Prof. Madeddu has received consultancy and/or speakers' fees from Gilead Sciences, Janssen, Merck Sharp & Dohme, ViiV ant Thera technologies

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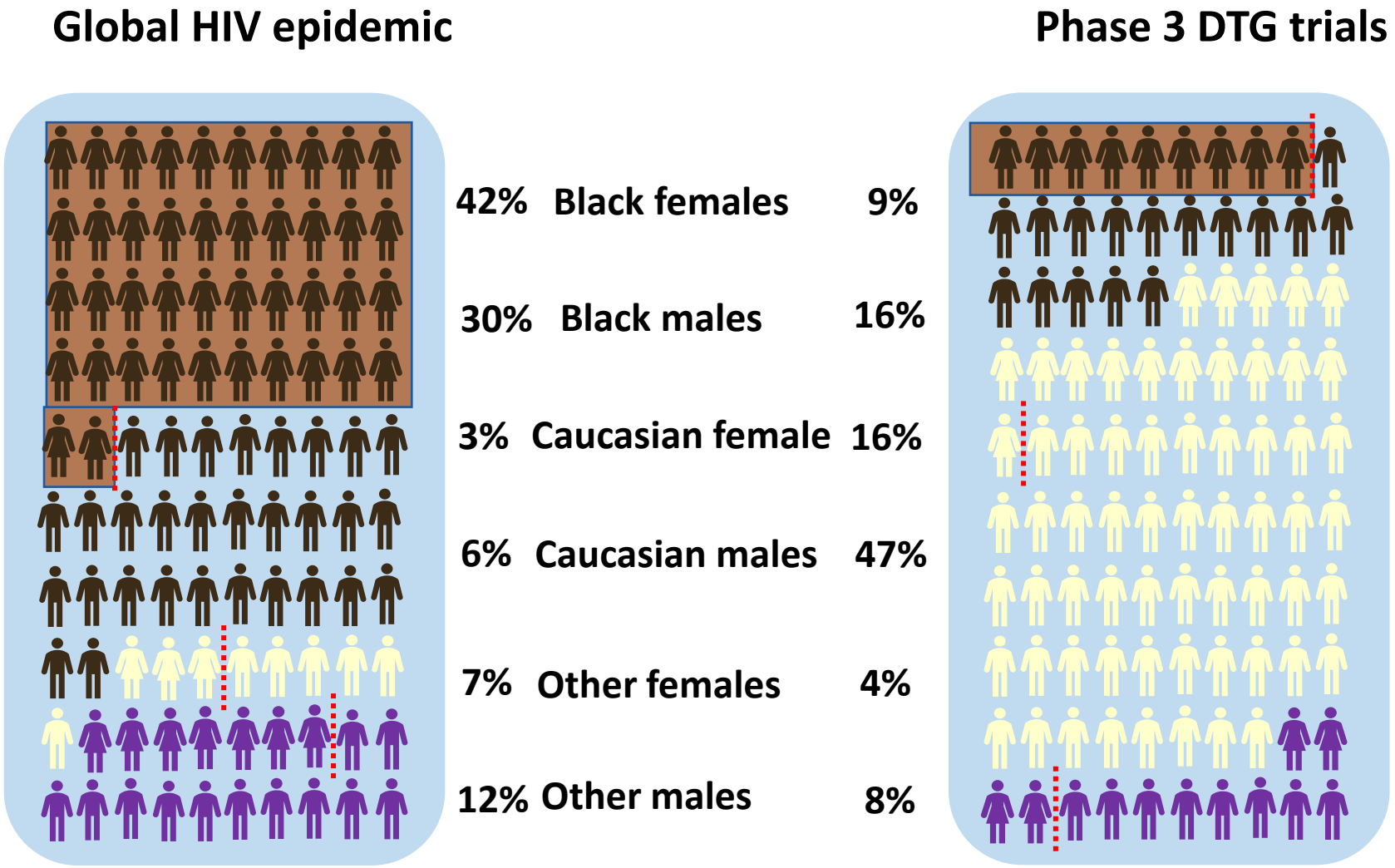
Year	HIV weight gain
2014	Modern ART is safe
2017	Reports of generalised weight gain
2018	Larger cohorts – INSTI link
2019	"TAF / INSTI cause fat gain" "TDF / EFV prevent fat gain"

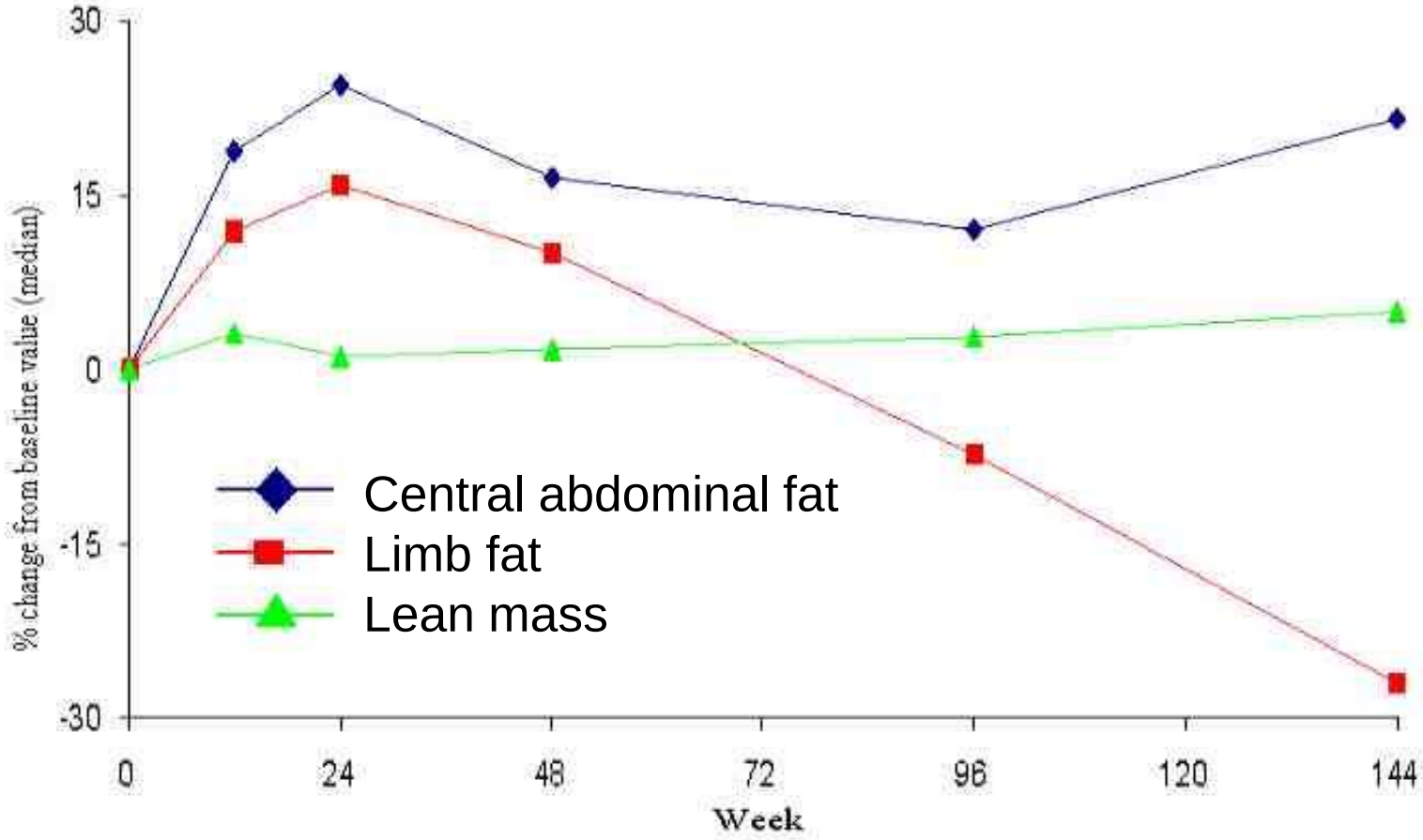
Phase 3 trials under-represent the people at highest risk of adverse events



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



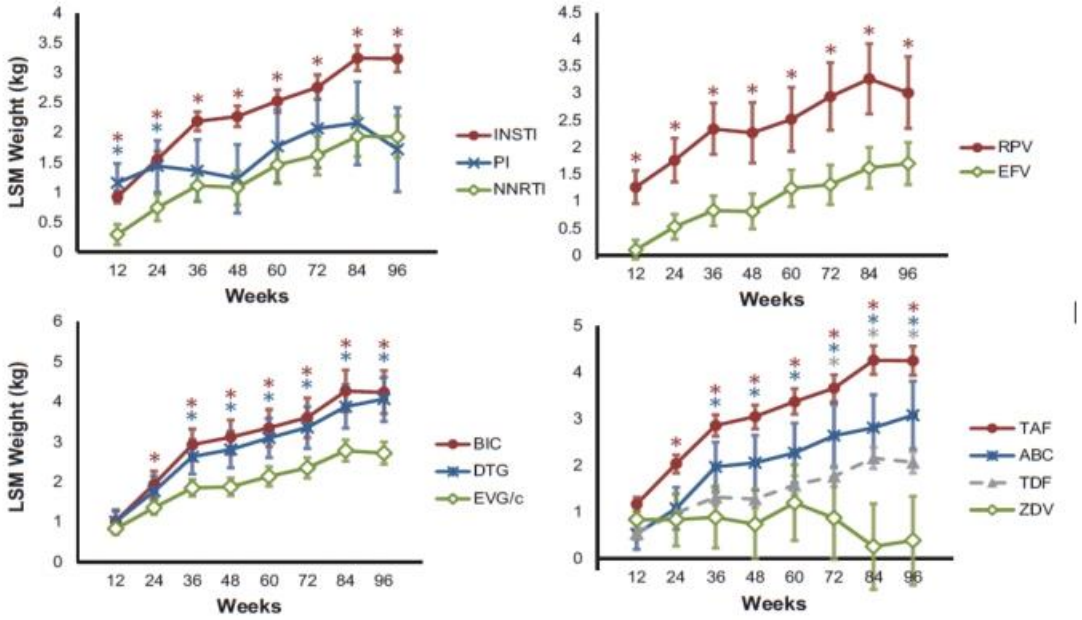
PI:
IDV, NFV, SQV
NNRTI:
EFV, NVP
NRTI:
ZDV/3TC
d4T/3TC

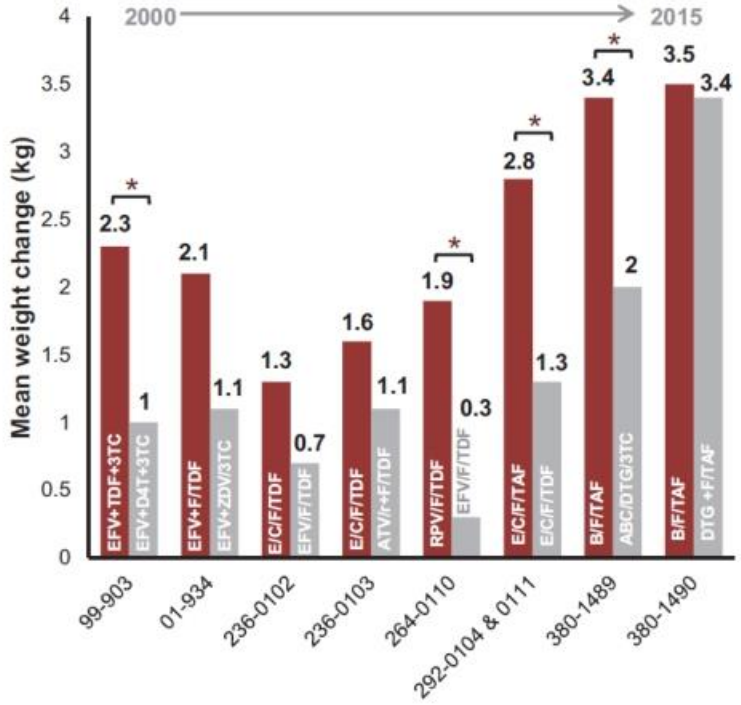
Median 20% increase in body fat to week 24

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

Antiretrovirals and weight gain

8 studies in naïve patients



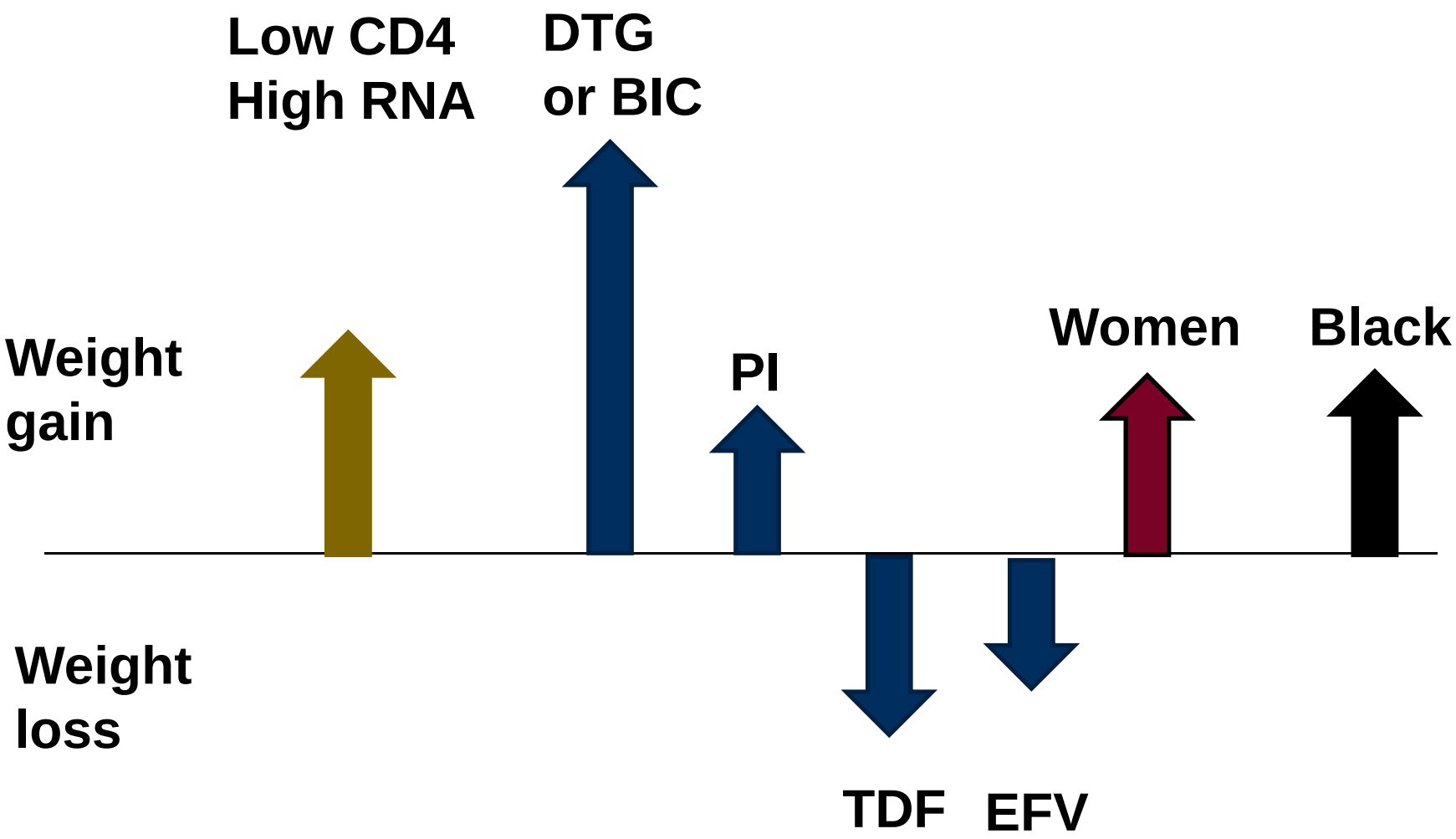


Risk factor	Odds ratio
CD4 <200	4.36
HIV RNA >100,000	1.98
BMI>25, >30	1.54, 1.66
Female	1.54
Black origin	1.32

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

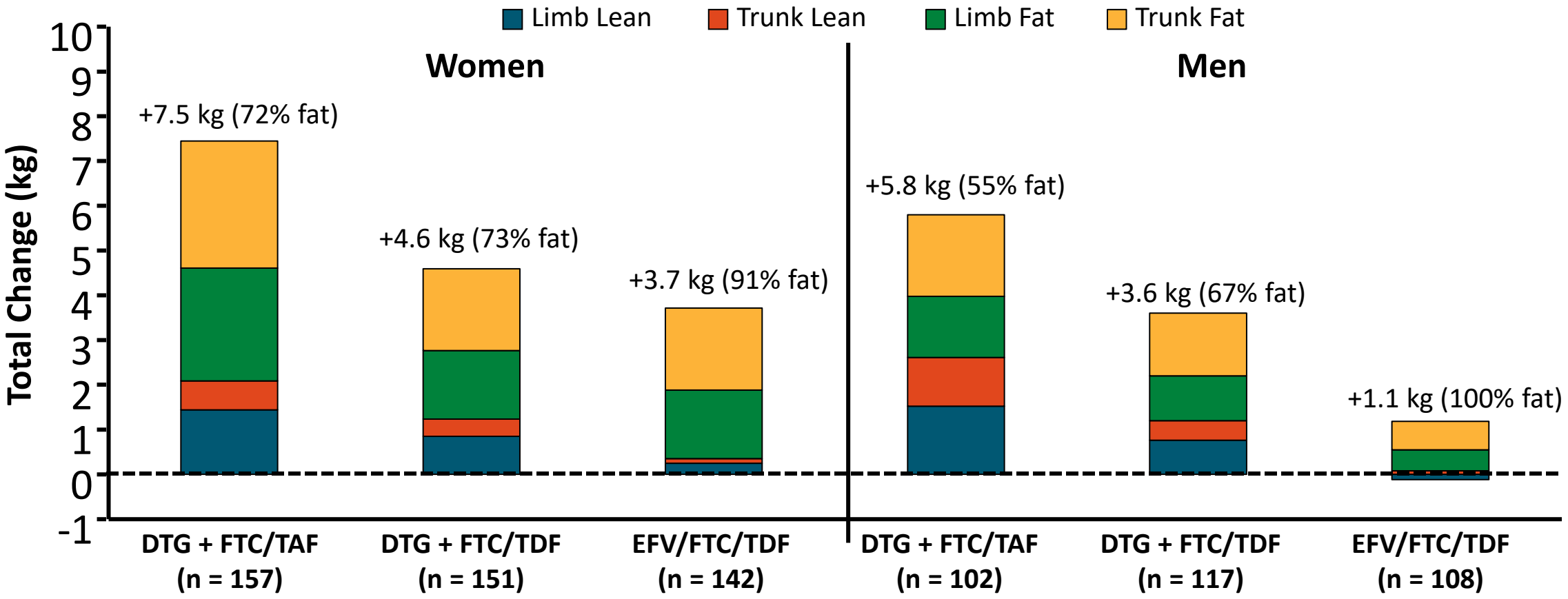
TAF: greater than comparator

INSTI: greater than comparator

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

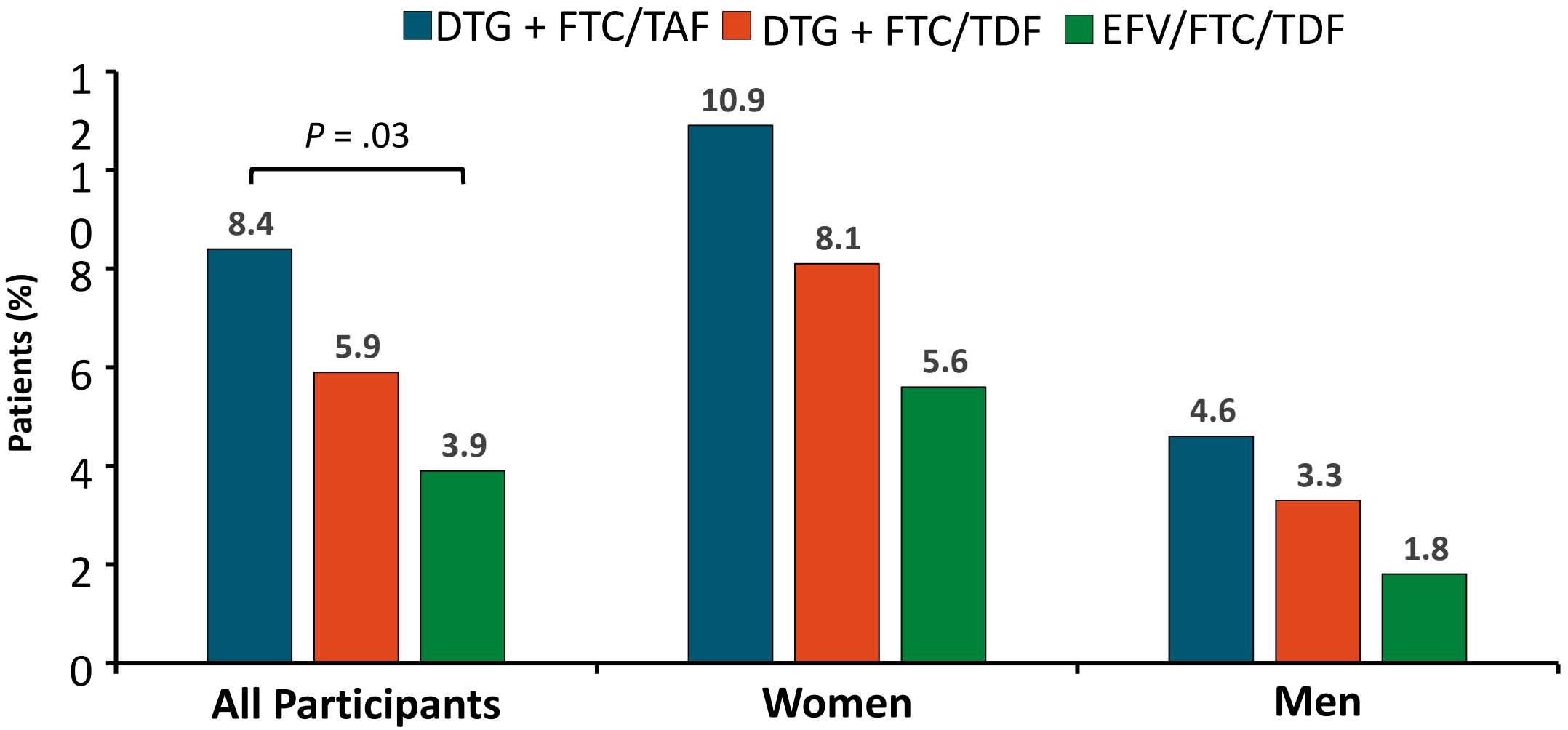
ADVANCE 96-Wk Analysis: Body Composition Changes to Wk 96

- 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 ($P < .001$)



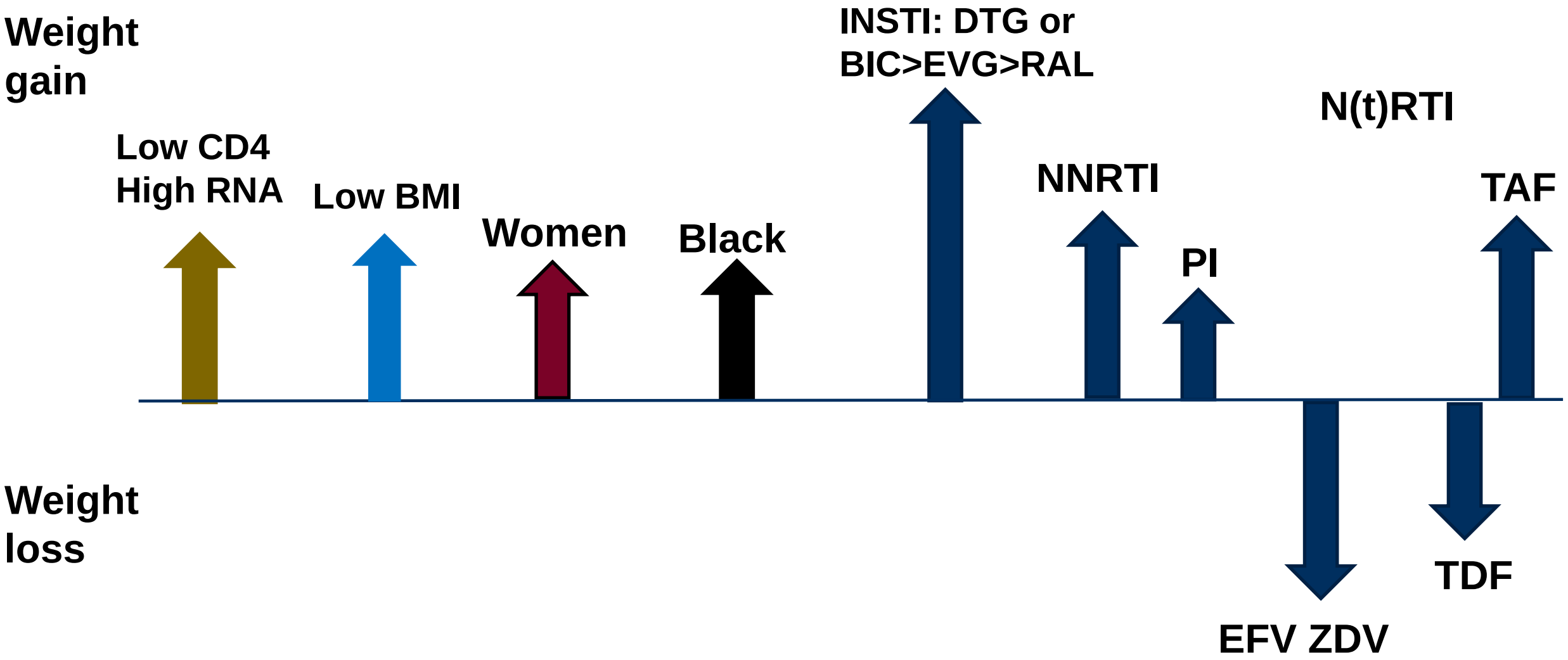
Sokhela. AIDS 2020. Abstr OAXLB0104.

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



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.

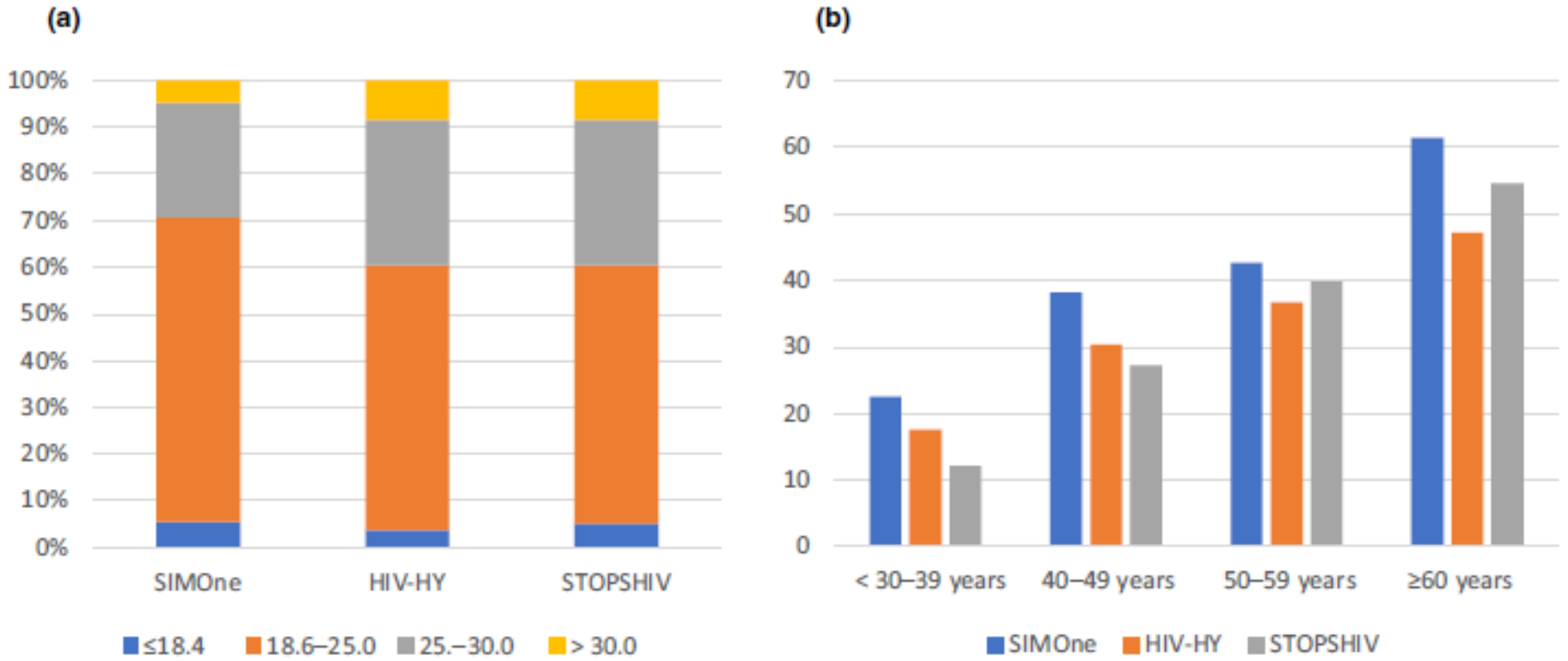


FIGURE 1 Body mass index categories (a) and metabolic syndrome by age (b) in study periods 2005, 2011 and 2015

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.

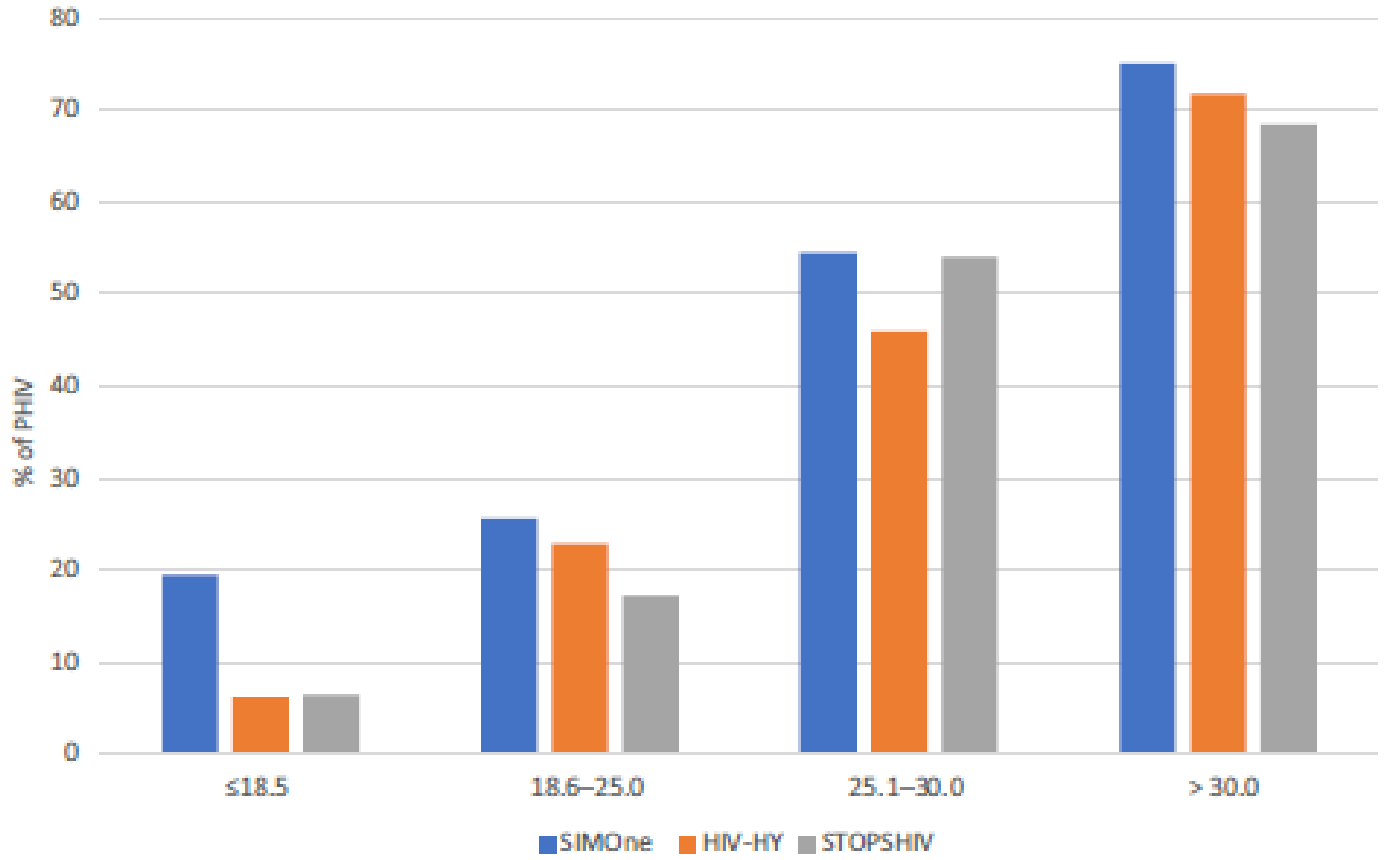


FIGURE 2 Prevalence of Metabolic Syndrome in underweight (body mass index, BMI, ≤ 18.5 kg/m^2), normal weight (BMI 18.6-25.0 kg/m^2), overweight (BMI 25.1-30 kg/m^2) and obese (BMI >30 kg/m^2) study participants

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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2018	Larger cohorts – INSTI link
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?

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.

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2020+	3 DR vs 2 DR? Mechanism(s)? Biology of risk factors? Hierarchy in drug classes? Does weight gain stabilise? Reversibility / treatment? Clinical consequences?

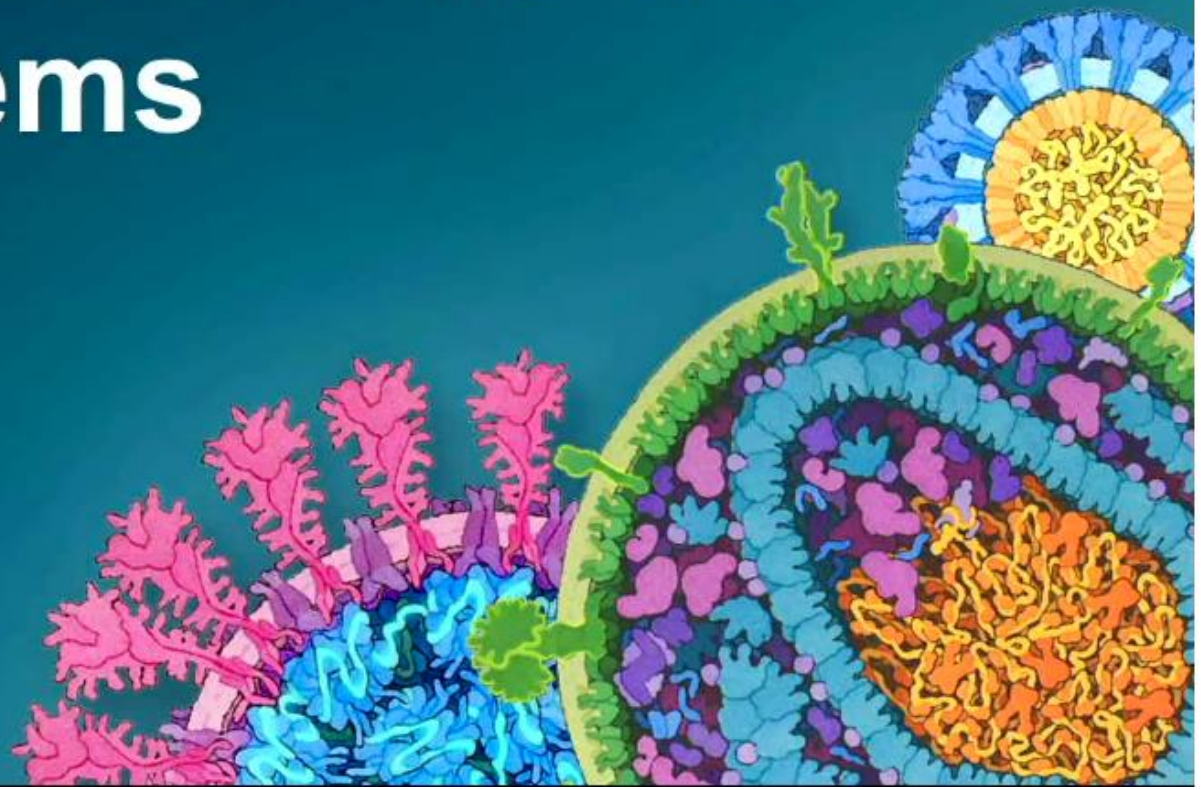
CROI 2022

Trends in Myocardial Infarction Risk by HIV Status in Two US Healthcare Systems

Michael J. Silverberg

Kaiser Permanente Northern California
Oakland CA USA

Disclosure: None



Trends of myocardial infarction risk by HIV status in two US healthcare systems

Study Settings

Kaiser Permanente Northern California (KPNC)

- Integrated healthcare delivery system serving San Francisco Bay Area
- 4.5 million current members, with ~30,000 cumulative members with HIV

Mass General Brigham (Partners)

- Integrated health care system serving Boston, MA and surrounding regions
- Brigham and Women's and Massachusetts General Hospitals and affiliated outpatient centers
- 1.5 million served annually; ~7,000 cumulative with HIV

Silverberg MJ et al CROI 2022. Abstr 39.

Methods

- Study design: cohort study
- Study population:
  - PWH: adults (≥18 years) identified between 2005-2017 from KPNC or Partners. Those with history of CVD excluded.
  - PWoH: 3:1 propensity-matched in KPNC and 4:1 in Partners, with propensity scores informed by baseline* demographics (age, race, sex, year) and baseline* Framingham risk score components (total cholesterol, HDL, diabetes, systolic BP, hypertension treatment, smoking)

*baseline: The first year Framingham risk score components were measured, anchored at lipids date

- Outcome: New diagnosis of MI during 2005-2020 (all events adjudicated at Partners; validated case definition at KPNC)
- Exposure: HIV status and baseline calendar era (2005-2009 and 2010-2017)
- Follow-up: From baseline until earliest of: MI, death, loss-to-follow-up, 5 years after baseline, or administrative end of follow-up (2020)

Baseline Characteristics by HIV and Calendar Era
reflects matching by HIV status

	PWH		PWoH	
Baseline Calendar Era	2005-2009	2010-2017	2005-2009	2010-2017
N	4,280	5,121	14,059	15,359
Mean age, years	44.5	43.7	44.2	43.3
Men, %	87	89	85	90
White / Black / Other, %	53 / 17 / 30	49 / 18 / 34	51 / 19 / 30	49 /17 / 34
Mean total cholesterol, mg/dL	182.6	177.2	182.9	178.4
Mean HDL cholesterol, mg/dL	42.6	45.8	43.7	45.4
Mean systolic blood pressure, mmHg	123.0	123.6	123.8	123.0
Current smoker, %	27	22	28	23
Hypertension medications, %	26	25	28	23
Diabetes, %	7	5	6	6

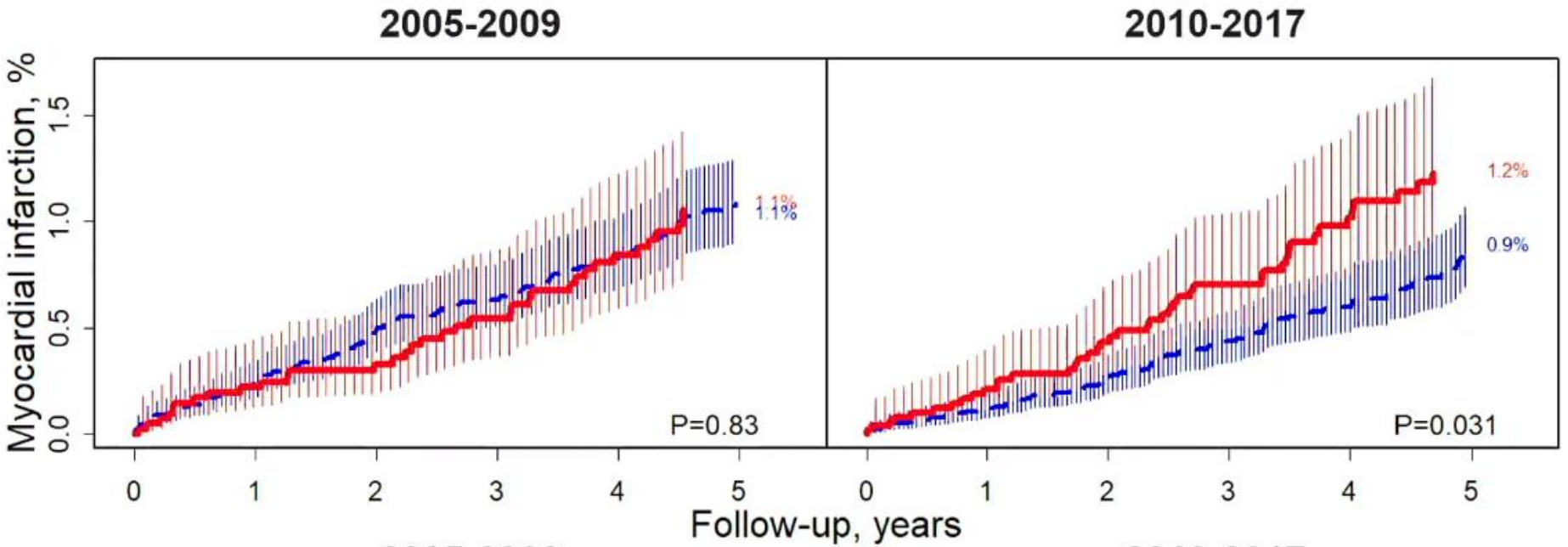
Silverberg MJ et al CROI 2022. Abstr 39.

HIV-specific Baseline Characteristics

	PWH	
Baseline Calendar Era	2005-2009	2010-2017
N	4,280	5,121
HIV RNA>400 copies/mL, %	39	23
Mean CD4, cells/μL	470	587
ART use, %	76	88
Mean years HIV	7.8	9.1
Prior ART Class experience (among ART users), %		
NNRTI	52	46
PI	54	27
INSTI	3	40

Silverberg MJ et al CROI 2022. Abstr 39.

Cumulative incidence of MI similar by HIV status in 2005-2009 but higher for PWH compared with PWoH in 2010-2017



2005-2009

	KPNC		Partners		Overall	
HIV Status	PWH	PWoH	PWH	PWoH	PWH	PWoH
N	3,584	10,740	696	3,319	4,280	14,059
MI events	33	105	2	12	35	117
MI rate*	0.24	0.25	0.08	0.10	0.21	0.22

* per 100 person-years

2010-2017

	KPNC		Partners		Overall	
HIV Status	PWH	PWoH	PWH	PWoH	PWH	PWoH
N	4,615	13,857	506	1,502	5,121	15,359
MI events	39	81	4	6	43	87
MI rate*	0.25	0.17	0.22	0.12	0.25	0.16

* per 100 person-years

Silverberg MJ et al CROI 2022. Abstr 39.

Adjusted* HRs for MI by HIV Status (PWoH reference), and stratified by Calendar era and Cohort

	KPNC		Partners		Overall	
Era	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
2005-2009	1.0 (0.7, 1.5)	0.90	1.2 (0.3, 5.8)	0.82	1.1 (0.8, 1.5)	0.61
2010-2017	1.6 (1.1, 2.4)	0.02	2.1 (0.6, 7.5)	0.28	1.6 (1.1, 2.4)	0.007

*Stepwise adjusted models considering demographics and Framingham risk score components.

P-interaction (Era*HIV)=0.12

Sensitivity analyses:

(1) evaluate events over 10 years: similar inferences

(2) stratify by sex: similar inferences with reduced precision for women

(3) alternative calendar era strata: Evaluated only in KPNC, with similar inferences

Silverberg MJ et al CROI 2022. Abstr 39.

Summary / Conclusions

- Among PWH and PWoH with similar CVD risk profiles at baseline, we observed no difference in MI risk for baseline years 2005-2009, and a 60% higher risk in PWH for years 2010-2017
- Results appear to be driven by decrease in MI risk for PWoH, that was not seen for PWH
- HIV-specific factors, such as longer HIV duration and newer ART (e.g., INSTIs), may have prevented PWH from realizing the same improvements in MI risk as PWoH
- Clinical implications for PWH include continued surveillance for CVD and primary prevention, including possibly more aggressive interventions.

Authors: Michael J. Silverberg, PhD, MPH[1], Asya Lyass, PhD[2], Leo B. Hurley, MPH[1], Rachel Q. Ehrbar, MA[3], Taylor F. Mahoney, MA[3], Leila H. Borowsky, MPH[4], Wei He[4], Jorge Plutzky, MD[5], Daniel Klein, MD[1], Joseph M. Massaro, PhD[3], Ralph B. D'Agostino Sr., PhD[2], Virginia A. Triant, MD, MPH[4,6,7]

1-Kaiser Permanente Northern California, Oakland, CA; 2-Department of Mathematics and Statistics, Boston University, Boston, MA; 3-Department of Biostatistics, Boston University School of Public Health, Boston, MA; 4-Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA; 5-Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston MA; 6-Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA; 7-Mongan Institute, Massachusetts General Hospital, Boston, MA

Contact
Michael.J.Silverberg@kp.org
@mjsilverb

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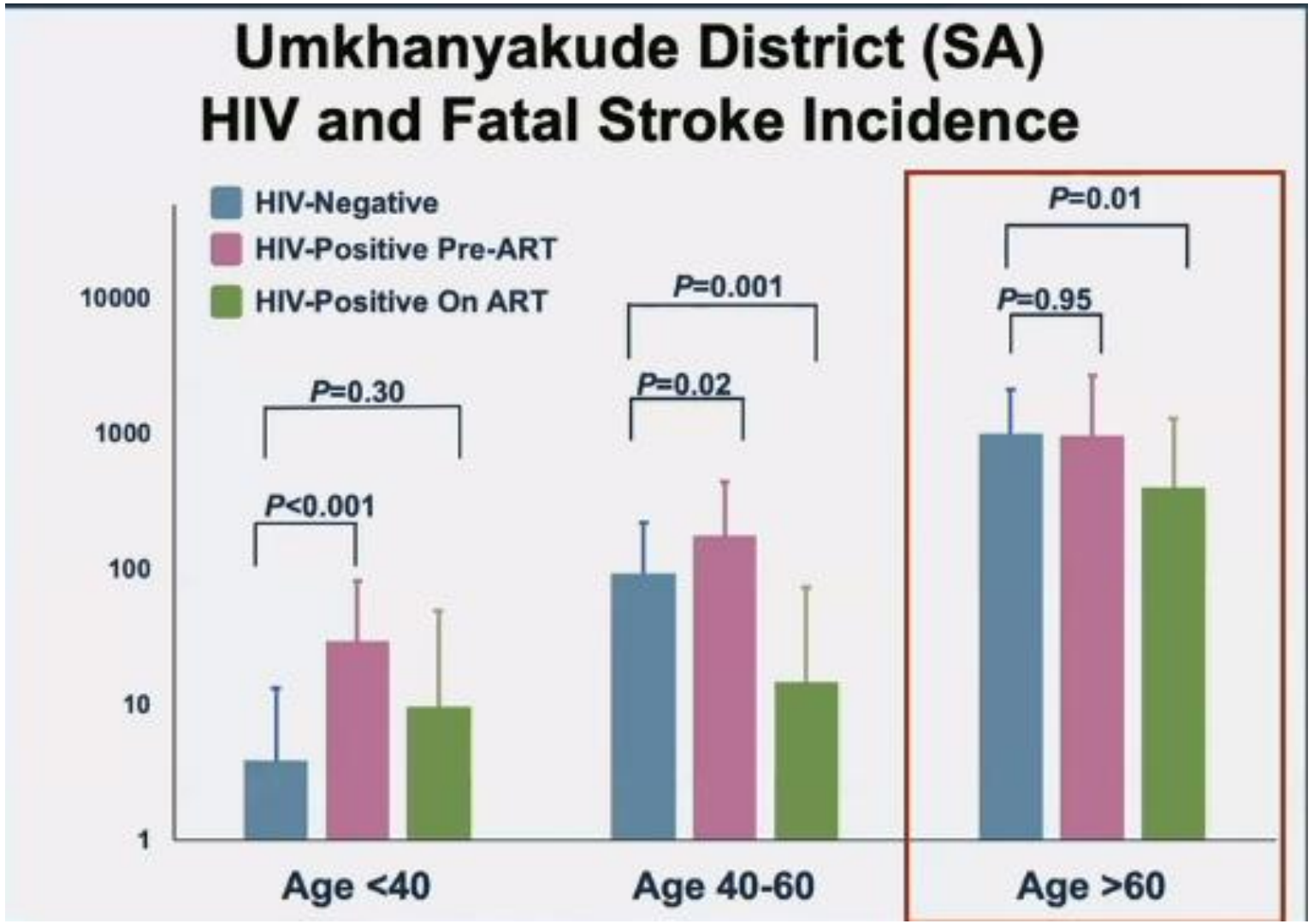
HIV, ART and stroke incidence in rural South Africa



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Revised Conceptual Framework?

HIV Infection

Inflammation

ART

Timing of Treatment Initiation

Toxicity

Atherosclerosis

Cancer

Aging-Related Syndromes

Longevity, Health and Wellbeing

Socioeconomic Status & other Social Determinants of Health

Healthcare Access

Environment

Quality of Care

Social Support

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Conclusioni

La sindrome metabolica rappresenta una frequente comorbidità nei pazienti con infezione da HIV e la sua prevalenza non sembra essersi modificata negli ultimi anni.

L'utilizzo diffuso degli INSTI sembra aver temporalmente coinciso con un migliore controllo del profilo metabolico, dei valori pressori e con un incremendo dei pazienti che hanno smesso di fumare. D'altra parte si è osservato un progressivo incremento del peso e della circonferenza vita dei pazienti nella pratica clinica.

Le conseguenze cliniche di questi fenomeni meritano una attenta valutazione e un approfondimento clinico e scientifico.

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.