

HIV e Sindrome Metabolica

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Sistema Socio Sanitario



Regione
Lombardia

Disclosure

- Paolo Bonfanti ha ricevuto grant da:
 - Gilead
 - ViiV
 - Janssen
 - Merck
 - Pfizer

METABOLIC SYNDROME

**ONCE UPON A
TIME**

Definition of Metabolic Syndrome

<i>World Health Organization</i>	<i>Adult Treatment Panel III</i>	<i>International Diabetes Federation</i>
• Required DM, IFG, IGT, or IR and at least two of the following: • WHR >0.9 in men, >0.85 in women • TG >150 mg/dL • BP >140/90 mmHg • Urinary albumin excretion rate >2 mg/minor • Albumin to creatinine ratio >30 mg/g	• Any three of the following: • Waist circumference >102 in men, >88 in women • TG >150 mg/dL • BP >130/85 mmHg • HDLC <40 mg/dL in men, <50–110 mg/dL • FBS >110 mg/dL	• Required waist circumference by the cutoffs and at least two of the following: • TG >150 mg/dL • SBP >130 mmHg or DBP >85 mmHg • HDLC <40 mg/dL in men, <50 in women • FBS >100 mg/dL
DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; WHR, waist to hip ratio; TG, TG, triglyceride; BP, blood pressure; HDLC, high-density lipoprotein cholesterol; FBS, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure.		

Joint Scientific Statement

Harmonizing the Metabolic Syndrome

A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL

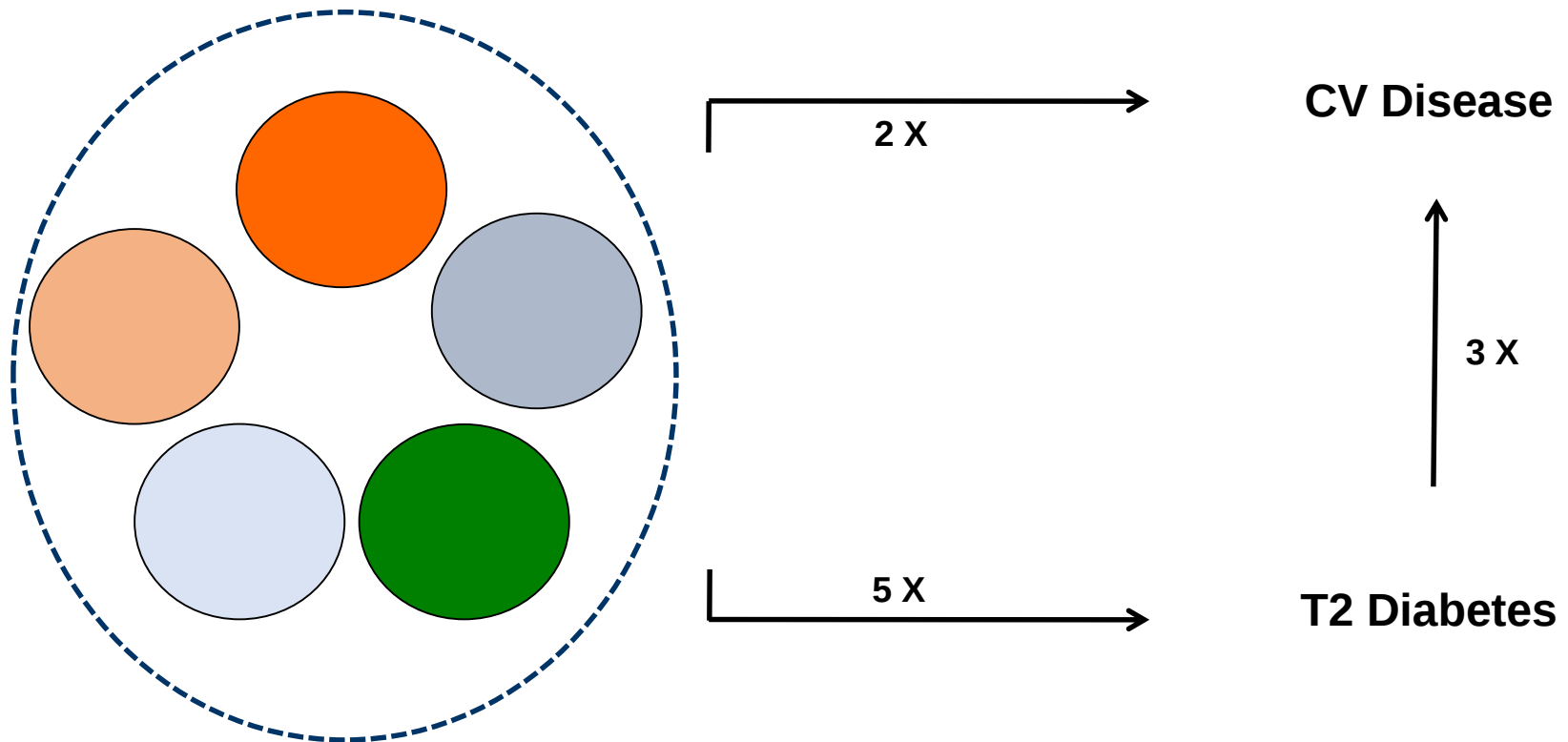
Ferrari KG et al, *Circulation* 2009

Ethnic specific values for waist circumference

Country/Ethnic group		Waist circumference
Europids* In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians Based on a Chinese, Malay and Asian-Indian population	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese**	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

Morbidities related to Metabolic Syndrome

Metabolic Syndrome



Kassi E et al, *BMC Medicine* 2011

Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study

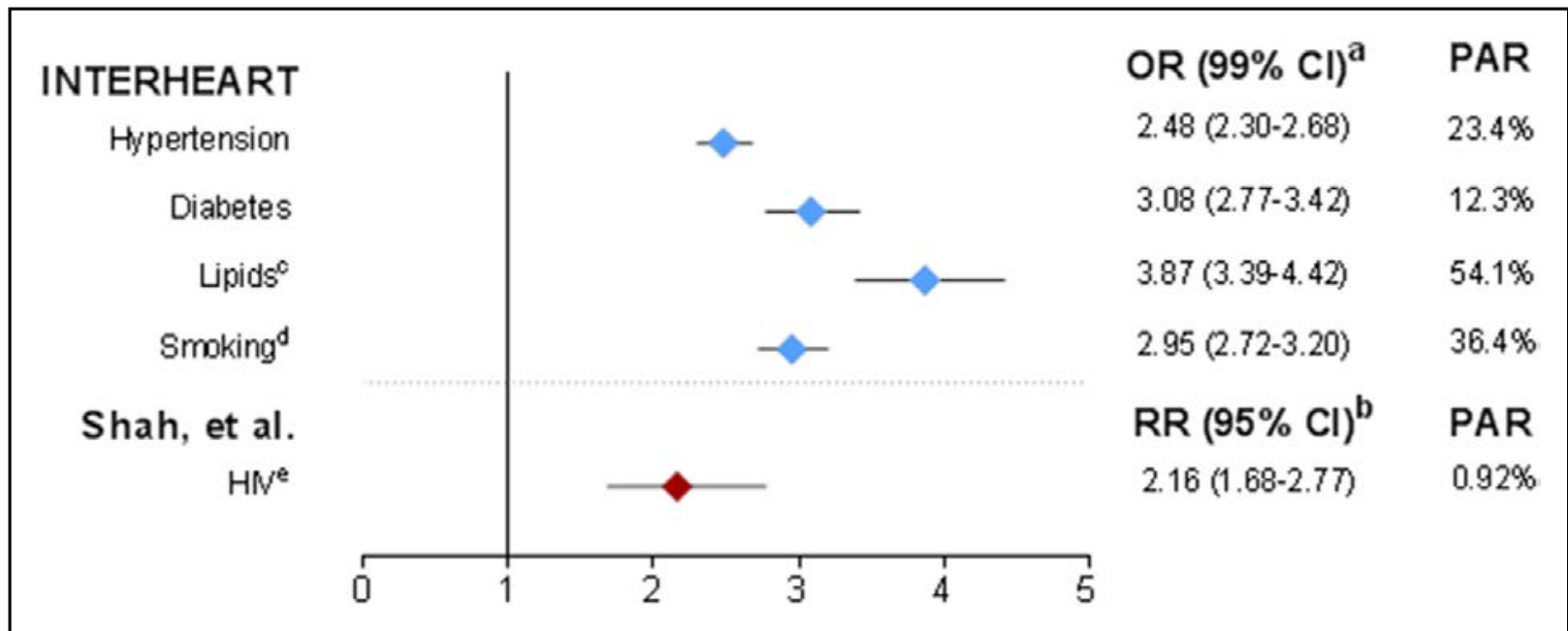
Characteristic	MACS (n = 5622)	Current Study Population (N = 1278)	HIV-Seronegative (n = 710)	HIV-Infected Not Using HAART (n = 157)	HIV-Infected Using HAART (n = 411)	P Value†
White subjects, No. (%)	4681 (83)	1089 (85)	618 (87)	119 (76)	352 (86)	.53
College degree, No. (%)	3121 (56)	787 (62)	477 (67)	74 (47)	236 (57)	<.001
Age (IQR range), y	33 (28, 38)	48 (43, 53)	50 (45, 56)	46 (41, 50)	46 (42, 51)	<.001
Body mass index‡	23 (22, 25)	26 (24, 28)	26 (24, 29)	25 (23, 28)	25 (23, 27)	<.001
Waist-hip ratio	NA	0.95 (0.91, 0.99)	0.94 (0.90, 0.99)	0.94 (0.91, 0.97)	0.95 (0.91, 0.99)	.17
Total cholesterol level, mg/dL	NA	202 (176, 229)	201 (178, 227)	188 (158, 218)	210 (182, 239)	<.001
Glucose level, mg/dL	NA	90 (83, 98)	90 (83, 97)	88 (82, 98)	91 (84, 101)	.03
Nadir CD4 count, cells/mm ³	NA	NA	NA	318 (187, 432)	211 (108, 318)	NA
Duration of receiving HAART§	NA	NA	NA	NA	3.26 (2.63, 3.81)	NA

Patient Group	Diabetes Mellitus*	
	No. (%) of Patients	PR (95% CI)†
Overall (N = 1278)	101 (8)	NA
HIV seronegative (n = 710)	33 (5)	1
HIV infected not using HAART (n = 157)	11 (7)	2.21 (1.12-4.38)
HIV infected using HAART (n = 411)	57 (14)	4.64 (3.03-7.10)

Brown TT et al, *Arch Intern Med* 2005

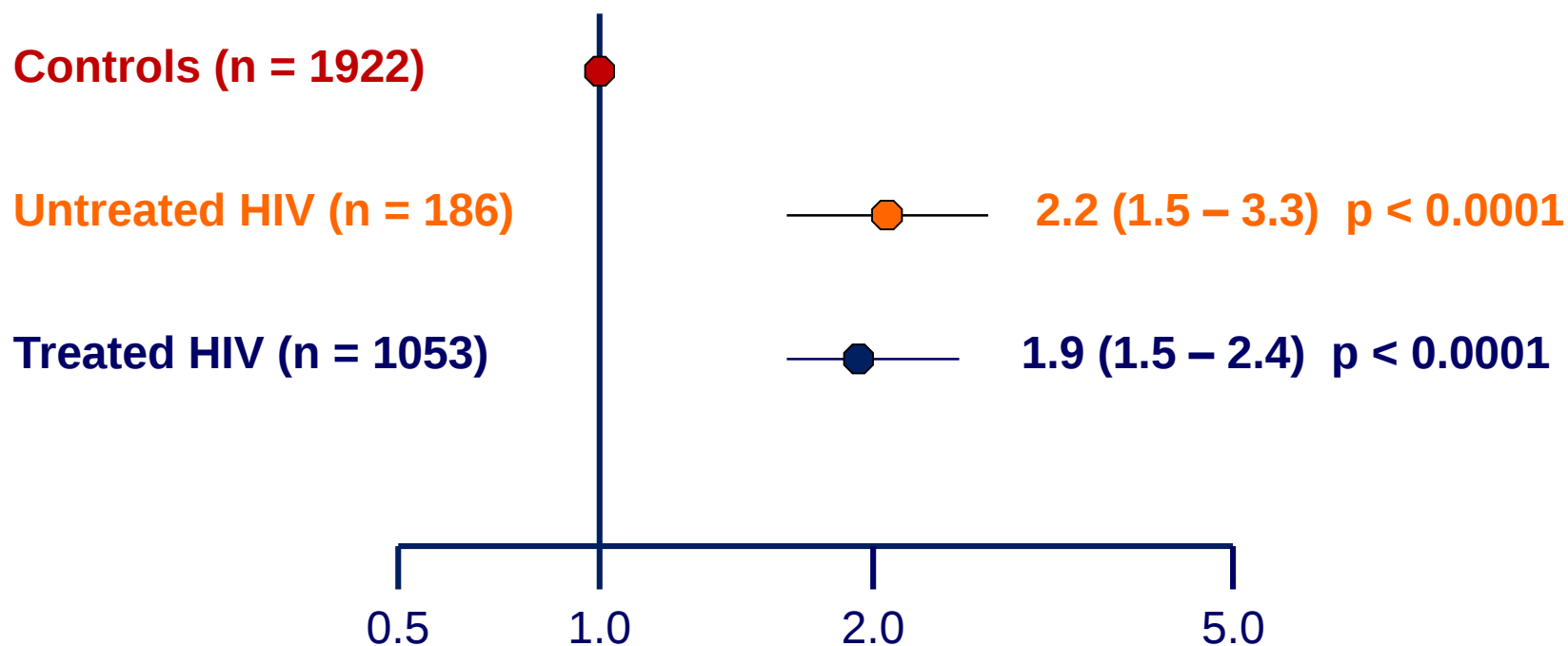
EDITORIAL

Time to Recognize HIV Infection as a Major Cardiovascular Risk Factor

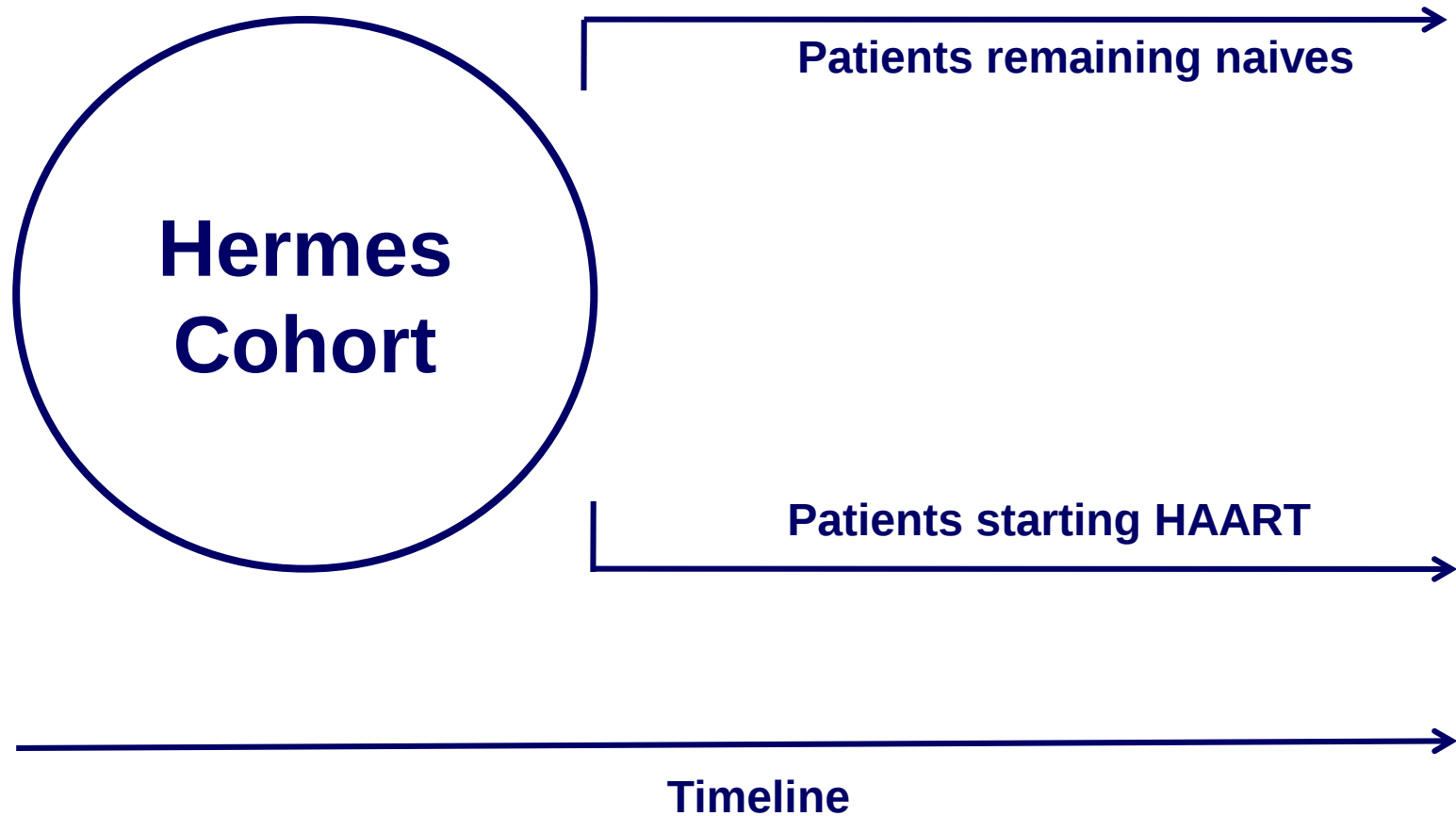


Hsue P et al, *Circulation* 2018

HIV and Metabolic Syndrome: a comparison with the general population

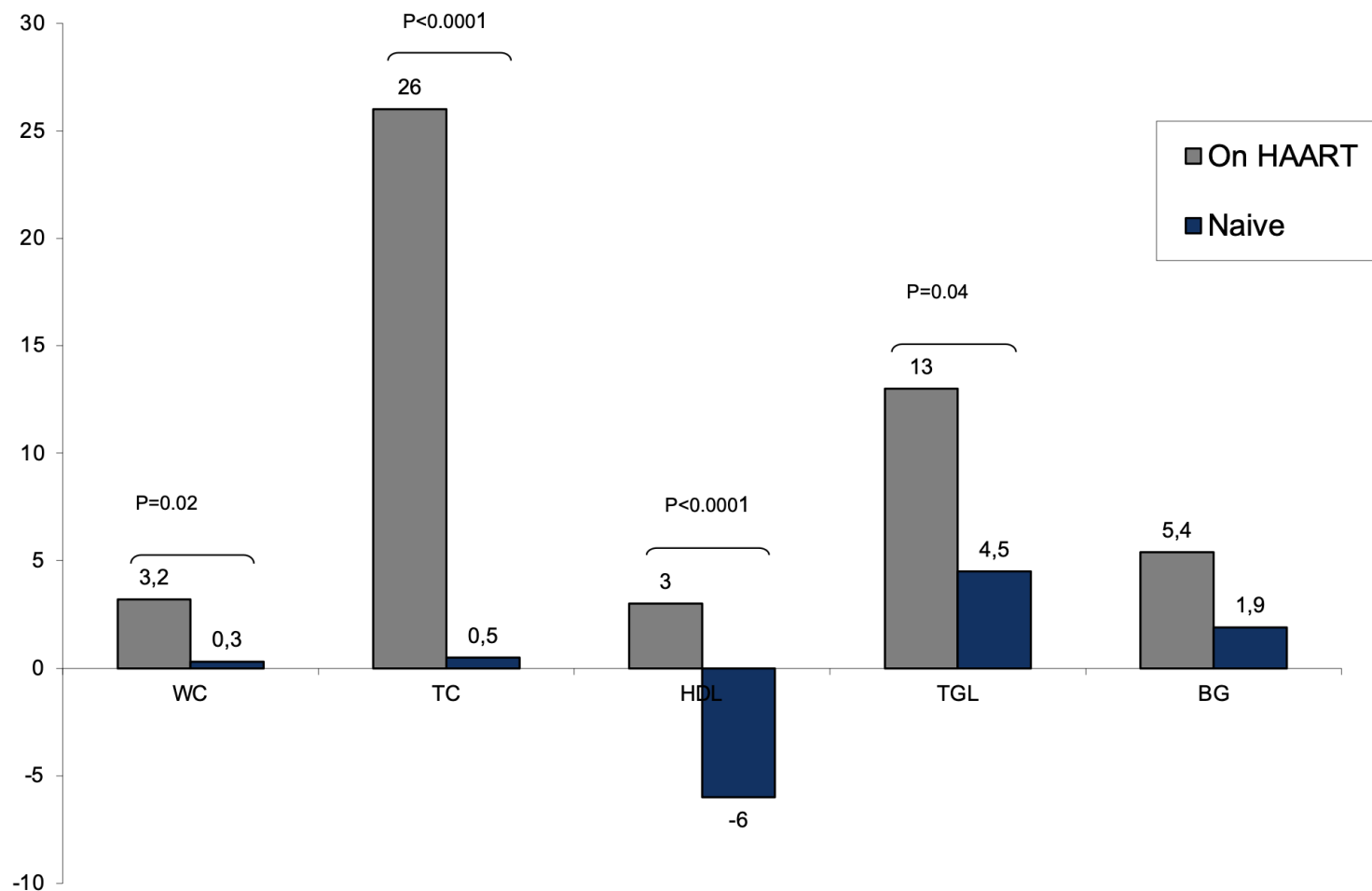


Bonfanti P et al, *J Acquir Immune Defic Syndr* 2007



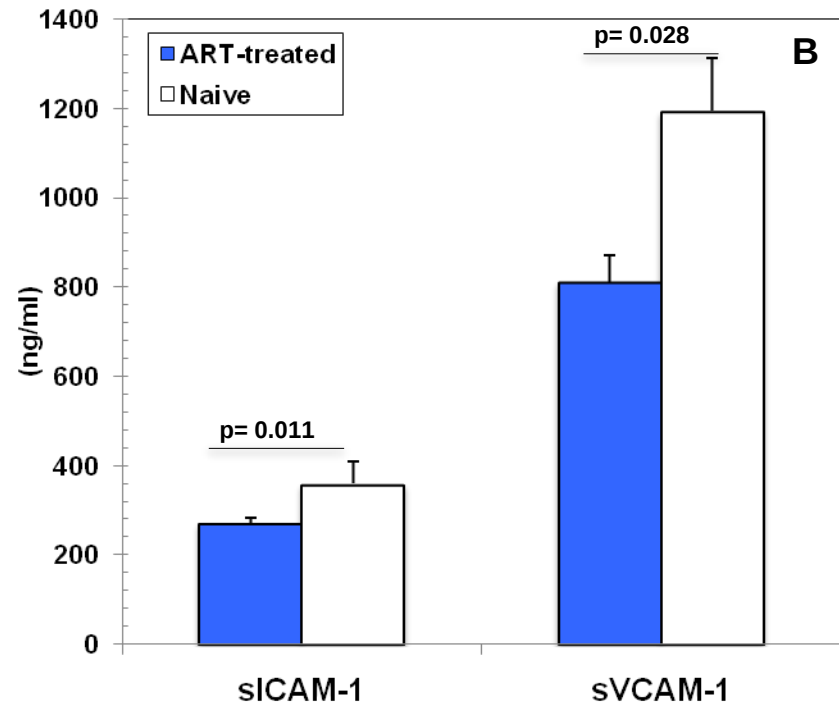
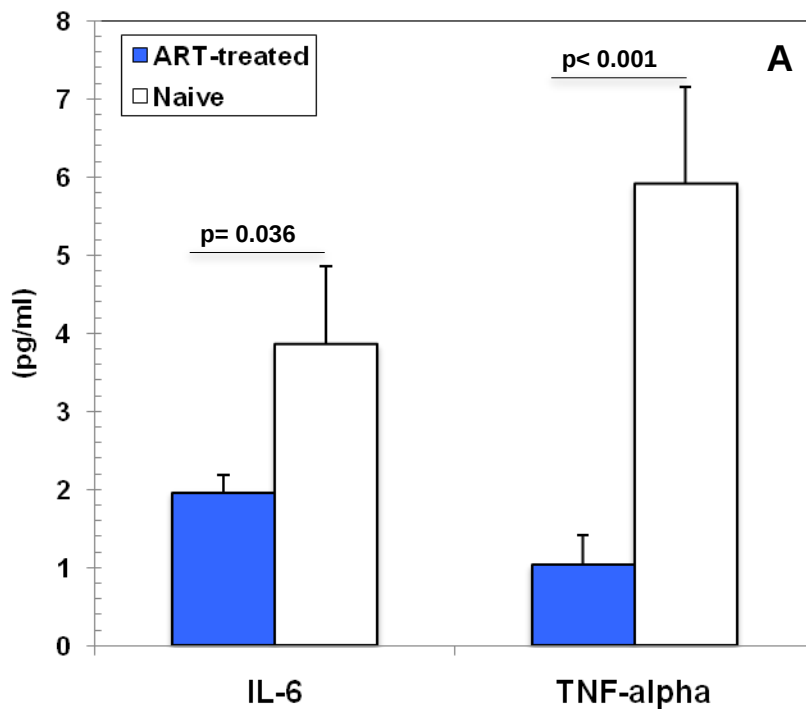
Original article

The feature of Metabolic Syndrome in HIV naive patients is not the same of those treated: Results from a prospective study



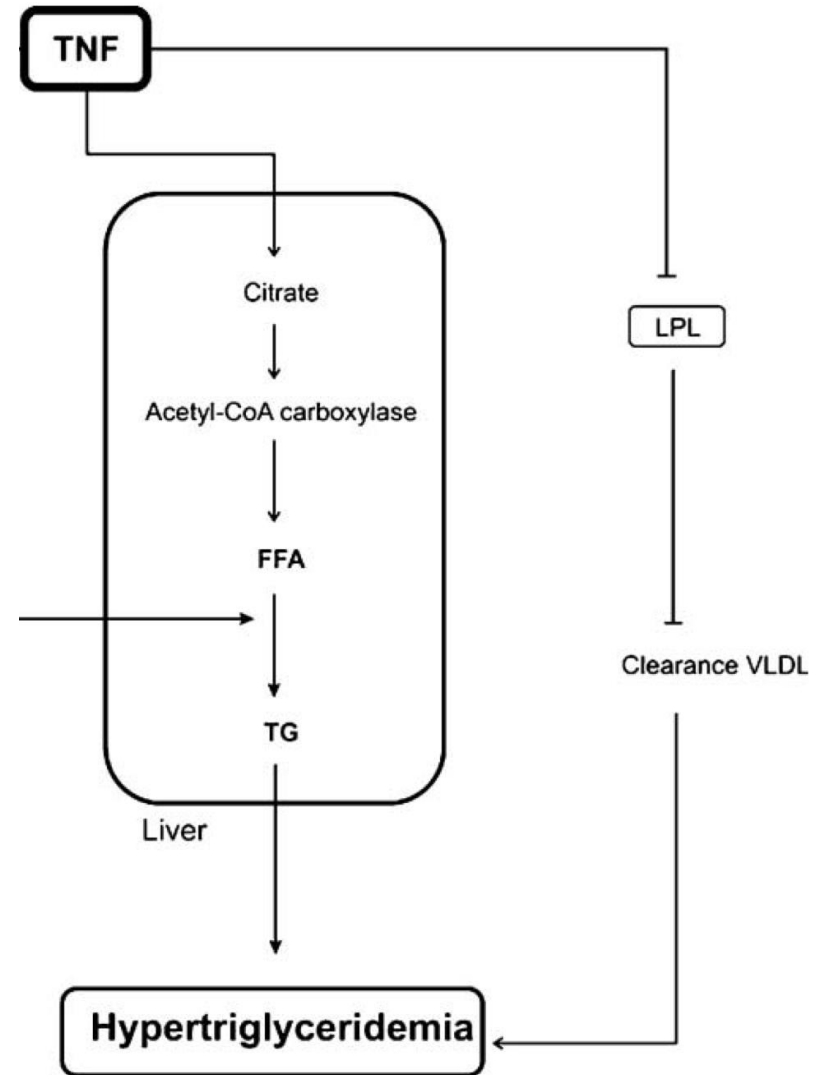
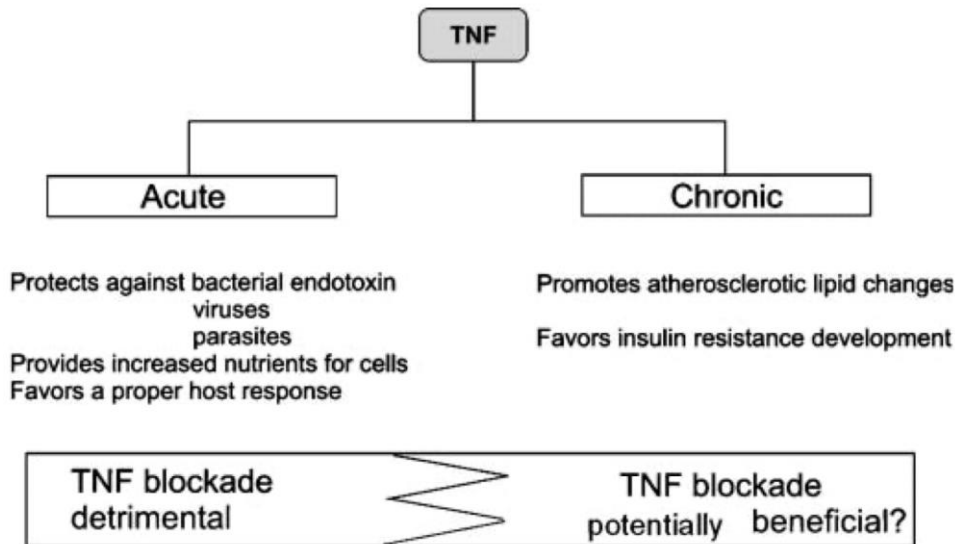
Bonfanti P et al, *Biomed Pharmacother* 2012

Plasma pro-inflammatory cytokines and soluble adhesion molecules are lower in ART-treated HIV infected patients



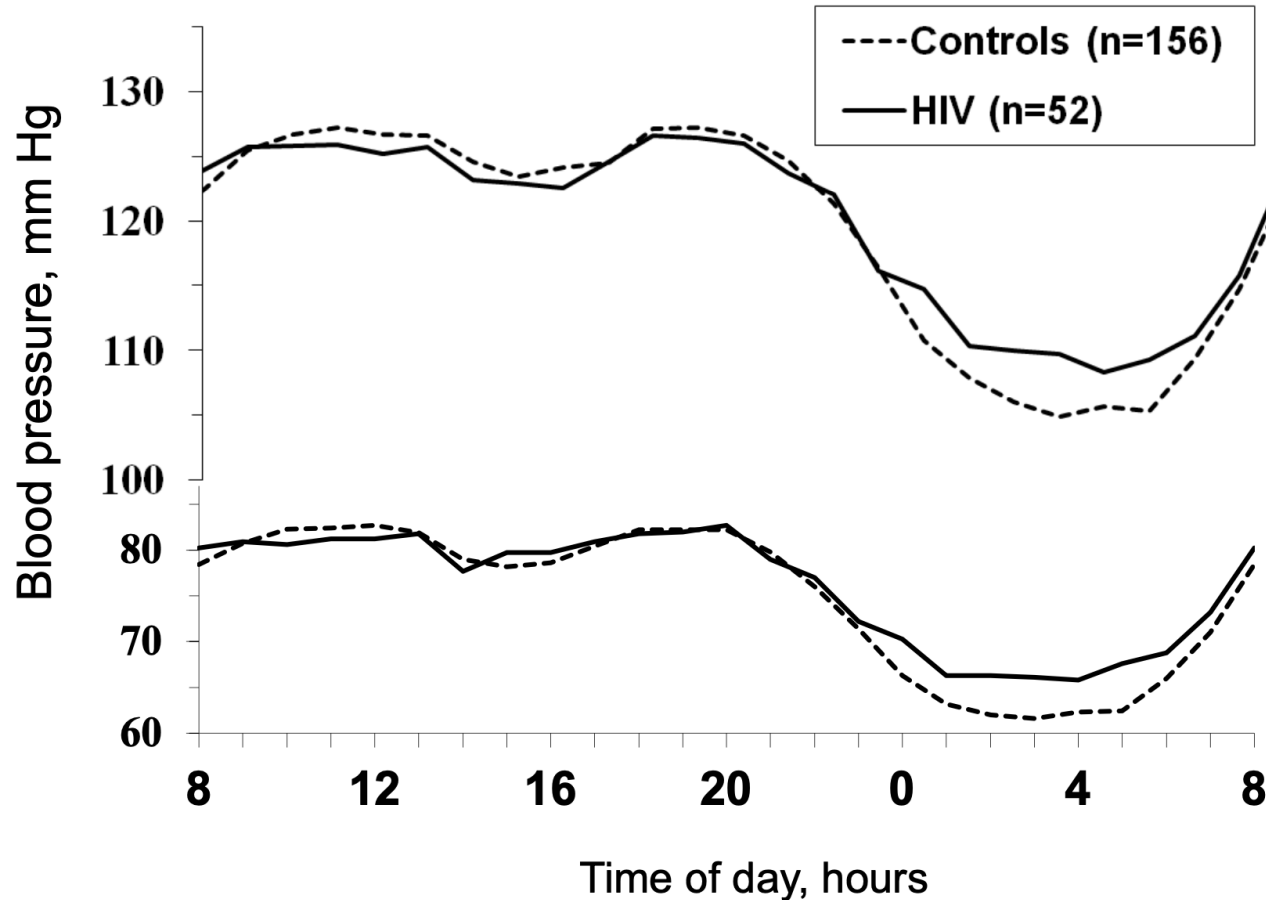
Piconi S et al, *AIDS* 2013

The role of TNF- α in chronic inflammatory conditions

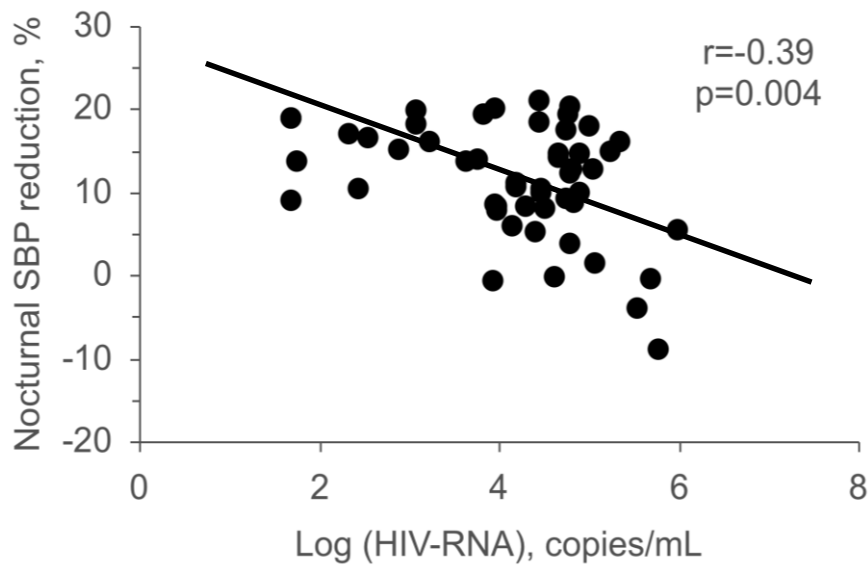


Popa C et al, J Lipid Res 2007

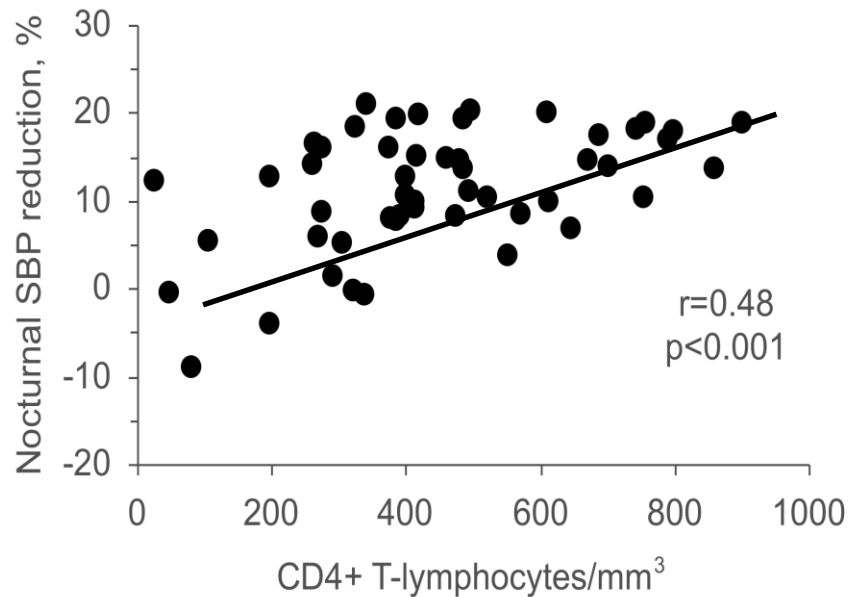
Day-night blood pressure changes in untreated HIV infection



De Socio G et al, *J Acquir Immune Defic Syndr* 2010

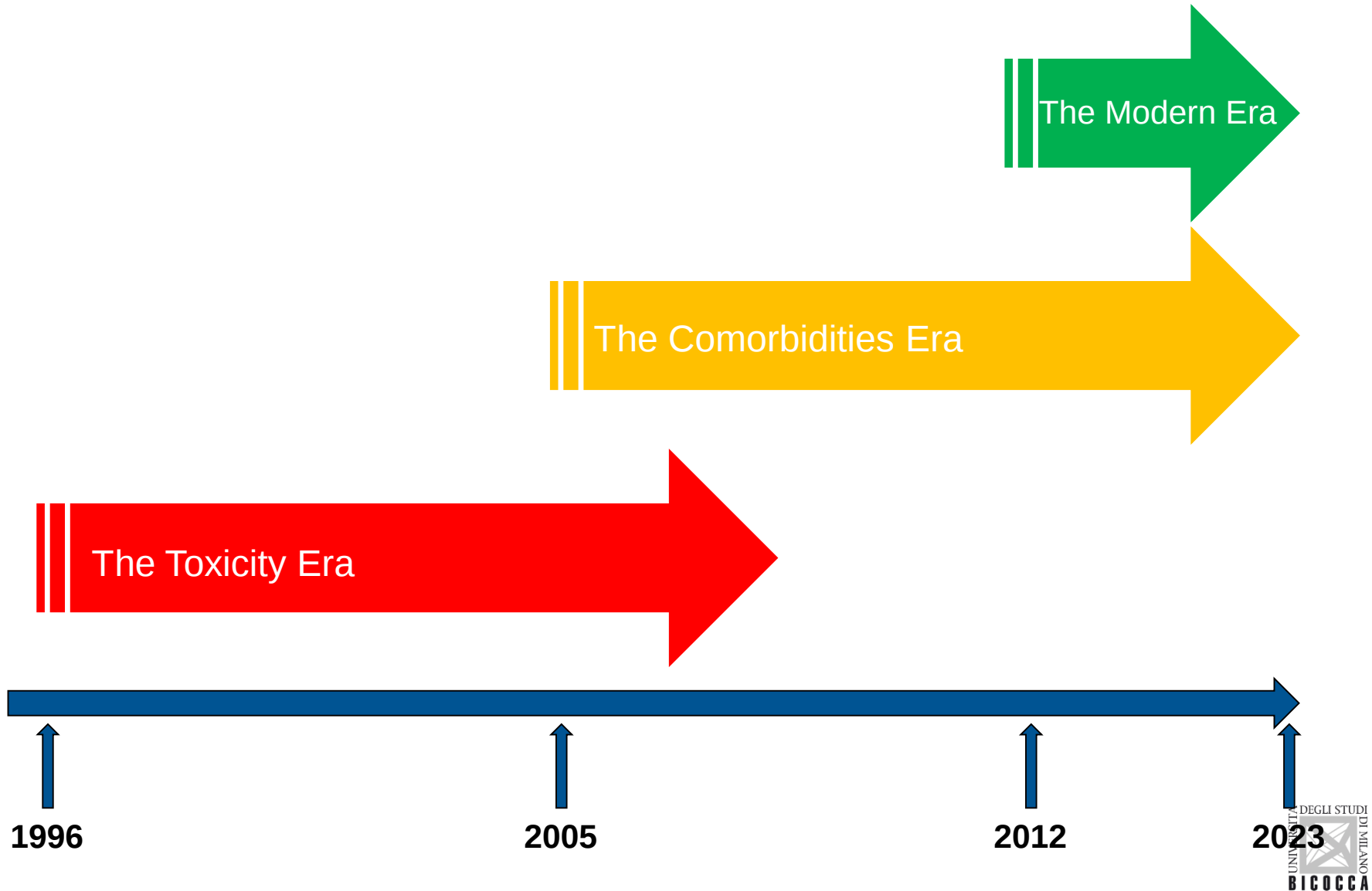


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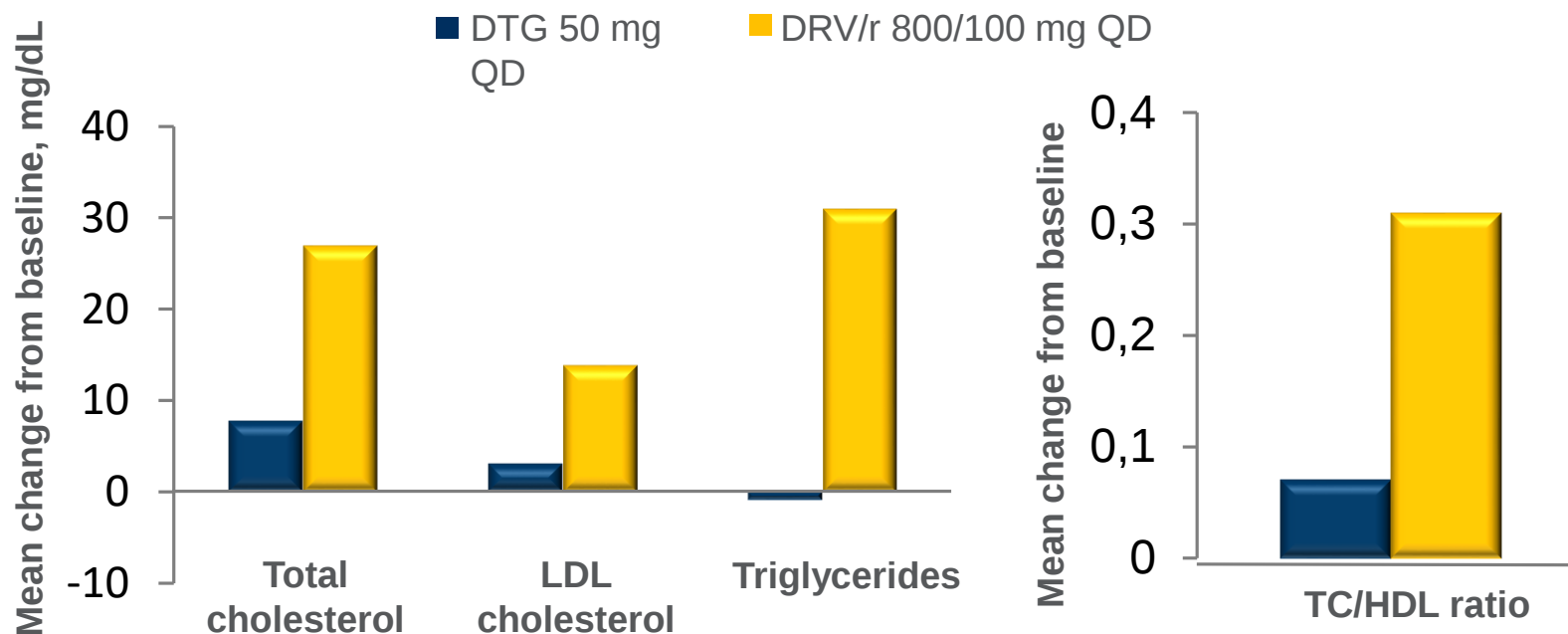
De Socio G et al, *J Acquir Immune Defic Syndr* 2010

The Evolving Eras of Antiretroviral Therapy



FLAMINGO STUDY

LABORATORY RESULTS AT WEEK 96



Values are mg/dL (TC, LDL: 1 mg/dL = 0.026 mmol/L; Triglycerides, creatinine: 1 mg/dL = 0.011 mmol/L)

- Grade ≥ 2 fasting LDL lab abnormalities were more frequent in the DRV/r arm (22%) vs the DTG arm (7%) ($p < 0.001$; pre-specified LOCF analysis)
- Mean change from baseline in serum creatinine was higher in the DTG arm (0.17 mg/dL) compared to the DRV/r arm (0.04 mg/dL)

HIV

— AND —

WEIGHT GAIN:

STATE OF THE
EVIDENCE

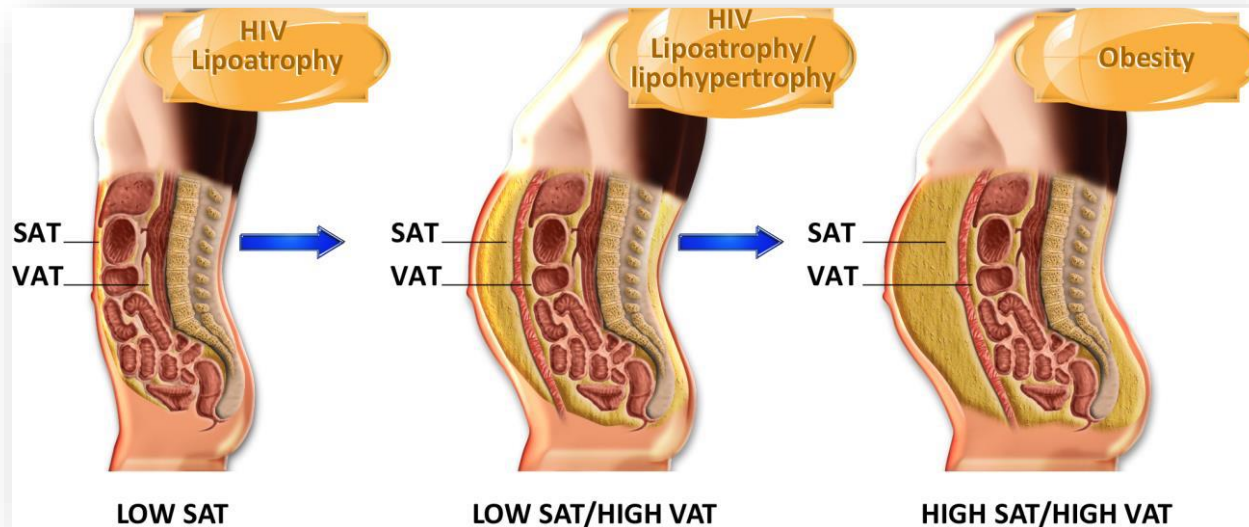
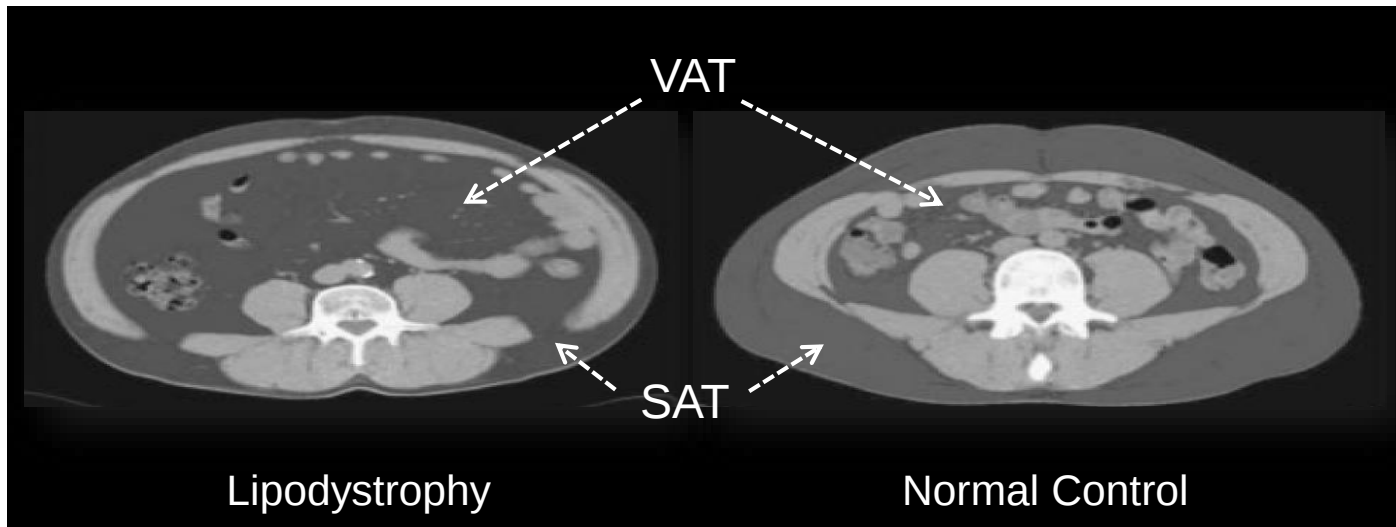
Weight gain: key questions

- What kind of body fat abnormality: lipodystrophy or obesity?
- Trend to Obesity or Restore to Health?
- Which are the contributors to WG in PLWH?
- Does ART cause weight gain? Which drugs?
- What is the clinical significance of WG in PLWH?
- Metabolic Syndrome and Weight Gain: the same thing?

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Body-Fat Abnormalities in HIV-Infected Adults



Grinspoon S et al, *N Engl J Med* 2005; Godfrey C et al, *J Infect Dis* 2019

A5260s Study Schema

A5257: Phase III, prospective, multi-center, randomized, open-label trial
ART-naïve, HIV+ subjects ≥ 18 yr, VL ≥ 1000 c/mL (N=1809)

Randomized 1:1:1 to three NNRTI-sparing ARV regimens

A5260s Substudy (n=328): No known CVD, diabetes mellitus, or use of lipid-lowering medications. Participants followed for 96 weeks after enrollment of last subject: all subjects received Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF)

Atazanavir/Ritonavir (ATV/r)
(N=109)

+ Raltegravir (RAL)
(N=106)

+ Darunavir/Ritonavir (DRV/r)
(N=113)

ITT

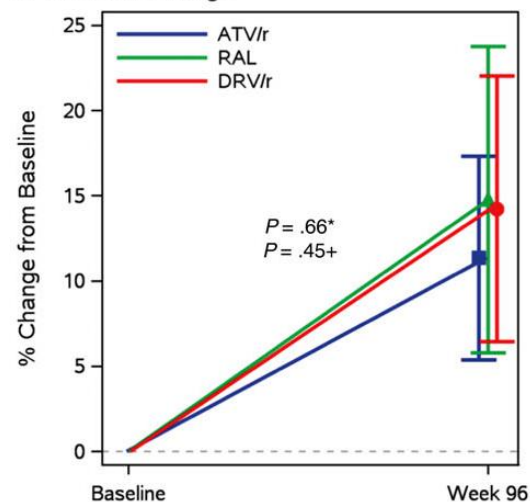
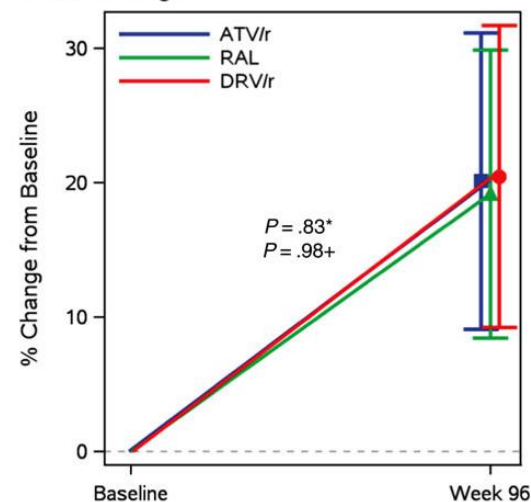
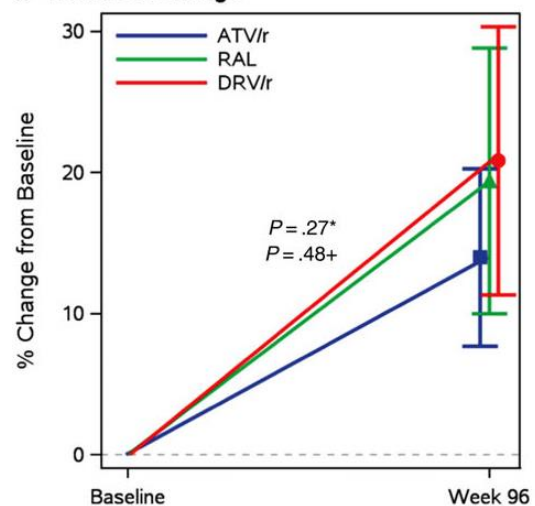
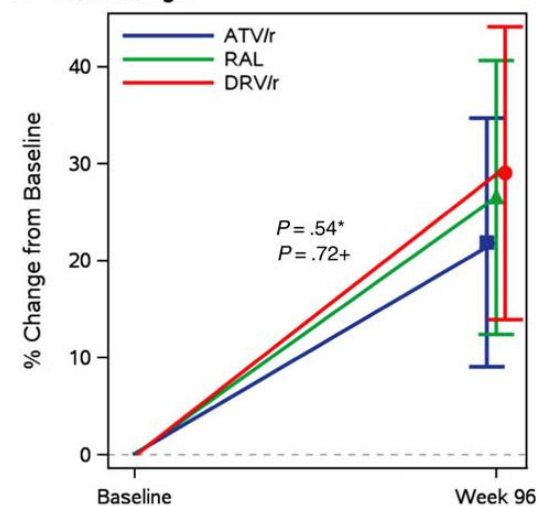
oints

N=99

- Single-slice computed tomography (scan at the L4–L5)
- DeXA

N=96

Changes in body composition parameters

A Limb Fat Change**B SAT Change****C Trunk Fat Change****D VAT Change**

McComsey G et al, *Clin Infect Dis* 2016

A5260s Study Conclusions

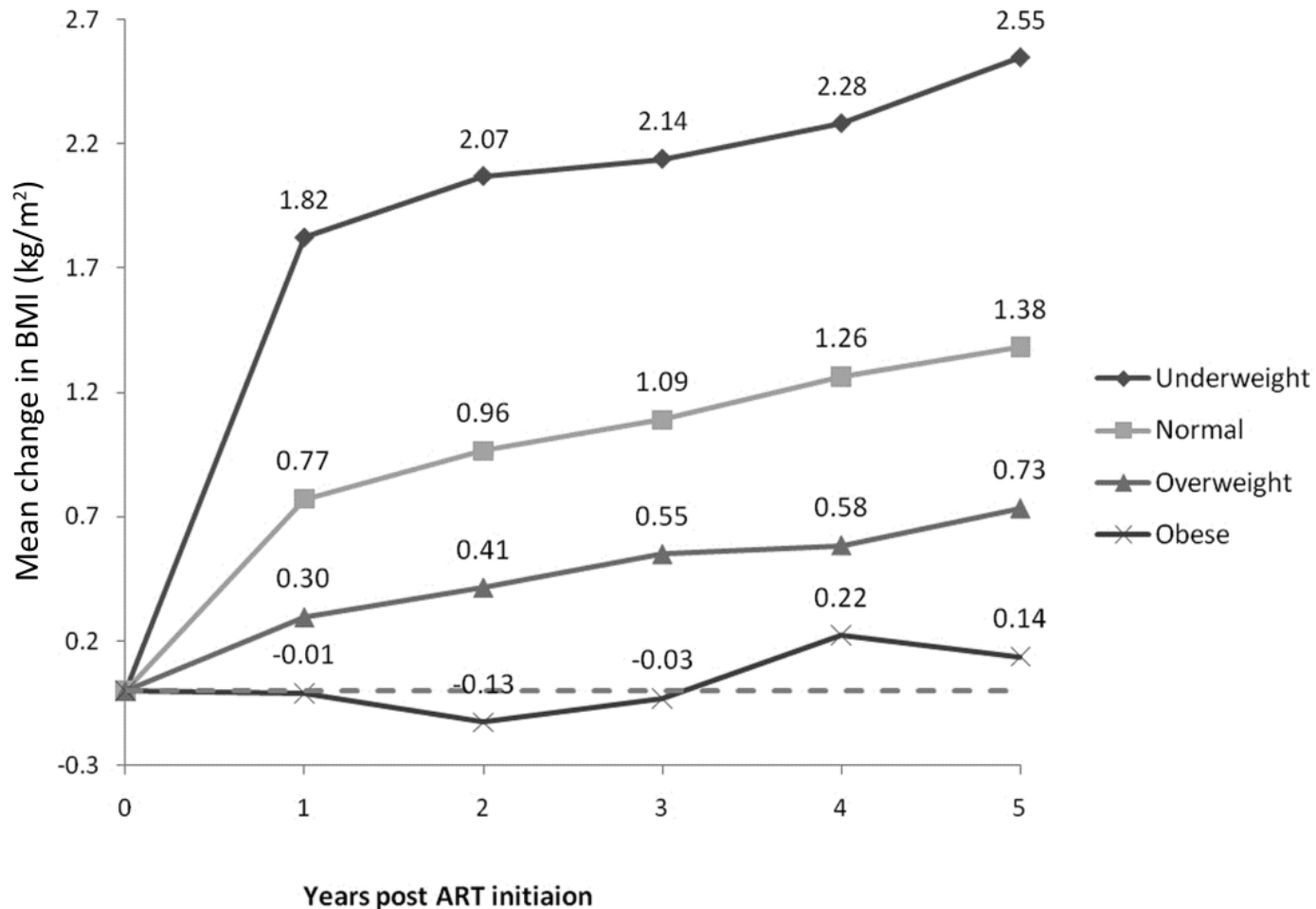
- For the first time in a large randomized ART-initiation trial, we showed that central and peripheral **fat changes were not different after 96 weeks** of treatment with 2 boosted PIs or with the integrase inhibitor RAL.
- The **VAT:TAT ratio remained unchanged** and BMI significantly increased, suggesting that the **fat gained was generalized** and proportionally distributed in the visceral and subcutaneous compartments, regardless of the regimen used.
- This **increase in BMI surpasses what is expected** from return-to-health and may have unfavorable consequences on health.
- We found that **higher pre-ART viral load** was a major determinant of fat gains, regardless of the regimen type.
- The reason for this association is unclear and may be due to the persistent HIV-infected macrophages in adipose tissue, which could enhance local **inflammation** and cause expansion of fat tissues.

McComsey G et al, *Clin Infect Dis* 2016

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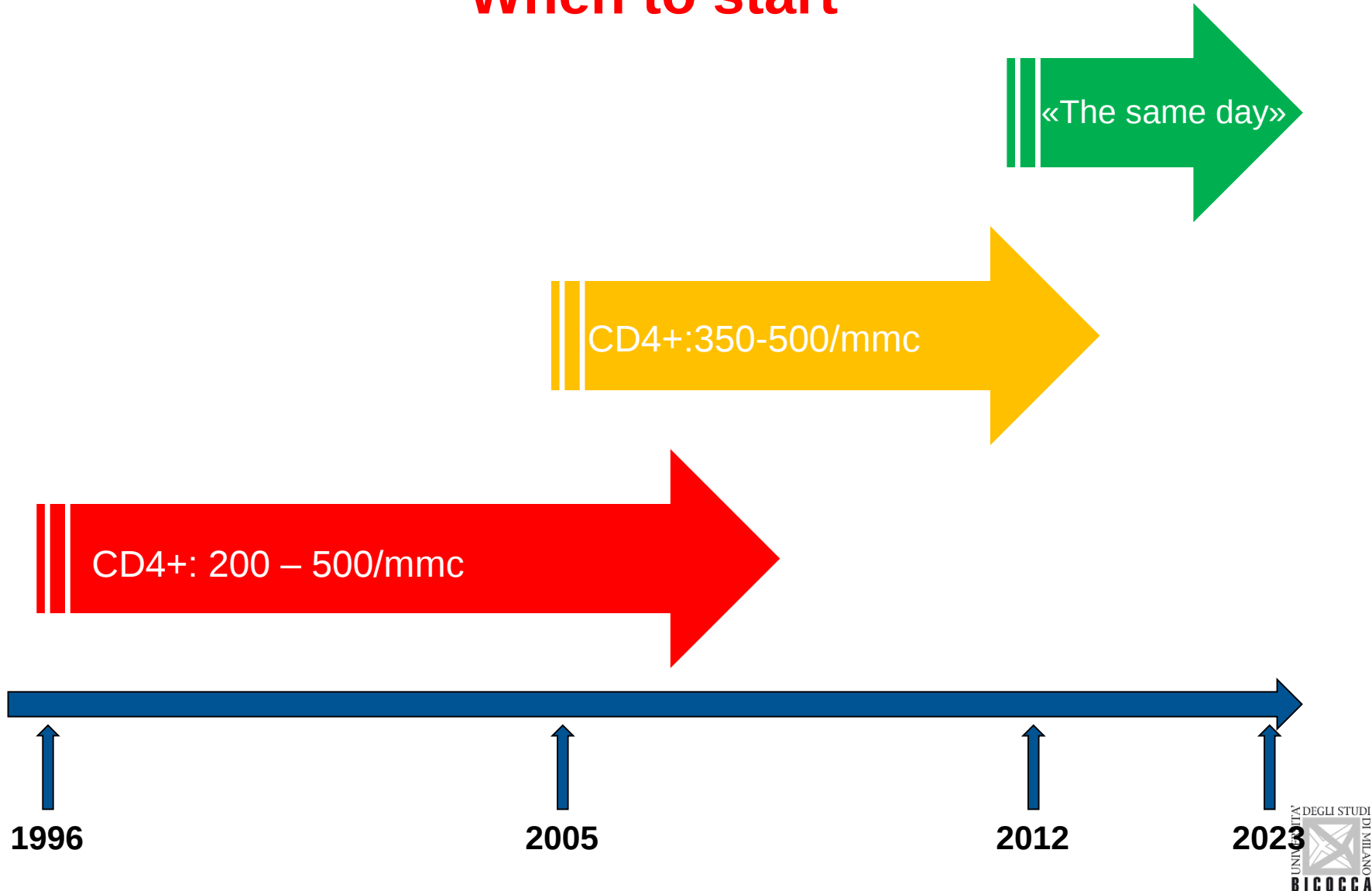
Mean change in BMI at years 1 to 5 from antiretroviral therapy initiation



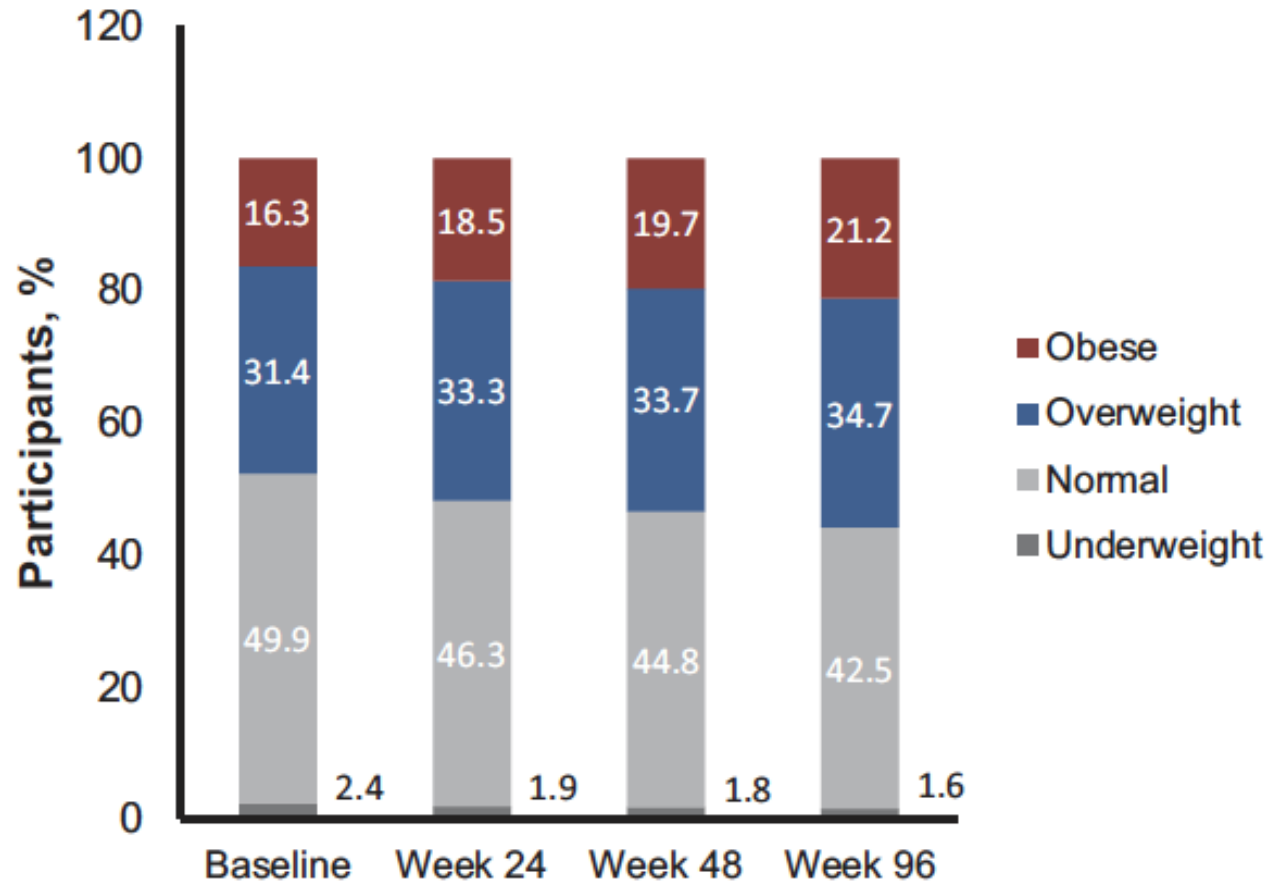
Achhra AC et al, *HIV Med* 2016

The Evolving Eras of Antiretroviral Therapy

When to start



Weight Gain Following Initiation of Antiretroviral Therapy in Randomized Comparative Clinical Trials

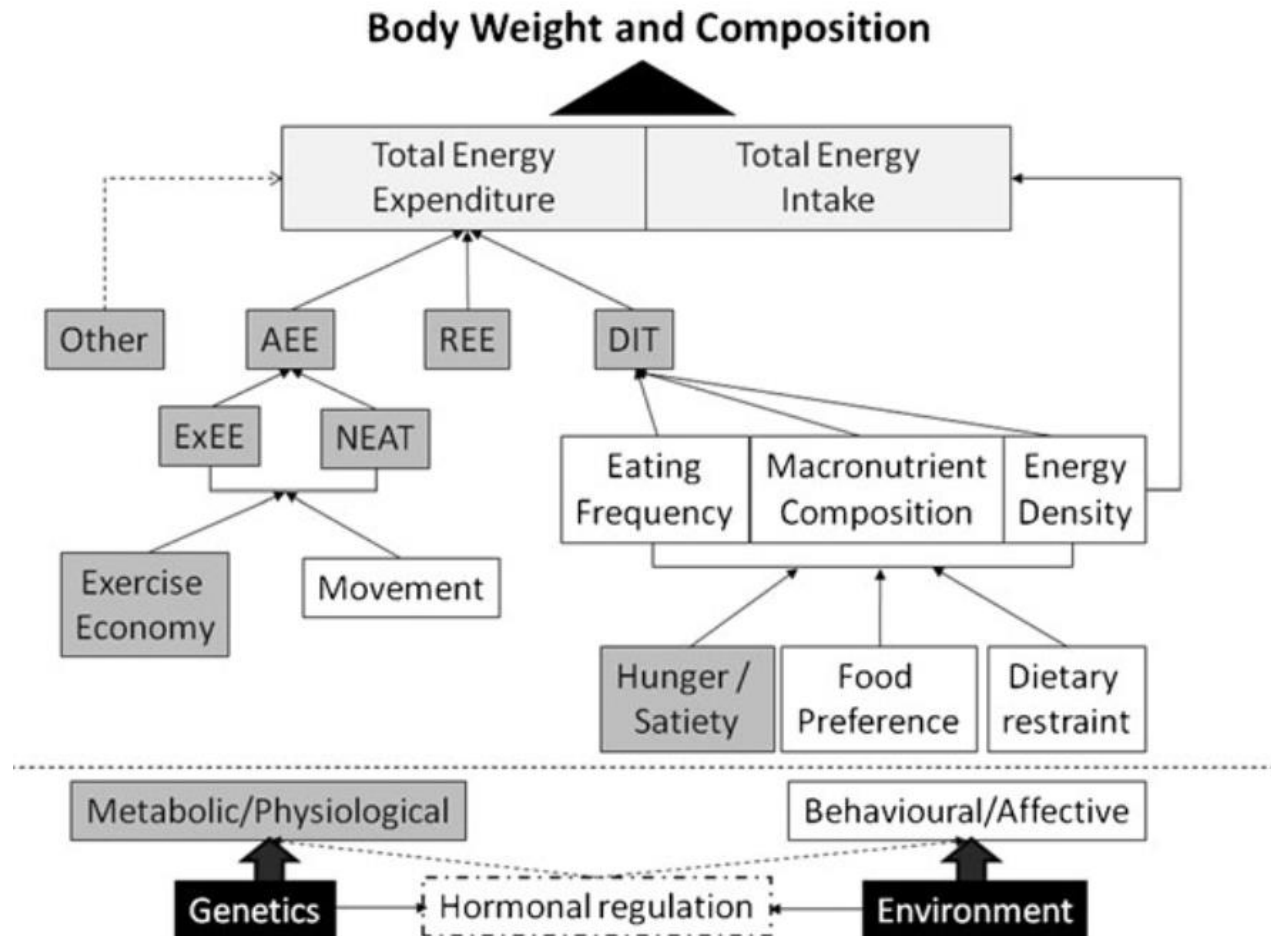


Sax PE et al, *Clin Infect Dis* 2020

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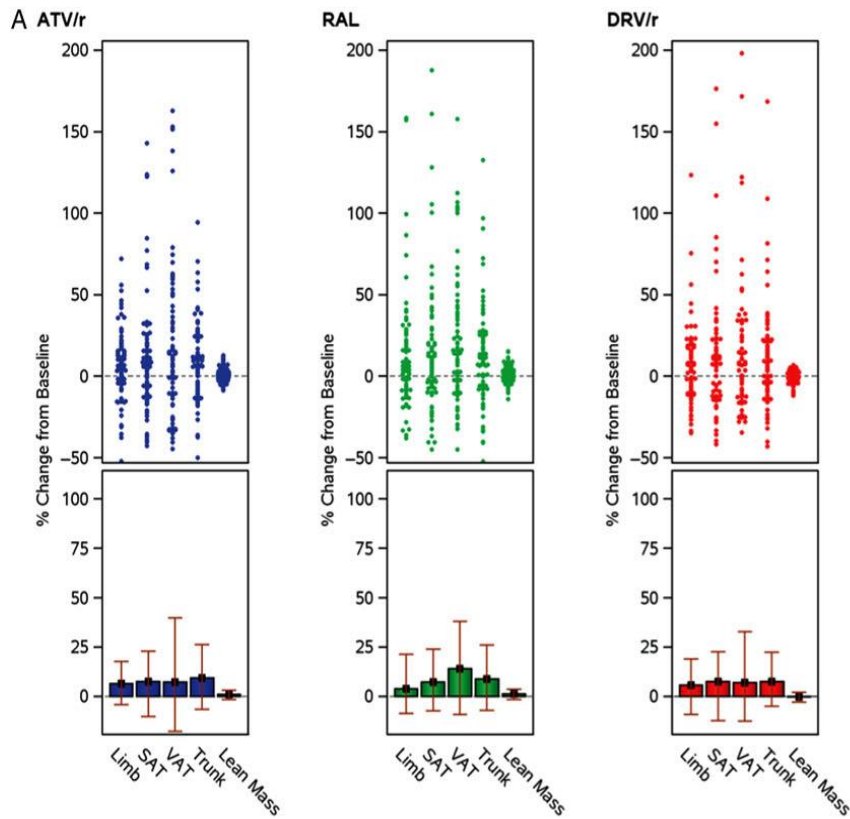
Biology or Behavior: Which Is the Strongest Contributor to Weight Gain?



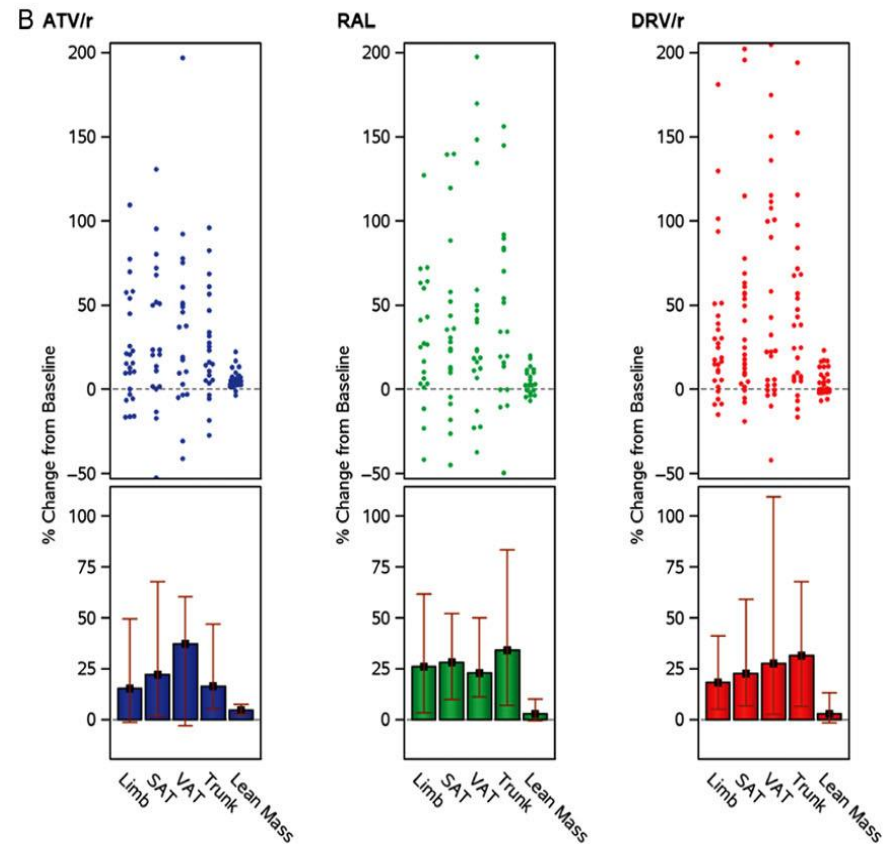
Byrne NM et al, *Curr Obes Rep* 2013

Effect of baseline HIV-RNA levels on changes in body composition

HIV-1 RNA <100 000 copies/mL



HIV-1 RNA >100 000 copies/mL



McComsey G et al, *Clin Infect Dis* 2016

Contributors to Weight Gain in PLWH

- **Environment**

- Sociocultural knowledge, Economic resources
- Attitudes, beliefs, & practices regarding diet, nutrition, exercise
- Conception of 'health'

- **ARV drugs**

- INSTI > PI > NNRTI^{1,2,3}
- DTG > RAL > EVG²
- TAF > TDF⁴
- (Lack of weight gain in HPTN 077 with cabotegravir)⁵

- **HIV Infection**

- Inflammation
- Higher viral load^{1,2}
- Lower CD4 count^{1,2}

- **Host factors**

- Female sex^{7,8,9}
- Older age^{7,10}
- Black race^{2,7}
- Comorbidities
- Habits
- Mental Health

1. McComsey G et al, *Clin Infect Dis* 2016; 2. Bhagwat P et al, CROI 2017

3. Bourgi K, et al. CROI 2019; 4. Gomez M et al, *Infection* 2019; 5. Landovitz RJ et al, *Clin Infect Dis* 2019; 6. Couturier J et al, *Antiviral Res* 2018; 7. Lake J, et al. CROI 2019; 8. Kerchberger AM et al, CROI 2019; 9. Menard A et al, *AIDS* 2019;

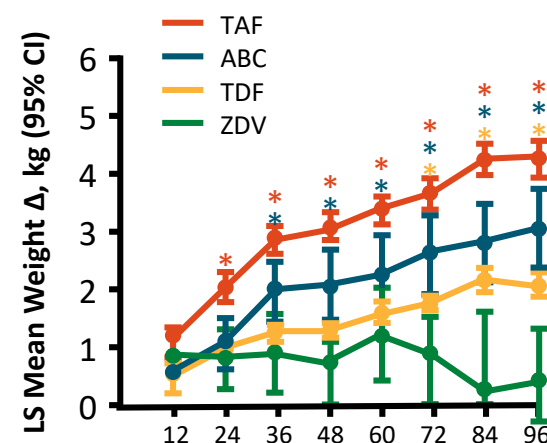
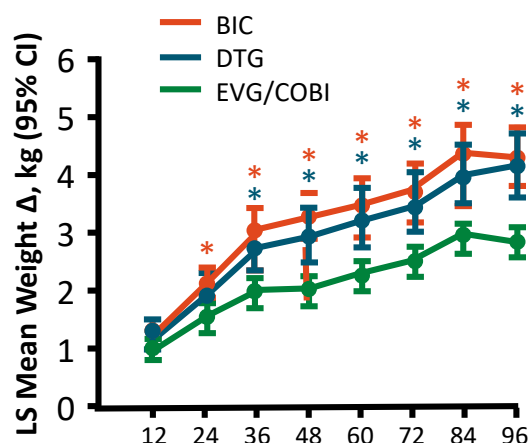
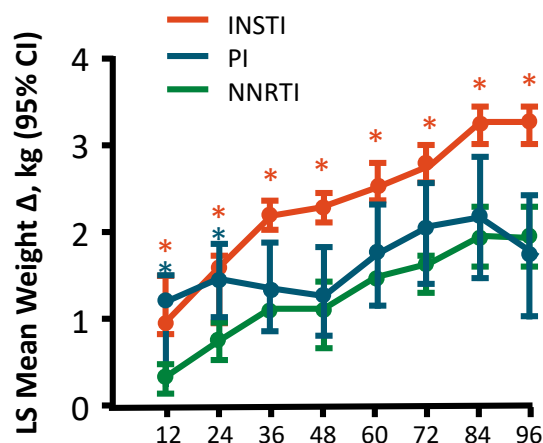
10. Taramasso L et al, *Open Forum Infect Dis* 2017

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Multivariate Analysis of Weight Gain Following ART Initiation in RCTs

- Pooled analysis of weight gain across 8 randomized phase III clinical trials of first-line ART initiation occurring in 2003-2015 (N = 5680)



*Color-coded to match respective comparators, denoting $P \leq .05$ vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

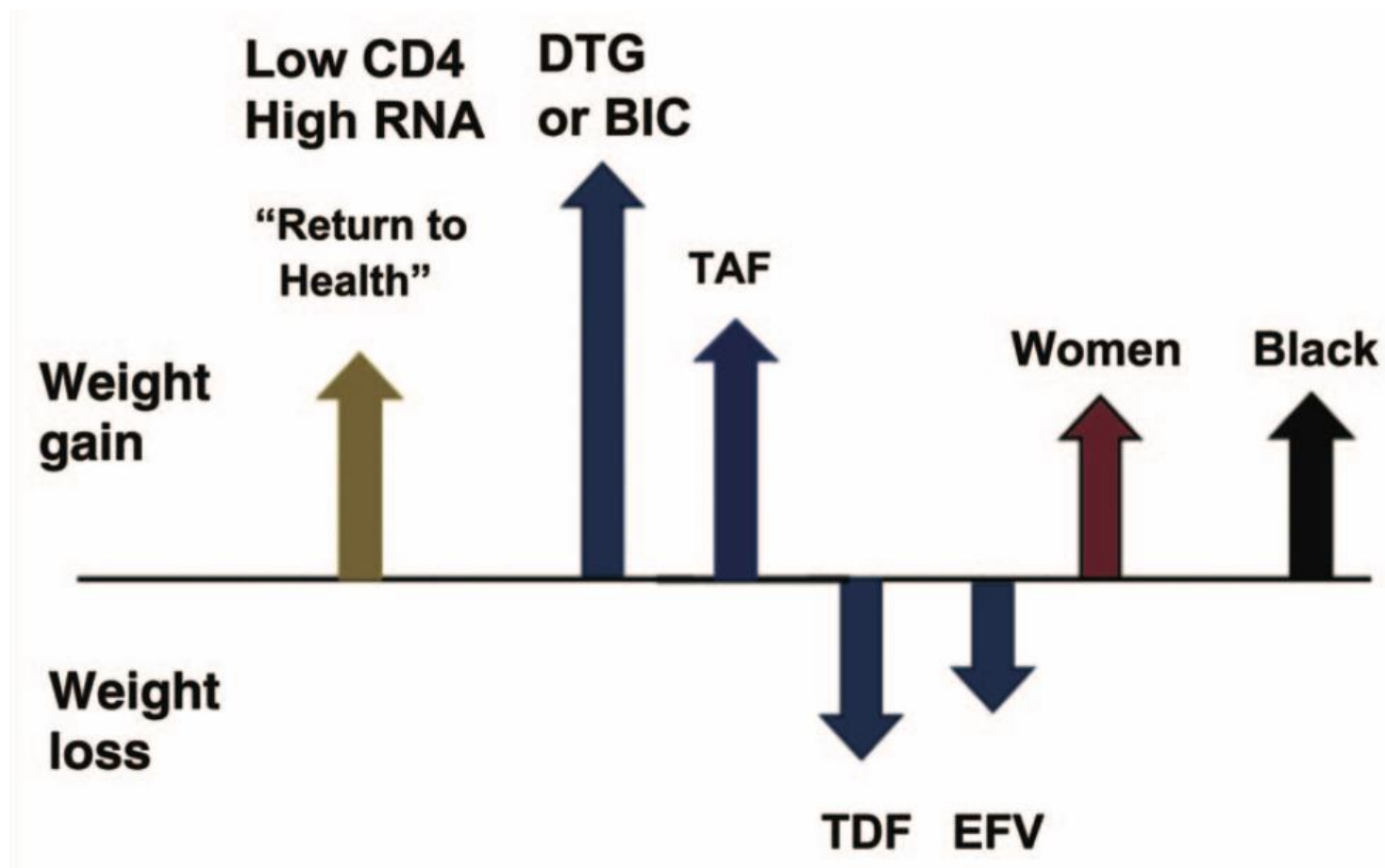
Overview of the prognostic factors analysis for weight change while on antiretroviral therapy

Baseline Characteristics	ACTG 5224s	ACTG 5257	ADVANCE	AMPATH	Belkhir 2019	Calza 2020b	DRIVE-AHEAD	Gilead Sciences Trials	McComsey 2020	McComsey 2021	NA-ACCORD	NAMSAL	SCOLTA	RESPOND	Vanderbilt ccc	Wei 2020	Emond 2021	Lomlak 2021
Study location	US	US	ZA	KE	BE	IT	Global	US	--	--	US	CM	IT	Europe /AU	US	CN	US	PL
Female Sex (vs male)	↑	↑	↑	↑	□	↑	□	↑	□	□	↑	↑	↓	□	↑	□	↑	--
African origins (vs Other)	□	□	--	--	□	--	↑	↑	□	↑	□	--	--	↑	□	--	□	--
Older Age (vs young)	□	□	↑	↑	↑	↑	□	--	□	↓	↓	--	□	--	--	↑	□	↑
Lower Weight (vs higher weight)	--	--	--	--	--	--	□	--	↑	--	--	--	↑	--	--	--	--	--
Lower or Normal BMI (vs higher BMI)	□	□	↓	↑	--	↑	□	↓	↑	↑	--	--	--	↑	--	--	↑	□
Low CD4 count (vs high CD4)	↑	↑	↑	↑	--	↑	↑	↑	--	↑	↑	--	↑	--	--	↑	--	□
High HIV-1 RNA (vs low RNA)	↑	↑	↑	--	--	□	↑	↑	--	--	--	↑	--	--	--	--	--	--

 Significant positive factor
  Positive factor
  No effect
  Negative factor
  Significant negative factor
 -- Not reported

Kanters S et al, *EClinicalMedicine* 2022

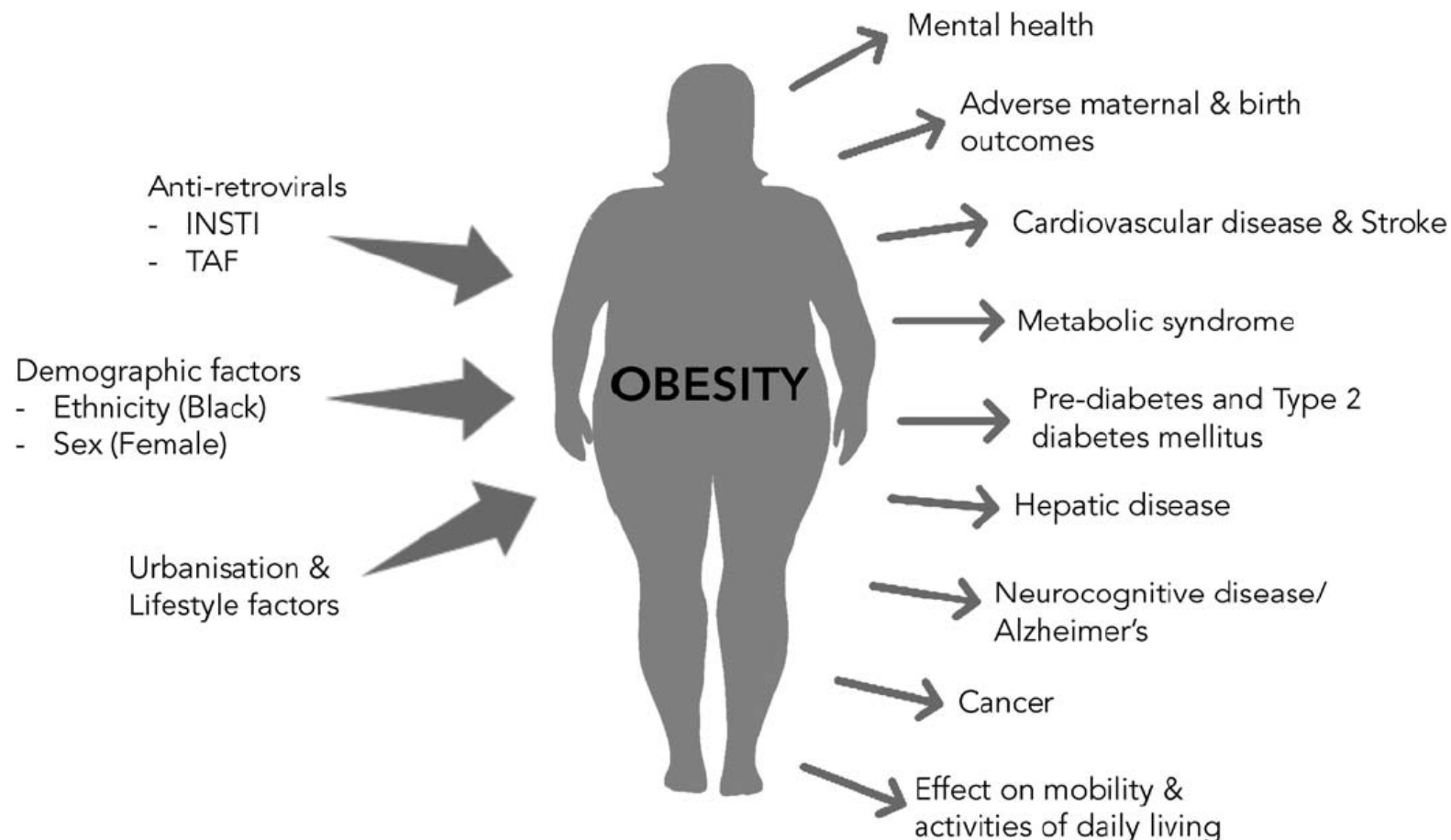
Summary of factors driving or mitigating weight changes for PLWH on ART



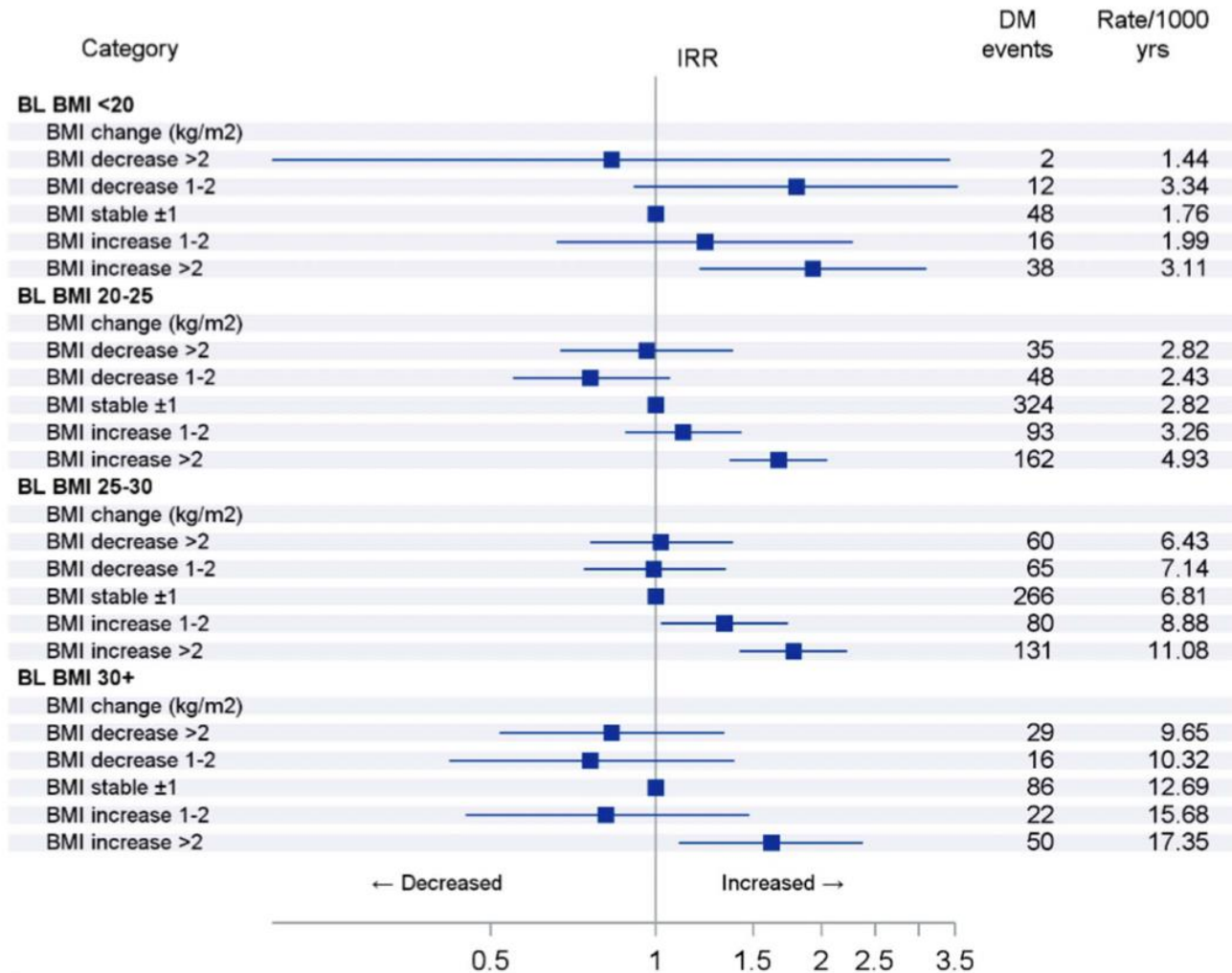
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Potential drivers and consequences of obesity in PLWH



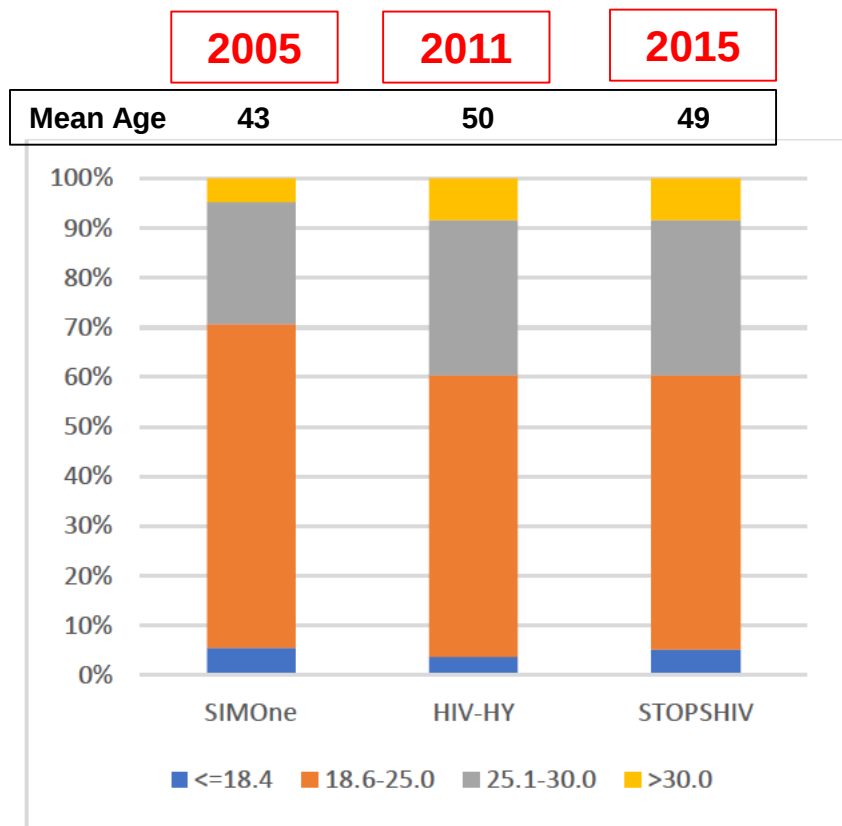
Effect of Changes in BMI on Diabetes Mellitus in HIV-Positive Individuals: Results From the D:A:D Study



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BMI categories and Metabolic Syndrome by age



Taramasso L et al, *HIV Med* 2021

Weight gain: key questions

- What kind of body fat abnormality: lipodystrophy or obesity?
 - Obesity
- Trend to Obesity or Restore to Health?
 - Both
- Which are the contributors to WG in PLWH?
 - Many, the pathogenesis is multifactorial
- Does ART cause weight gain? Which drugs?
 - ART is not the main determinant. INSTIs and TAF have a greater effect than other drugs
- What is the clinical significance of WG in PLWH?
 - Need for further studies to evaluate the relationship between weight gain and clinical outcome
- Metabolic Syndrome and Weight Gain: the same thing?
 - Not completely, need to study the two phenomena separately