

9°

WORKSHOP NAZIONALE CISAI

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

# Alterazioni del grasso corporeo: Il ritorno di antichi fantasmi?

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Antonella Castagna

FONDAZIONE ASIA



BARI | 21-22 MARZO 2019

CENTRO CONGRESSI PALACE HOTEL BARI

CASEY  
AFFLECK

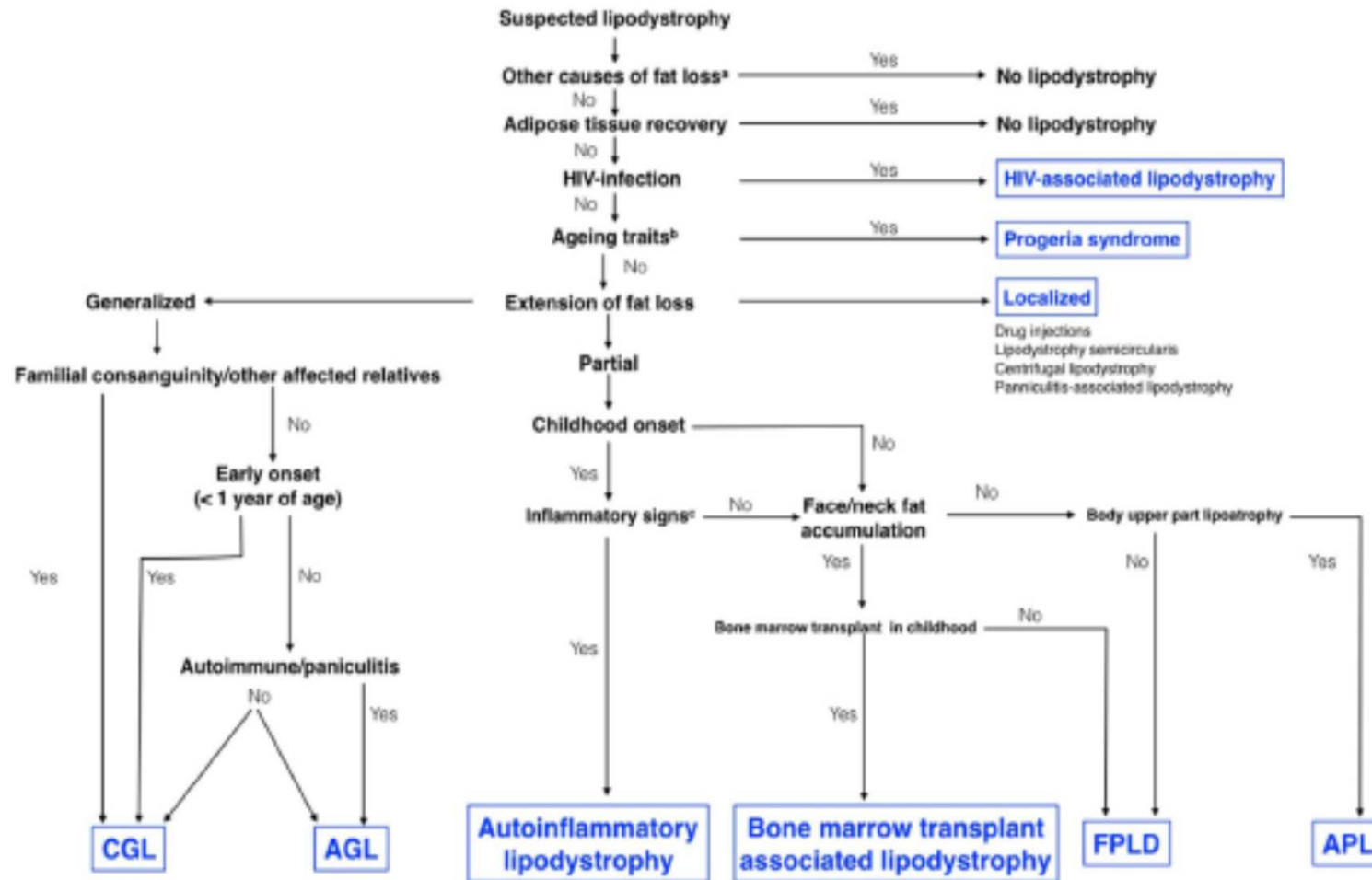
ROONEY  
MARA

STORIA  
DI UN  
FANTASMA

È SOLO UNA QUESTIONE DI TEMPO.

David Lowery, 2017

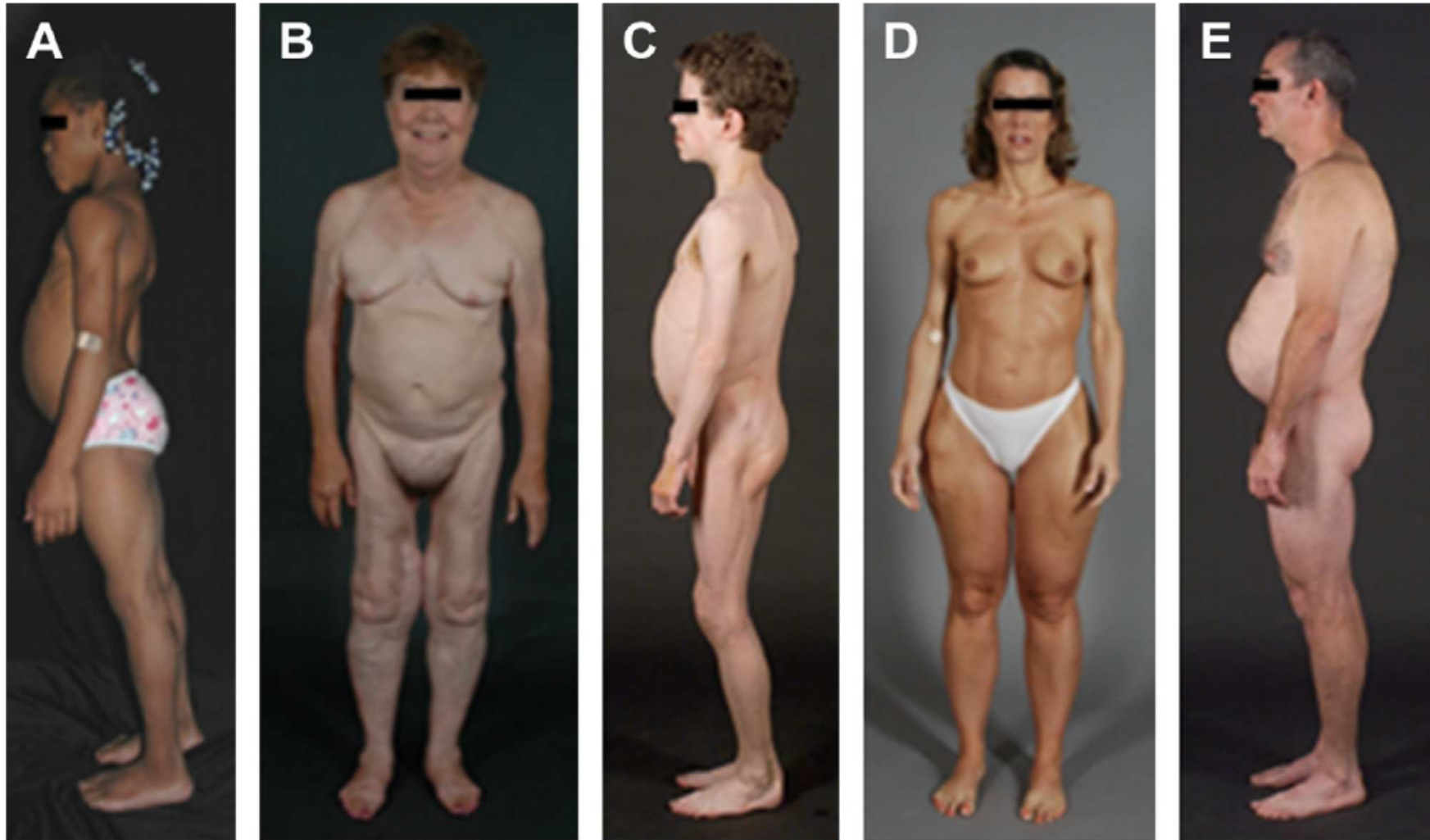
# Diagnosis and treatment of lipodystrophy: a step-by-step approach



# Lipodystrophy Syndromes



Iram Hussain, MD<sup>a</sup>, Abhimanyu Garg, MD<sup>b,\*</sup>



# LONG-LASTING ALTERATIONS IN FAT DISTRIBUTION IN PLWH EXPOSED TO THYMIDINE ANALOGUES

Poster number 0676

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**Table 3 - Association between cumulative exposure to TA and ddi and VAT and SAT**

	Visceral adipose tissue		Subcutaneous adipose tissue	
	Adjusted $\beta$ [95% CI]	p-value	Adjusted $\beta$ [95% CI]	p-value

## Cumulative time of exposure to TA and/or ddi

< 3.6 years	Ref		Ref	
3.6 – 6.3 years	17.5 [0.2;34.8]	0.047	-1.3 [-16.2;13.6]	0.862
6.4 – 9.2 years	40.8 [23.2;58.5]	< 0.001	7.6 [-7.6;22.8]	0.328
> 9.2 years	44.4 [26.0;62.7]	< 0.001	2.2 [-13.6;18.1]	0.781

## Time since discontinuation of TA and/or ddi

< 8.1 years	Ref		Ref	
8.1 – 9.6 years	-13.5 [-30.8;3.8]	0.127	8.1 [-6.8;23.1]	0.288
9.7 – 10.7 years	1.0 [-16.7;18.8]	0.906	-4.1 [-19.5;11.2]	0.595
> 10.7	8.62 [-9.4;26.7]	0.351	14.2 [-1.4;29.9]	0.075

\* $\beta$  coefficients represent the degree of change in cm<sup>2</sup> of VAT and SAT, respectively, associated with each level of the explanatory variables.

# LONG-LASTING ALTERATIONS IN FAT DISTRIBUTION IN PLWH EXPOSED TO THYMIDINE ANALOGUES

Poster number 0676

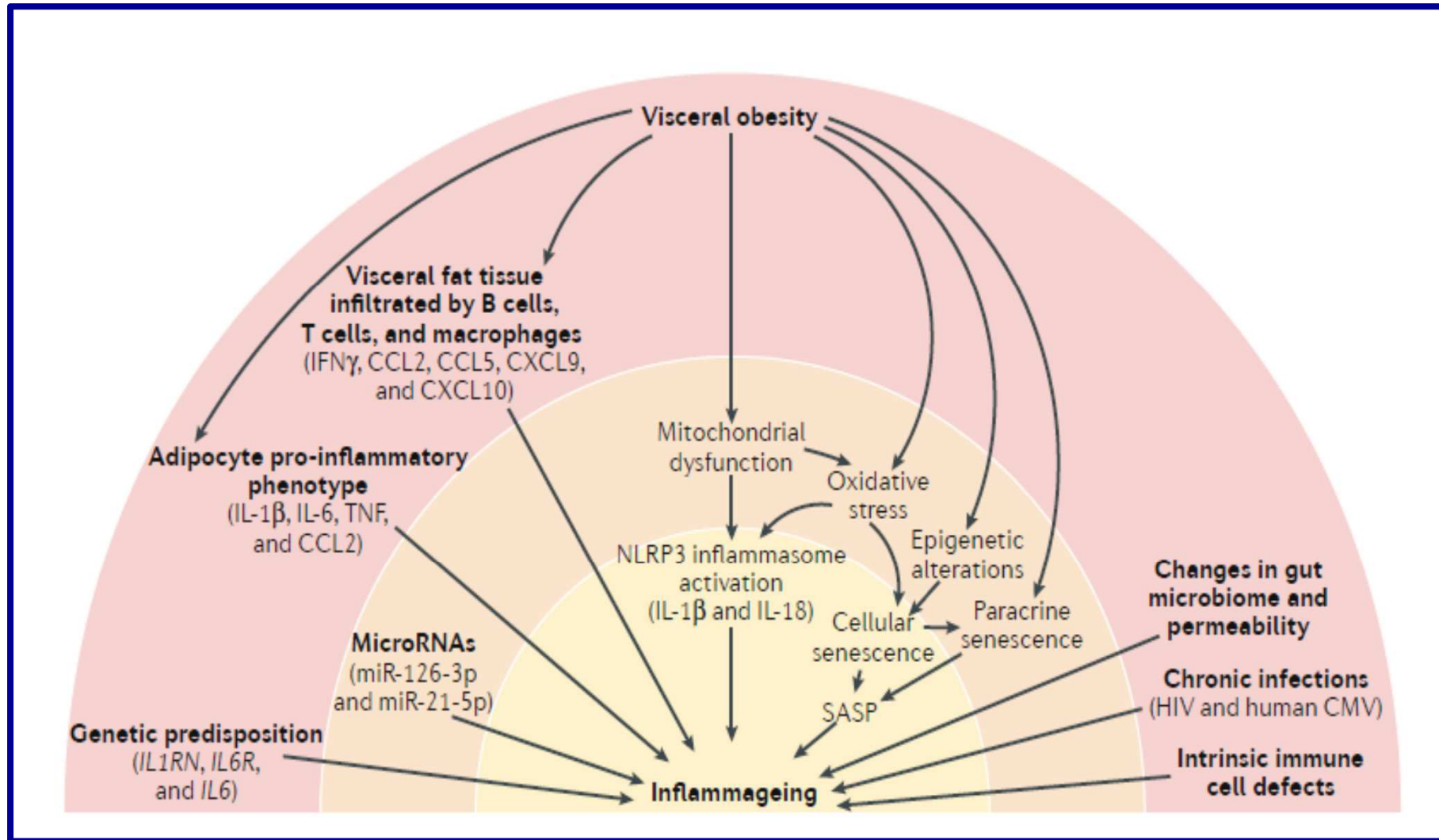
Marco Gelpi<sup>1</sup> MD; Shoab Afzal<sup>2</sup> MD, PhD; Andreas Fuchs<sup>3</sup> MD; Jens Lundgren MD DMSc Professor<sup>1,3</sup>; Andreas Dehlbæk Knudsen MD<sup>1</sup>; Nimna Drivsholm<sup>1</sup>; Amanda Mocroft<sup>5</sup>, MSc Professor; Anne-Mette Lebech<sup>1</sup> MD DMSc; Birgitte Lindegaard<sup>6,7</sup> MD, PhD; Jørgen Tobias Kühl<sup>8</sup> MD; Per Ejstrup Sigvardsen, MD<sup>3</sup>; Lars Køber<sup>3</sup>, MD DMSc Professor; Børge G. Nordestgaard<sup>2,8</sup>, MD DMSc Professor; Klaus Fuglsang Kofod<sup>3,9</sup>, MD DMSc Associate Professor; Susanne Dam Nielsen<sup>1</sup> MD DMSc Associate Professor

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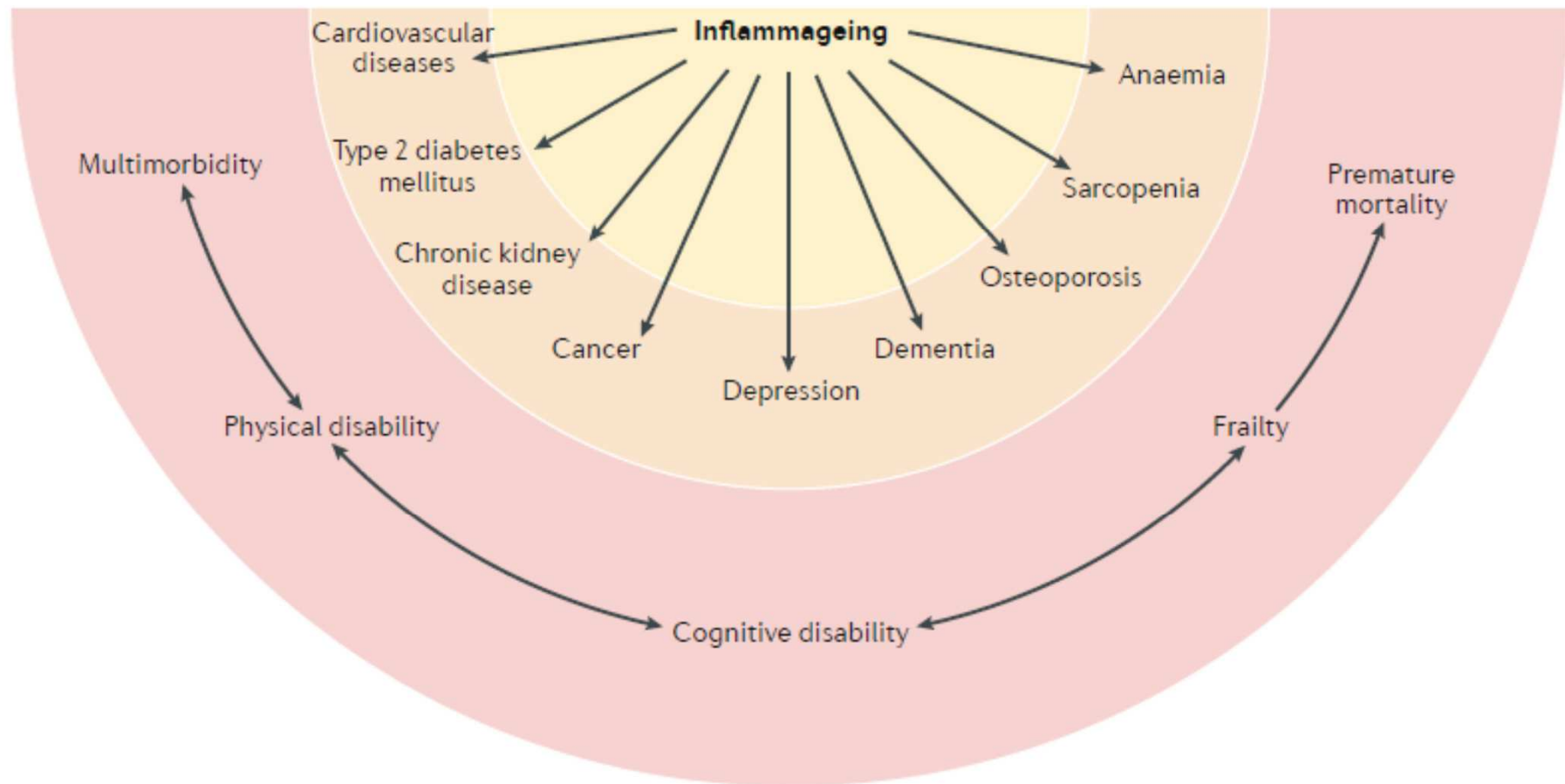
## CONCLUSIONS

Prior exposure to TA and/or ddl was associated with long-lasting alterations in abdominal fat distribution, persisting after TA and/or ddl discontinuation, which may be involved in the excess risk of hypertension, hypercholesterolemia, and low HDL found in PLWH with prior exposure to TA and/or ddl. Our findings may help to identify a subgroup of PLWH who may benefit from more intensive monitoring and cardiovascular prevention interventions.

# Potential causes of inflammaging

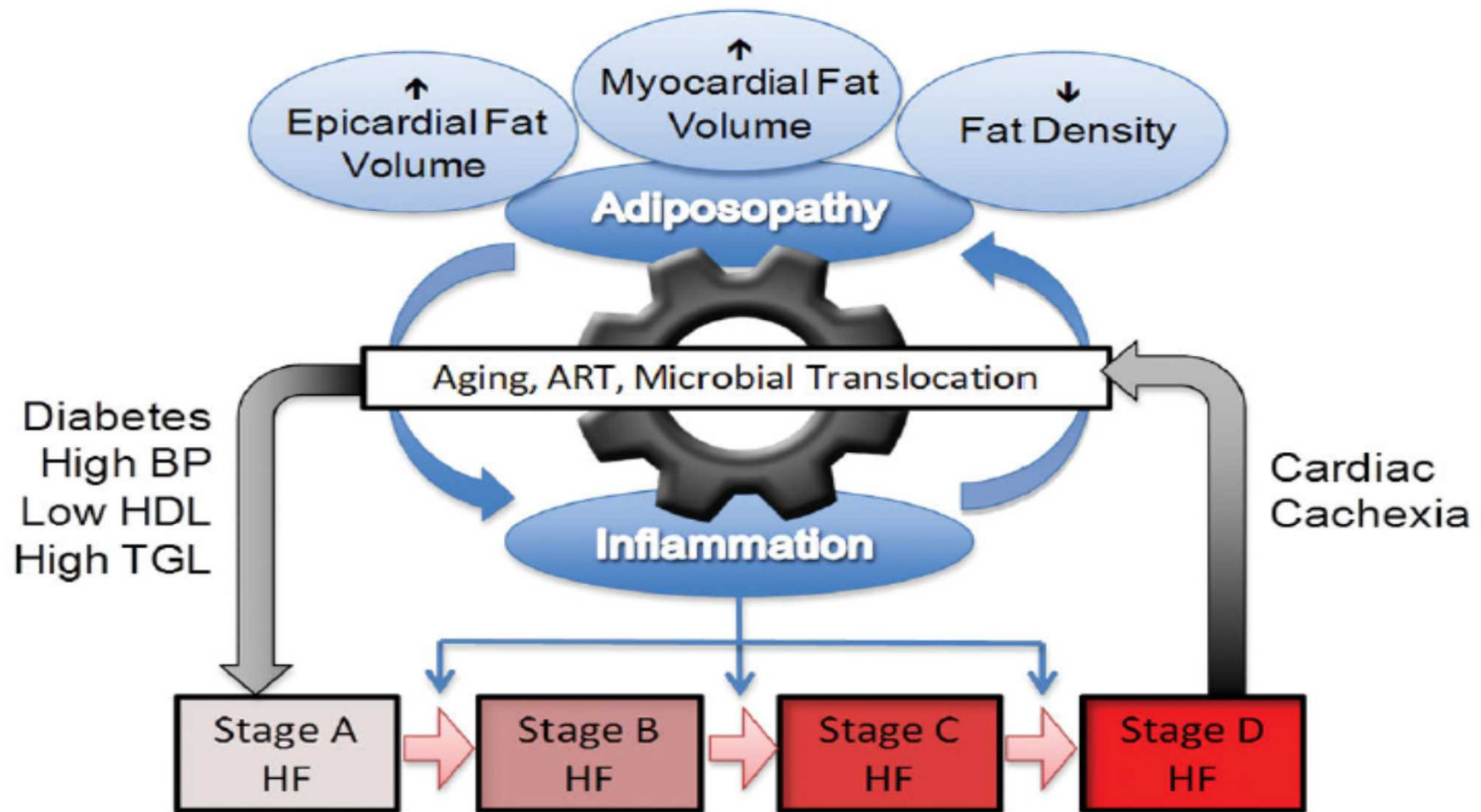


# Inflammageing is a risk factor for multiple chronic diseases



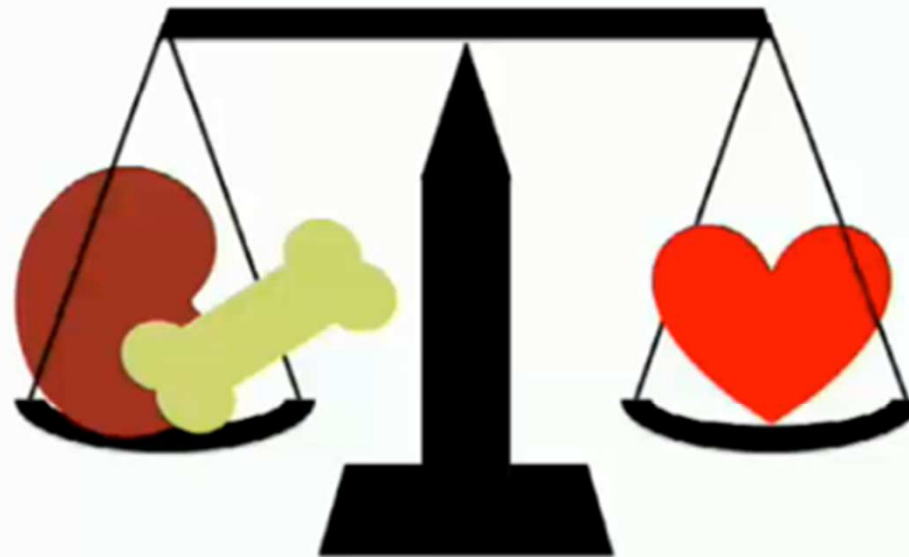


# Heart Fat in HIV: marker or mediator of risk?



## **NRTI: tenofovir-DF vs abacavir**

**mtDNA**



**DNA  
methylation**

**Telomerase & telomere length**

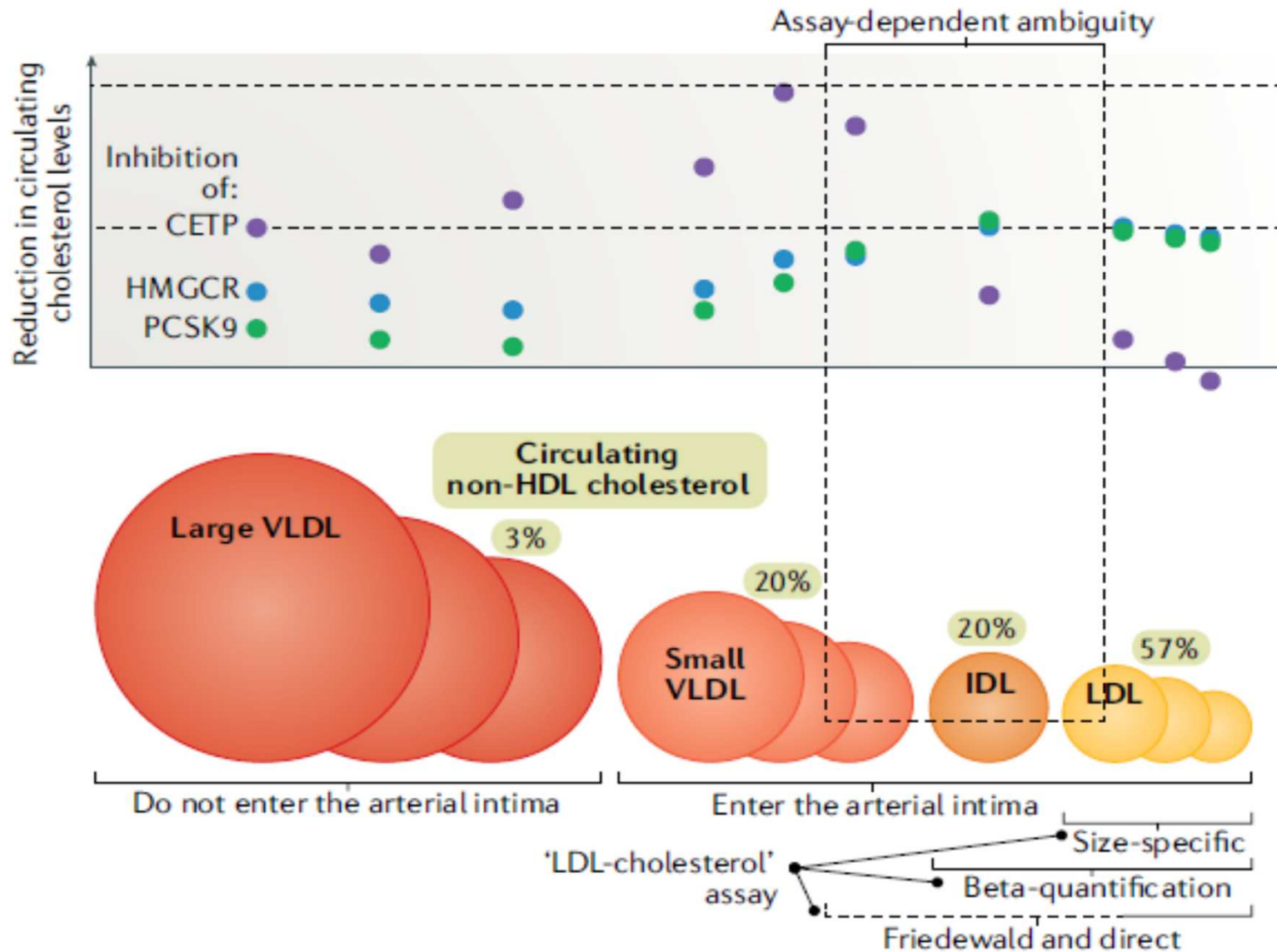
1. Marsit CJ et al. *Epigenetics*. 2015;10(8):708-16; 2. Stella-Ascariz N et al. *JAIDS* 2017;74(1):91-94; 3. Montejano R et al. *JAIDS* 2018. 4. Stella-Ascariz N et al. *J Infect Dis*. 2018 Jul 3.

## **WHAT ABOUT TAF ?**

## Results: Tenofovir-diphosphate Concentrations

Matrix	Tenofovir-diphosphate (fmol/10 <sup>6</sup> cells) Median (and Interquartile Range)	
	TAF (n=13)	TDF (n=45)
PBMC	497 (384, 639)	63 (44, 91)
LN	136 (88, 156)	22 (8, 27)
Ileum	82 (17, 250)	3056 (458, 5835)
Rectum	47 (31, 102)	441 (287, 985)

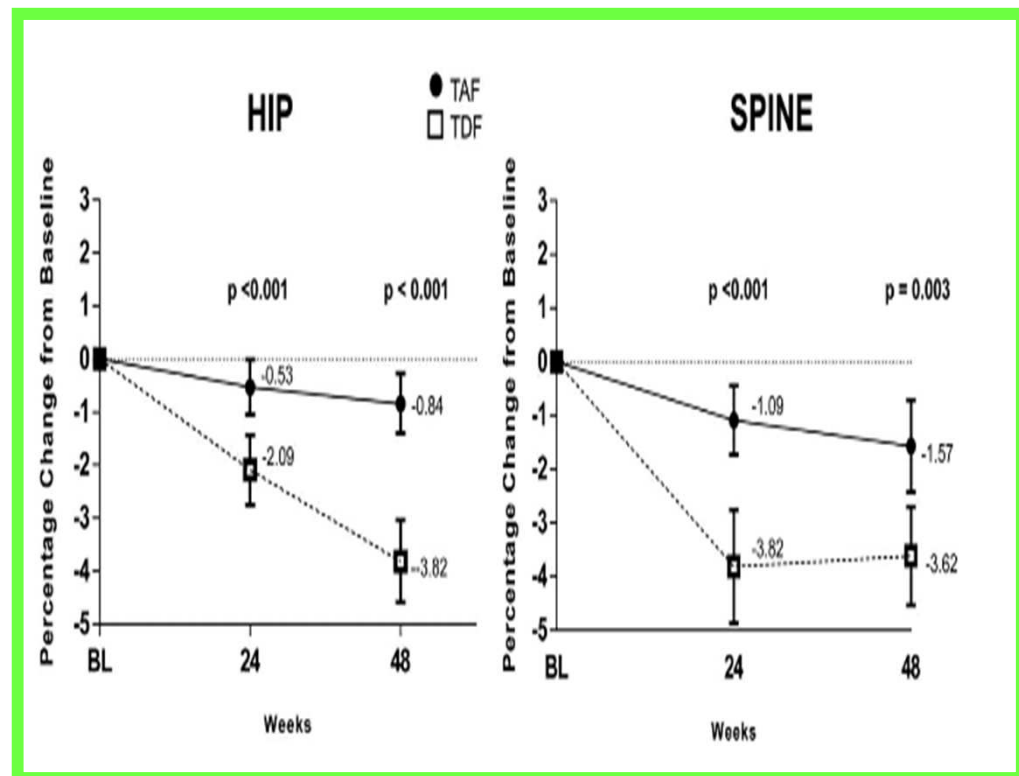
# What is LDL Cholesterol?



# Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate in the First Protease Inhibitor–Based Single-Tablet Regimen for Initial HIV-1 Therapy: A Randomized Phase 2 Study

**TABLE 2.** Median Change in Fasting Metabolic Assessments at Week 48

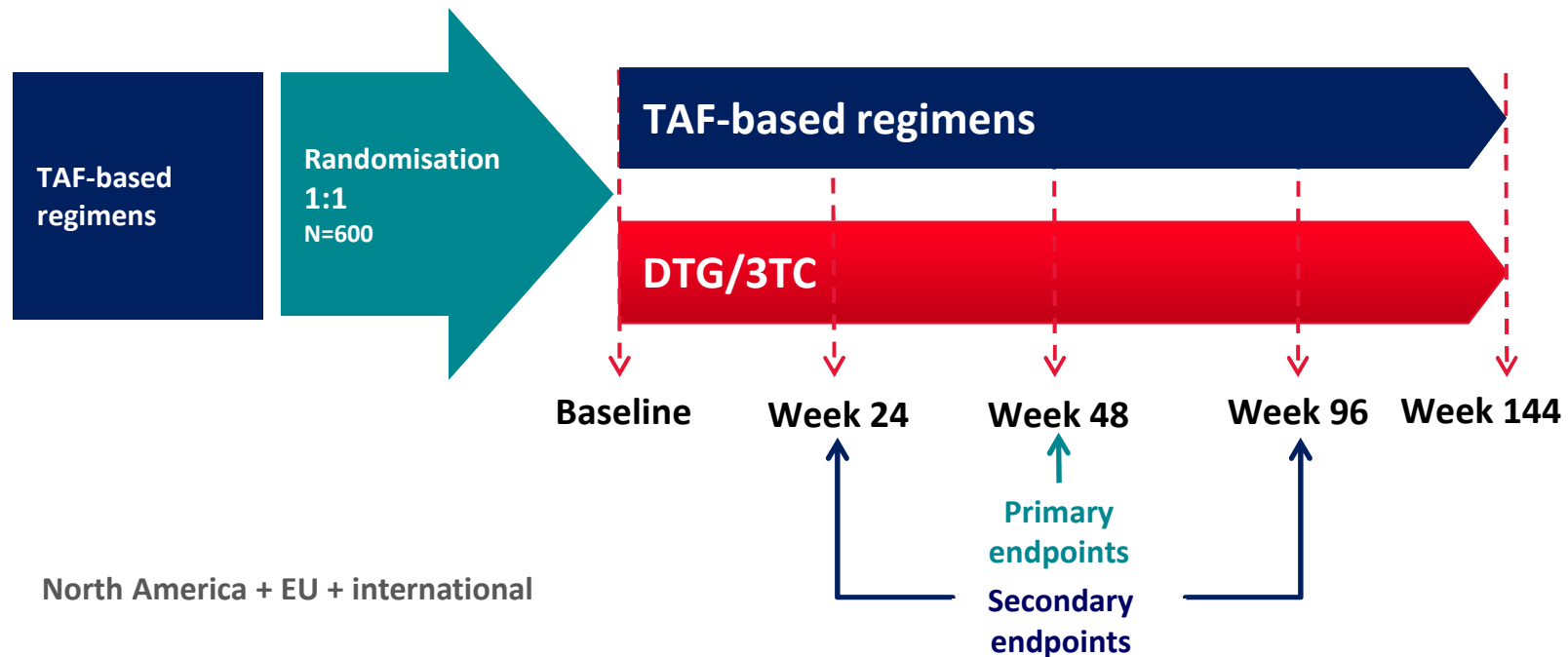
Assessment	D/C/F/TAF (N = 103)	DRV + COBI + F/TDF (N = 50)	P
Total cholesterol, mg/dL	40	5	<0.001
LDL, mg/dL	26	4	<0.001
HDL, mg/dL	7	3	0.009
TC:HDL ratio	0.0	-0.2	0.15
Triglycerides	29	-5	0.007
Serum glucose, mg/dL	5	2	0.33



# Switch study (TANGO)

## Phase III, randomised, multicentre, parallel-group, non-inferiority study

- **Objective:** To demonstrate the non-inferior antiviral activity of switching to DTG/3TC QD compared with continuation of current ARV regimen over 48 weeks in HIV-1-infected ART-experienced subjects
- **Primary endpoint:** The proportion of participants who meet the snapshot virological failure criteria at week 48 using the ITT-E population
  - Non-inferiority margin = 4%; week 48 primary endpoint



## **Long-term glucose tolerance in highly experienced HIV-infected patients receiving nucleoside analogue-sparing regimens**

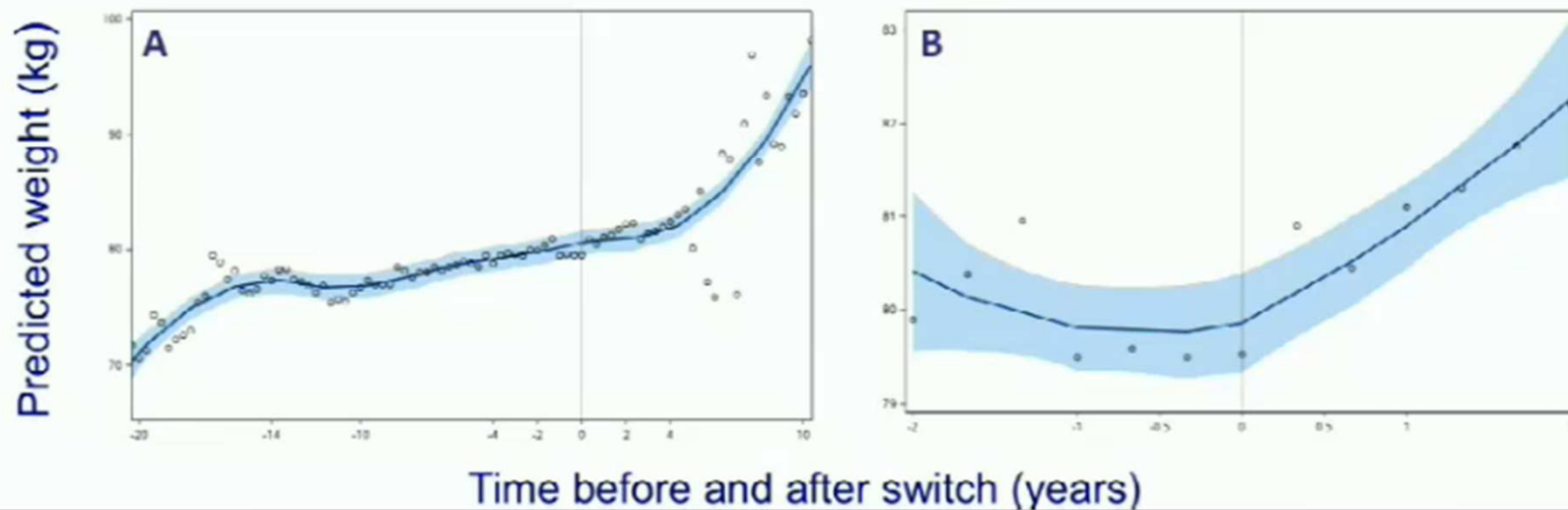
Alba Bigoloni<sup>a</sup>, Nicola Gianotti<sup>a</sup>, Vincenzo Spagnuolo<sup>a</sup>, Laura Galli<sup>a</sup>, Silvia Nozza<sup>a</sup>, Francesca Cossarini<sup>a</sup>, Stefania Salpietro<sup>a</sup>, Elisabetta Carini<sup>a</sup>, Piermarco Piatti<sup>c</sup>, Concetta Vinci<sup>a</sup>, Adriano Lazzarin<sup>a,b</sup> and Antonella Castagna<sup>a</sup>

**Thirty-nine HIV-1-infected patients treated for 156 weeks with a new nucleoside analogue-sparing regimen [raltegravir, etravirine and maraviroc (REM) or raltegravir, etravirine and darunavir/ritonavir (RED)] showed a uniform increase in fasting glucose levels and a uniform decrease in insulin secretory capacity. Diabetes mellitus occurred in one RED-treated and four REM-treated patients. A worsening glucose tolerance was observed in highly treatment-experienced HIV-infected patients receiving effective antiretroviral therapy after virological failure.**

## Results I

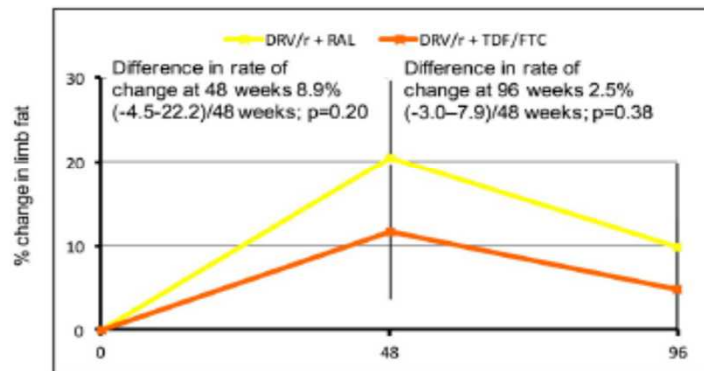
972 adults switched to INSTI at median 7.8 years after parent trial entry. 691 had suppressed HIV-1 RNA at time of switch:

- 82% male, 45% non-white
- Median age 51 years, CD4<sup>+</sup> T cell count 610 cells/ $\mu$ L, and BMI 26 kg/m<sup>2</sup>
- 63% switched from PI, 35% from NNRTI
- 289 switched to RAL, 204 to EVG and 198 to DTG (median follow-up 1.8 years)



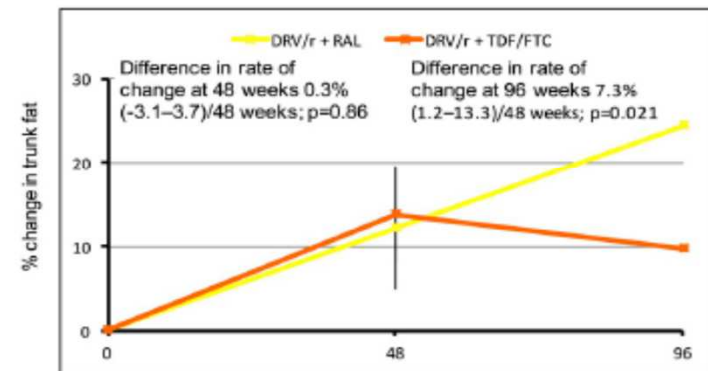


a. Mean (95% CI) percentage rate of change in limb fat DRV/r+RAL versus DRV/r+TDF/3TC



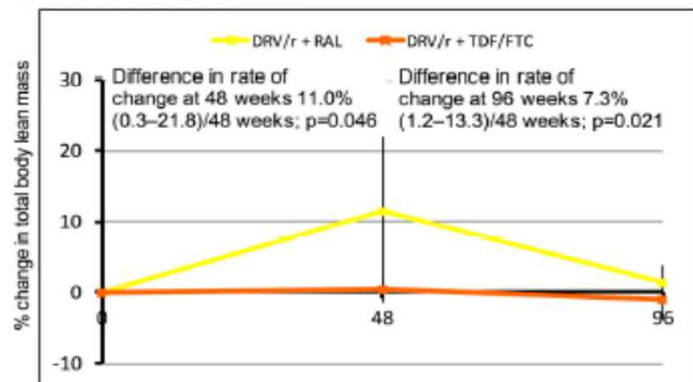
Subjects at visit	Baseline	48 weeks	96 weeks
DRV/r + RAL	61	53	48
DRV/r + TDF/FTC	65	62	56

b. Mean (95% CI) percentage rate of change in trunk fat DRV/r+RAL versus DRV/r+TDF/3TC



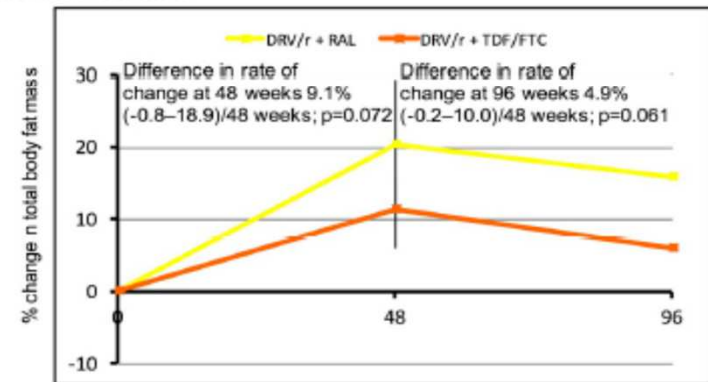
Subjects at visit	Baseline	48 weeks	96 weeks
DRV/r + RAL	61	49	49
DRV/r + TDF/FTC	65	49	56

c. Mean (95% CI) percentage rate of change in total body lean mass DRV/r+RAL versus DRV/r+TDF/3TC



Subjects at visit	Baseline	48 weeks	96 weeks
DRV/r + RAL	61	53	48
DRV/r + TDF/FTC	65	62	56

d. Mean (95% CI) percentage rate of change in total body fat mass DRV/r+RAL versus DRV/r+TDF/3TC

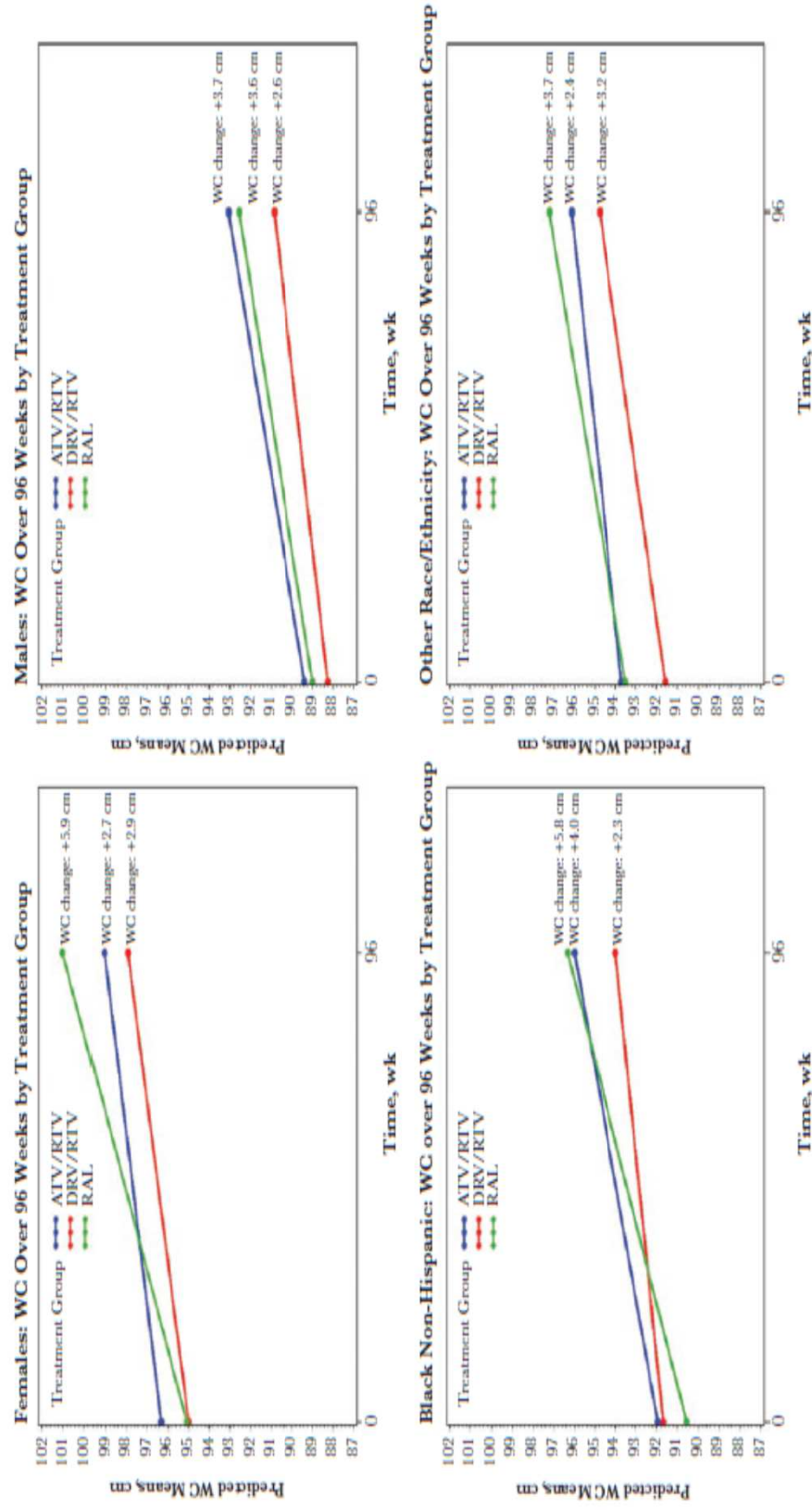


Subjects at visit	Baseline	48 weeks	96 weeks
DRV/r + RAL	61	53	48
DRV/r + TDF/FTC	65	62	56

\*The figures show the differences in the rate of change in body composition per 48 week period at week 48 and 96 compared to week 0 and comparing DRV/r+RAL versus DRV/r+TDF/3TC

# Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race

Priya Bhagwat,<sup>1</sup> Ighowwerha Ofotokun,<sup>2</sup> Grace A. McComsey,<sup>3</sup> Todd T. Brown,<sup>4</sup> Carlee Moser,<sup>5</sup> Catherine A. Sugar,<sup>1</sup> and Judith S. Currier<sup>1</sup>



**Figure 1.** Changes in waist circumference from baseline to week 96 by treatment group across sex and race subgroups in the ACTG A5257 study population (n = 1809). \*Waist circumference values for males and females are averaged over race, and values for black and others are averaged over sex. Abbreviations: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; RAL, raltegravir; WC, waist circumference.



# Homeostatic model assessment for insulin resistance (HOMA-IR) index trajectories in HIV-infected patients treated with first-line antiretroviral regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs), ritonavir-boosted protease inhibitors (PIs/r) or on integrase strand transfer inhibitors (InSTIs)

Muccini Camilla<sup>1</sup>, Gianotti Nicola<sup>2</sup>, Galli Laura<sup>2</sup>, Poli Andrea<sup>2</sup>, Galizzi Nadia<sup>1</sup>, Dell'Acqua Raffaele<sup>3</sup>, Mastrangelo Andrea<sup>1</sup>, Messina Emanuela<sup>2</sup>, Piatti Pier Marco<sup>4</sup>, Lazzarin Adriano<sup>2</sup>, Castagna Antonella<sup>1,2</sup>

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<sup>3</sup>University Hospital Policlinico, Bari, Italy;

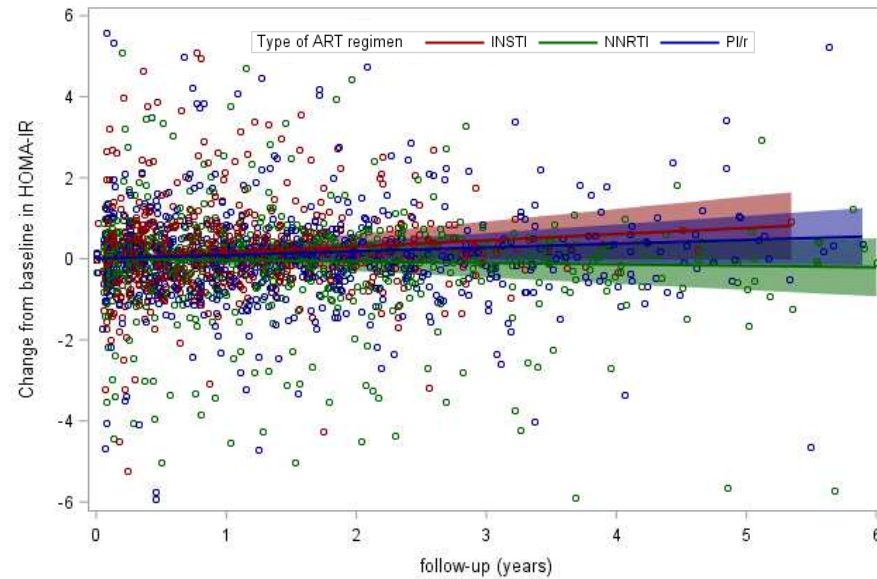
<sup>4</sup>Cardiometabolic Clinical Trials Unit, Internal Medicine Department, IRCCS San Raffaele Scientific Institute, Milan, Italy

## Material and methods

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- Retrospective analysis on a cohort of HIV-1 infected patients followed at the Infectious Diseases Unit of the San Raffaele Hospital of Milan:
- who started antiretroviral therapy (ART) since 2007;
- with 2 NRTIs (tenofovir, abacavir, lamivudine or emtricitabine) and 1 anchor drug [ritonavir-boosted PI, non-NRTI or integrase strand transfer inhibitor (InSTI)];
- with 1 HOMA-IR determination before starting ART and  $\geq 1$  determination after starting ART;
  
- Patients with known diabetes were excluded;
  
- Follow-up accrued from the start of ART (=baseline, BL) up to the stop of any drug of the regimen or lost to follow-up or data freezing (January, 22, 2018);
  
- Univariate and multivariate mixed linear models with random slope and intercept for each patient were fitted to estimate HOMA-IR changes according to the anchor drug.

# Changes from baseline in HOMA-IR index according to the type of the initial ART regimen



Type of ART regimen	Univariate mixed linear model	
	Crude mean (95%CI) change in HOMA-IR, units per year	P-value
<b>INSTI</b>	<b>0.149 (0.012, 0.287)</b>	<b>0.034</b>
<b>NNRTI</b>	<b>-0.071 (-0.174, 0.031)</b>	<b>0.174</b>
<b>PI/r</b>	<b>0.041 (-0.052, 0.134)</b>	<b>0.387</b>

**Conference Dates and Location:**  
March 4-7, 2019 | Seattle, Washington

**Abstract Number:**  
679

## **DOLUTEGRAVIR AND INSULIN RESISTANCE**

**Author(s):**

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Data from 4 DTG clinical trials (SPRING-1, STRIVING, SWORD-1 and -2) with fasting insulin and glucose measurements available, were included; subjects with diabetes were excluded. IR was determined by HOMA mathematical model and defined as a HOMA-IR value  $\geq 2$ ; additional cut-offs of 3 and 4 were also explored. Analysis of relationship between baseline (BL) risk factors and HOMA-IR was completed. Change in HOMA-IR over time and relative to controls were assessed with logistic regression and ANCOVA models, respectively.

HOMA-IR data was available at BL, week 24 and week 48 for 824, 304 and 543 DTG-exposed subjects and 713, 219 and 460 control subjects, respectively. At BL, subjects were mostly male (81%), white (76%) and had a median age of 43yrs; 50% were overweight/obese; 70% had a HOMA-IR $>2$ . Results are shown in the table. There were similar modest increases in HOMA-IR between DTG and control groups over time (24 and 48 weeks). Overall, there was no difference in the odds of HOMA-IR $>2$  between treatment groups at 48 weeks. An association between BL HOMA-IR and increasing age, geographic region, increased BMI/weight, the presence of metabolic or cardiac disorders, lipids, and elevated liver function tests (ALT, ALP and albumin) was observed. Risk factors for IR (HOMA-IR $>2$ ) at week 48 were BL HOMA-IR, Sex, BMI, AIDS CDC category, smoking history, and elevated ALT.

There was no association between treatment and insulin resistance observed in this analysis over a 48 week period, however IR modestly increased over time in all groups. In general, risk factors identified as being associated with IR at Week 48 were consistent with known risk factors for diabetes/IR. These results should be interpreted with caution as the studies were not primarily designed to assess effects of DTG exposure on insulin resistance.

# Lower Pretreatment Gut Integrity Is Independently Associated With Fat Gain on Antiretroviral Therapy

Vanessa El Kamari,<sup>1,2</sup> Carlee Moser,<sup>3</sup> Corri Lynn O. Hilleman,<sup>1,4</sup> Judith S. Currier,<sup>5</sup> Todd T. Brown,<sup>6</sup> Liz Johnston,<sup>3</sup> Peter W. Hunt,<sup>7</sup> and Grace A. McComsey<sup>1,2</sup>

**Table 2. Regression Estimates for Baseline I-FABP<sup>a</sup> With 96-Week Changes in Body Composition Parameters, Adjusting for Clinically Relevant Factors**

	BMI		Visceral Adipose Tissue		Subcutaneous Adipose Tissue		Total Adipose Tissue		Trunk Fat		Total Fat	
	Estimate <sup>b</sup>	P-Value	Estimate <sup>b</sup>	P-Value	Estimate <sup>b</sup>	P-Value	Estimate <sup>b</sup>	P-Value	Estimate <sup>b</sup>	P-Value	Estimate <sup>b</sup>	P-Value
Unadjusted I-FABP	2.5 (0.8–4.2)	.004	15.9 (4.5–27.2)	.006	5.6 (–3.2–14.4)	.216	8.6 (0.3–17.0)	.043	2.7 (–4.4–9.9)	.456	4.4 (–1.7–10.5)	.155
Adjustment												
Age	2.7 (1.0–4.5)	.002	17.0 (5.4–28.6)	.004	6.9 (–2.0–15.8)	.131	9.9 (1.4–18.4)	.022	4.2 (–3.1–11.5)	.259	5.4 (–0.8–11.7)	.087
Sex	2.6 (0.9–4.3)	.003	16.0 (4.7–27.3)	.006	5.8 (–2.8–14.4)	.188	8.8 (0.6–17.0)	.035	3.1 (–4.0–10.2)	.396	4.7 (–1.4–10.7)	.131
Race/ethnicity	2.1 (0.4–3.9)	.015	15.5 (3.8–27.3)	.009	4.2 (–4.8–13.1)	.361	7.5 (–1.0–16.1)	.083	1.3 (–6.0–8.6)	.726	3.2 (–3.1–9.4)	.321
Smoking history	2.5 (0.8–4.2)	.004	16.4 (5.0–27.8)	.005	5.5 (–3.3–14.3)	.224	8.6 (0.3–17.0)	.043	2.6 (–4.6–9.8)	.480	4.4 (–1.7–10.5)	.156
Alcohol history	2.6 (0.9–4.2)	.003	18.2 (7.3–29.1)	.001	6.8 (–1.9–15.6)	.125	9.9 (1.8–18.1)	.017	3.0 (–4.1–10.2)	.406	4.5 (–1.6–10.6)	.151
Drug history	2.6 (1.0–4.3)	.002	17.7 (7.0–28.4)	.001	6.3 (–2.3–15.0)	.150	9.6 (1.6–17.6)	.019	3.1 (–3.9–10.1)	.385	4.7 (–1.3–10.7)	.123
Physical Activity	2.4 (0.7–4.1)	.006	14.6 (3.9–25.3)	.008	4.5 (–4.4–13.4)	.320	7.6 (–0.8–16.0)	.076	1.4 (–5.7–8.6)	.691	3.5 (–2.6–9.6)	.260
CD4+ cell count	1.5 (–0.1–3.2)	.068	12.9 (1.4–24.5)	.028	3.7 (–5.2–12.7)	.414	6.5 (–1.9–15.0)	.130	–0.2 (–7.3–6.9)	.953	1.6 (–4.4–7.6)	.607
HIV-1 RNA	1.9 (0.3–3.5)	.022	12.5 (1.3–23.6)	.028	3.3 (–5.4–12.0)	.462	6.0 (–2.2–14.2)	.150	–0.0 (–6.8–6.8)	.997	2.1 (–3.7–7.9)	.482
All covariates	1.6 (0.0–3.2)	.046	14.7 (4.5–24.8)	.005	3.2 (–5.5–11.9)	.473	6.7 (–1.4–14.7)	.106	–0.9 (–7.8–6.0)	.801	0.9 (–5.1–6.8)	.773

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; I-FABP, intestinal fatty acid binding proteins; RNA, ribonucleic acid.

<sup>a</sup>I-FABP level estimates are presented as per 0.3 log<sub>10</sub> units, which is equivalent to a doubling of the marker.

<sup>b</sup>95% confidence interval.

## RESEARCH ARTICLE

# Probiotics Reduce Inflammation in Antiretroviral Treated, HIV-Infected Individuals: Results of the “Probio-HIV” Clinical Trial

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## OPEN ACCESS

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## Abstract

### Background

HIV infection results in damage to the gastrointestinal (GI) tract, microbial translocation and immune activation. These are not completely normalized with combined antiretroviral therapy (cART). Moreover, increase morbidity and mortality of cART-treated HIV-infected individuals is associated with inflammation.

### Methods

In order to enhance GI tract immunity, we recruited and treated 20 HIV-infected humans with cART supplemented with probiotics and followed inflammation and immunological parameters (clinical trial number NCT02164344). 11 HIV seronegative subjects were included as control group. The enumeration of CD4+, CD8+, CD38+ and HLA-DR+ lymphocytes were evaluated on peripheral blood; HIV-RNA levels, sCD14, d-dimer, C-reactive protein (CRP) high sensitivity C-reactive protein (hsCRP), IL-6 and Lipopolysaccharide Binding Protein (LBP) were assayed on plasma.

### Results

We observe that cART does not normalize the levels of immune activation in HIV positive patients anyway inflammation and markers of microbial translocation were significantly reduced with probiotic supplementation. Patients show a clear and statistically significant reduction in the levels of immune activation on CD4 T-lymphocytes, for both markers CD38 and HLA-DR and their simultaneous expression, LBP and hsCRP plasma levels after probiotic diet supplementation settling to values comparable to controls.





Poster #681

## Changes in Fat Density After ART Initiation

JE Lake<sup>1</sup>, C Moser<sup>2</sup>, M Olefsky<sup>2</sup>, KM Erlandson<sup>3</sup>, A Scherzinger<sup>3</sup>, JH Stein<sup>4</sup>, JS Currier<sup>5</sup>, TT Brown<sup>6</sup> and GA McComsey<sup>7</sup>

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<sup>7</sup>University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH, USA

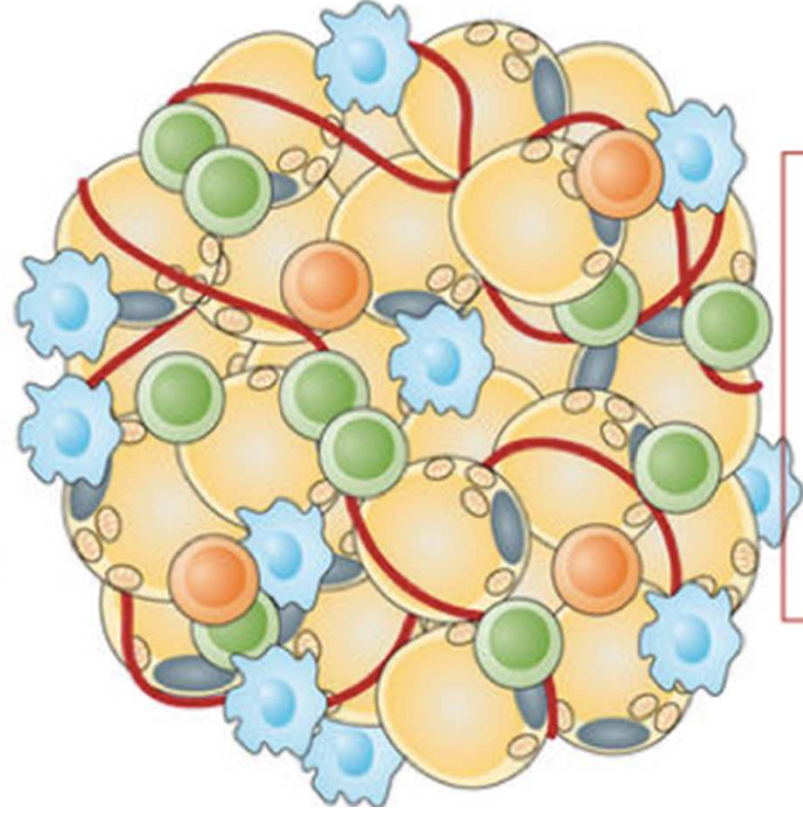


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## STUDY POPULATION & PURPOSE

- ACTG A5257 randomized ART-naïve, adult PLWH to raltegravir (RAL) or ritonavir-boosted atazanavir (ATV/r) or darunavir (DRV/r), each with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).
- Participants in A5260s, the metabolic sub-study of A5257, had L4-L5 single slice CT scans at weeks 0 and 96 (W0 and W96), from which visceral AT (VAT) and SAT density were measured.
- A5260s participants with W0 and W96 CT scans and W96 HIV-1 RNA <50 copies/mL were included in this analysis (n=288).
- We explored changes in AT density after ART initiation and associations with immuno-metabolic parameters.

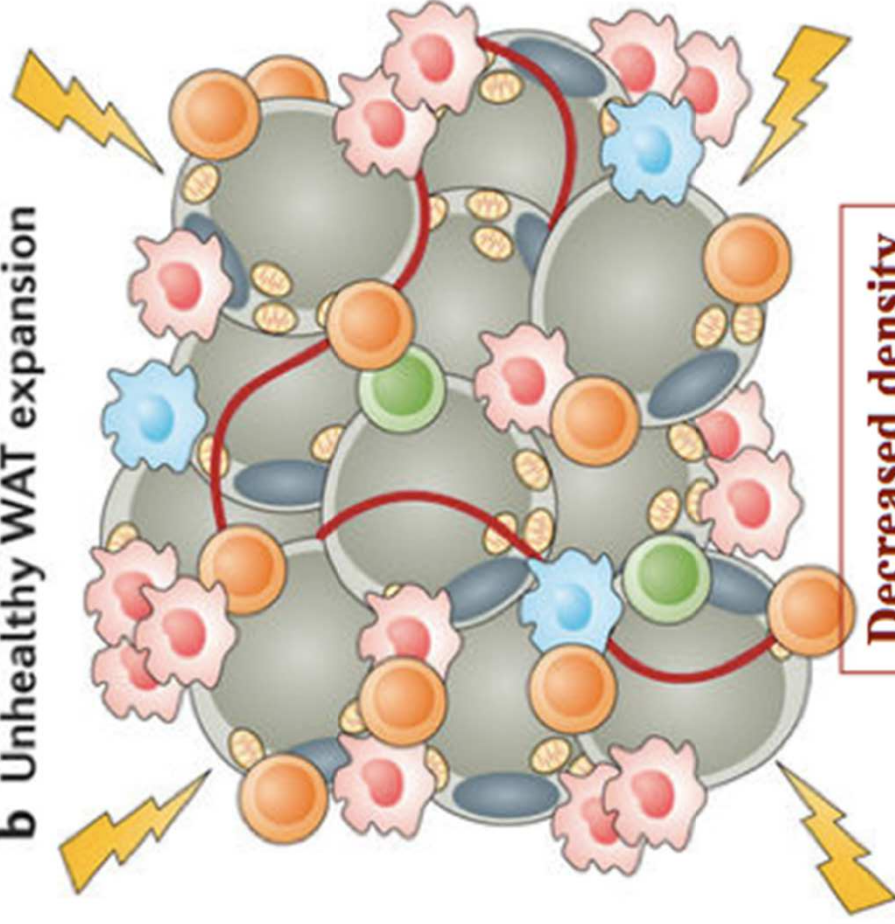
**a Healthy WAT expansion**



**Stable density**

- Adipocyte hyperplasia
- Anti-inflammatory state ( $\uparrow$  M2 ATMs and  $\uparrow$  T<sub>regs</sub>)
- $\uparrow$  Formation of new vasculature

**b Unhealthy WAT expansion**



**Decreased density**

- Adipocyte hypertrophy and cellular stress
- Pro-inflammatory state ( $\uparrow$  M1 ATMs and  $\uparrow$  NK cells)
- $\downarrow$  Angiogenesis
- $\uparrow$  Fibrosis and hypoxia

Insulin sensitivity

**Figure 1: Metabolically healthy vs unhealthy AT expansion.<sup>1</sup>**

## CT METHODS<sup>2</sup>

- CT scan images were read centrally at the University of Colorado by a reader blinded to treatment arm.
- AT was identified by a mean attenuation of -190 to -30 HU (**more negative=lower density**).
- VAT was distinguished from SAT by tracing along the facial plane of the internal abdominal wall.

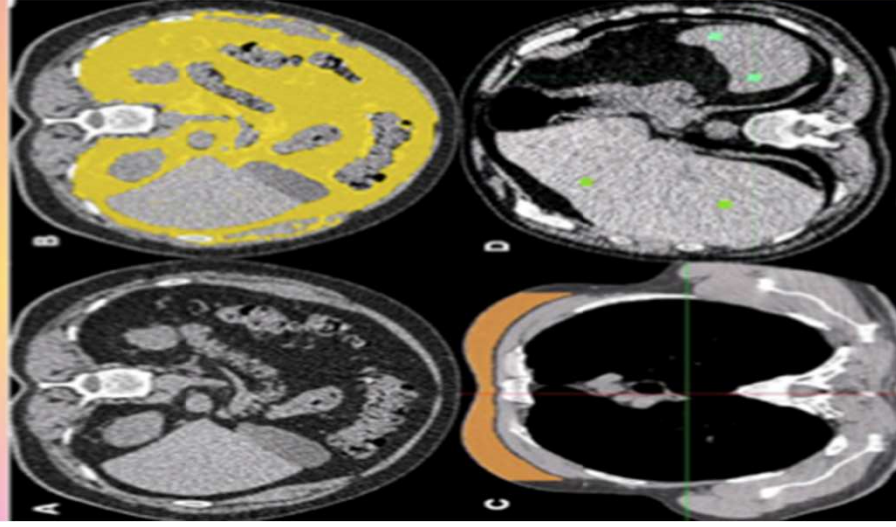


Figure 2: A=prior to AT isolation, B=omental and mesenteric AT, C=SAT, D=intra-hepatic and intra-splenic VAT.



Poster #681

## Changes in Fat Density After ART Initiation

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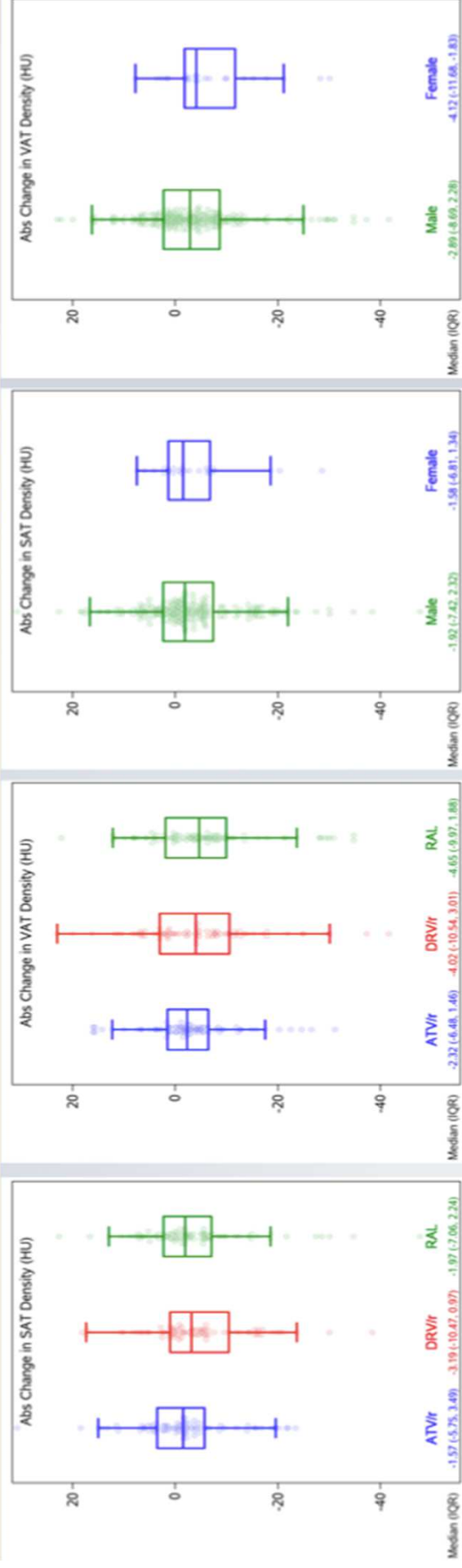
<sup>7</sup>University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH, USA



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## RESULTS

Figure 3: 96-Week Absolute Change in AT Density.



Significant\* (p<0.05) within-group decreases in VAT and SAT density were observed in all treatment arms and for both men and women.

\*except ATV/r p=0.06



Poster #681

## Changes in Fat Density After ART Initiation

**JE Lake<sup>1</sup>, C Moser<sup>2</sup>, M Olefsky<sup>2</sup>, KM Erlandson<sup>3</sup>, A Scherzinger<sup>3</sup>, JH Stein<sup>4</sup>, JS Currier<sup>5</sup>, TT Brown<sup>6</sup> and GA McComsey<sup>7</sup>**

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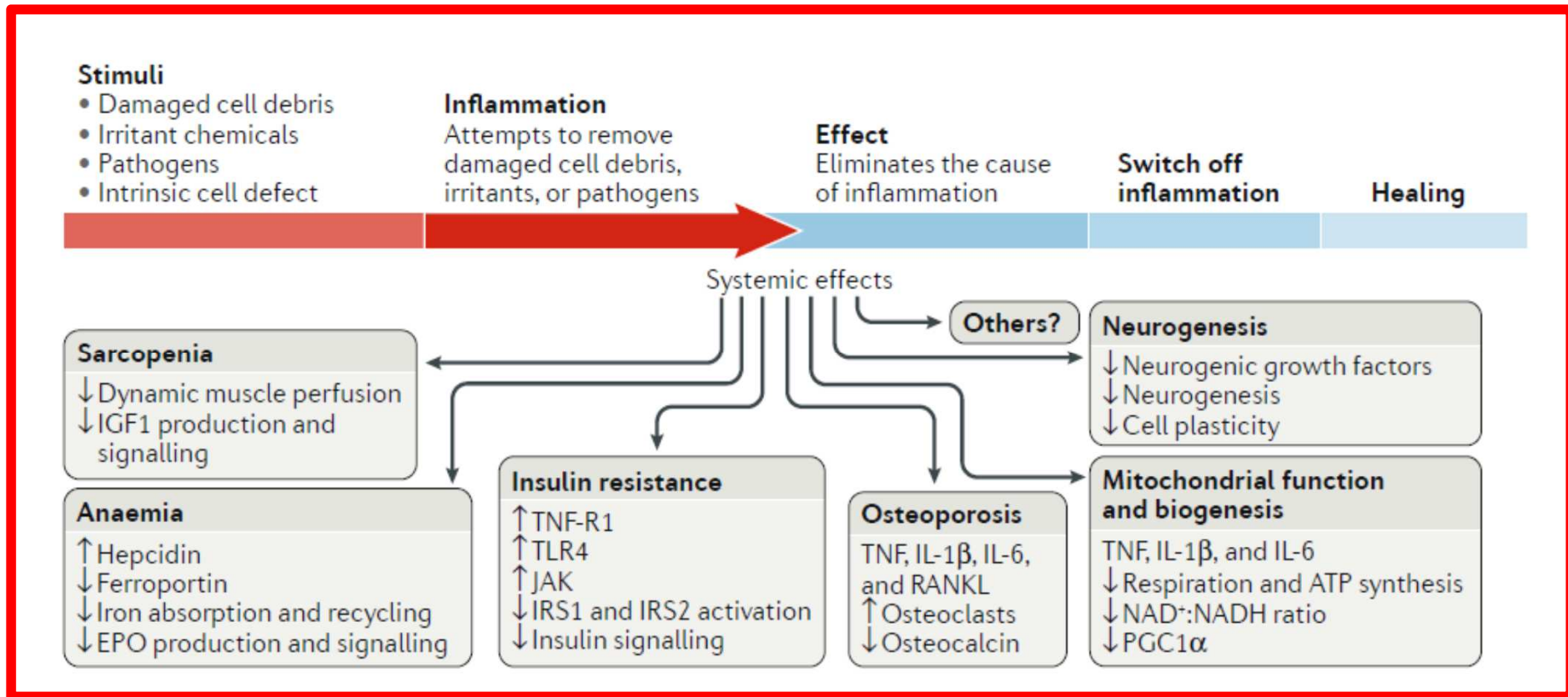


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## CONCLUSIONS

- In adult PLWH, VAT and SAT density decreased over 96 weeks of ART with ATV/r, DRV/r or RAL, each with TDF/FTC.
- Coupled with increased VAT and SAT quantity (previously demonstrated), this suggests unhealthy adipocyte hypertrophy following ART initiation.
- Female sex and higher W0 HIV-1 RNA were associated with greater decreases in AT density.
- Observed relationships between AT density and circulating markers of adipose tissue function, insulin resistance, lipid dysregulation and systemic inflammation were independent of AT quantity and HIV disease severity, highlighting the importance of understanding AT function as a moderator of comorbid disease in PLWH.

# Inflammageing induces a catabolic state.



# Tocilizumab alters lipids in HIV+ individuals in a randomized, double-blind study

ER Bowman<sup>1</sup>, M Cichon<sup>1</sup>, K Reidl<sup>1</sup>, J Baum<sup>2</sup>, ML Freeman<sup>2</sup>, MM Lederman<sup>2</sup>, B Rodriguez<sup>2</sup>, NT Funderburg<sup>1</sup>

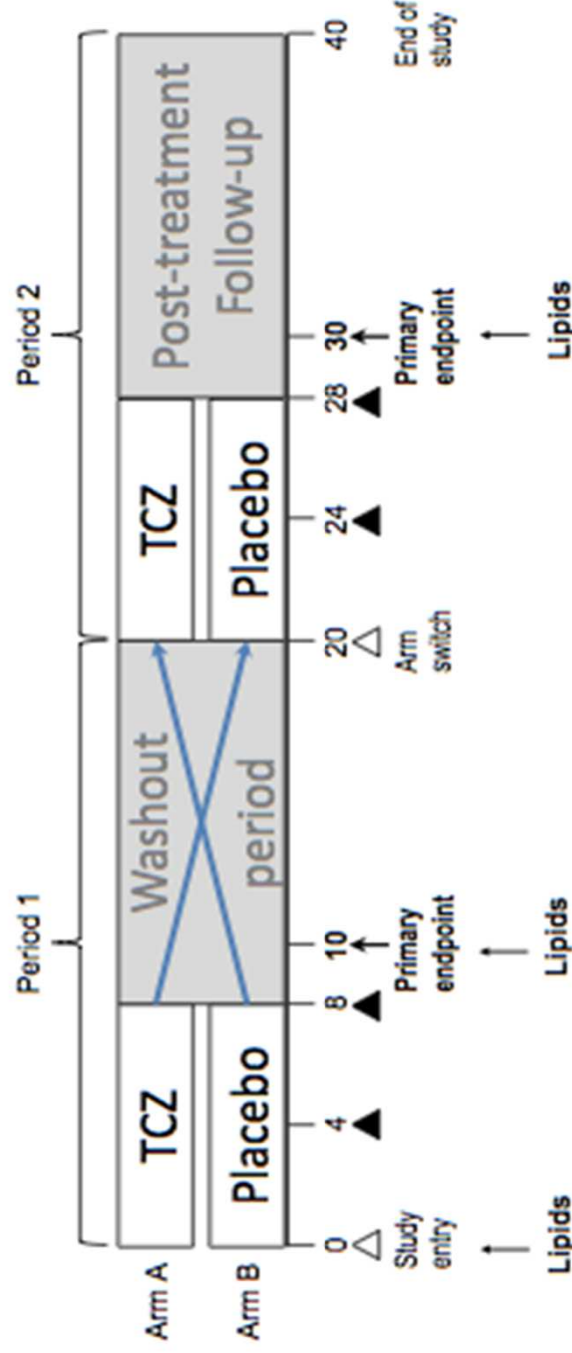
<sup>1</sup>The Ohio State University, Columbus, OH, USA; <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA



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## Study Design



**Figure 1.** Triangles indicate the dates of study agent administration. Empty symbols = 4 mg/Kg dose; solid symbols = 8 mg/Kg dose. Plasma lipid measurements were collected at indicated timepoints. Arm A: N=15; Arm B: N=16

# Tocilizumab alters lipids in HIV+ individuals in a randomized, double-blind study

ER Bowman<sup>1</sup>, M Cichon<sup>1</sup>, K Reidl<sup>1</sup>, J Baum<sup>2</sup>, ML Freeman<sup>2</sup>, MM Lederman<sup>2</sup>, B Rodriguez<sup>2</sup>, NT Funderburg<sup>1</sup>

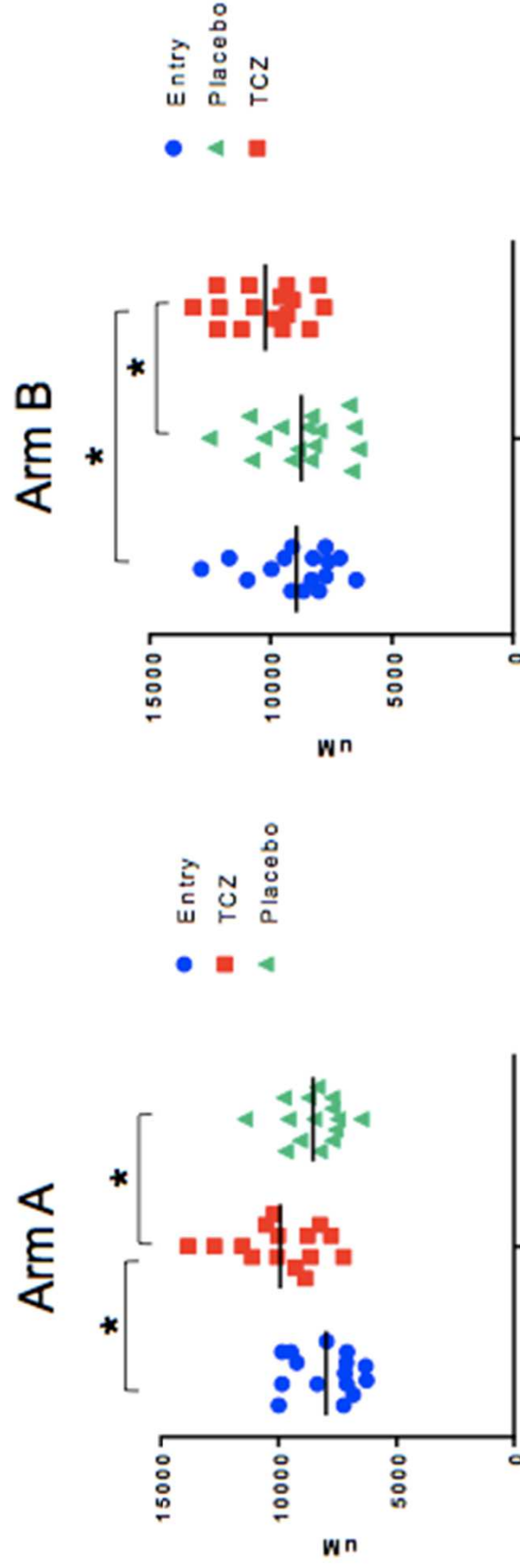
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## The concentration of total plasma lipids is increased following TCZ administration



**Figure 2.** Total plasma lipid concentration (uM) across all classes measured was performed by mass spectrometry. \* $p < 0.05$



## Tocilizumab alters lipids in HIV+ individuals in a randomized, double-blind study

ER Bowman<sup>1</sup>, M Cichon<sup>1</sup>, K Reidl<sup>1</sup>, J Baum<sup>2</sup>, ML Freeman<sup>2</sup>, MM Lederman<sup>2</sup>, B Rodriguez<sup>2</sup>, NT Funderburg<sup>1</sup>

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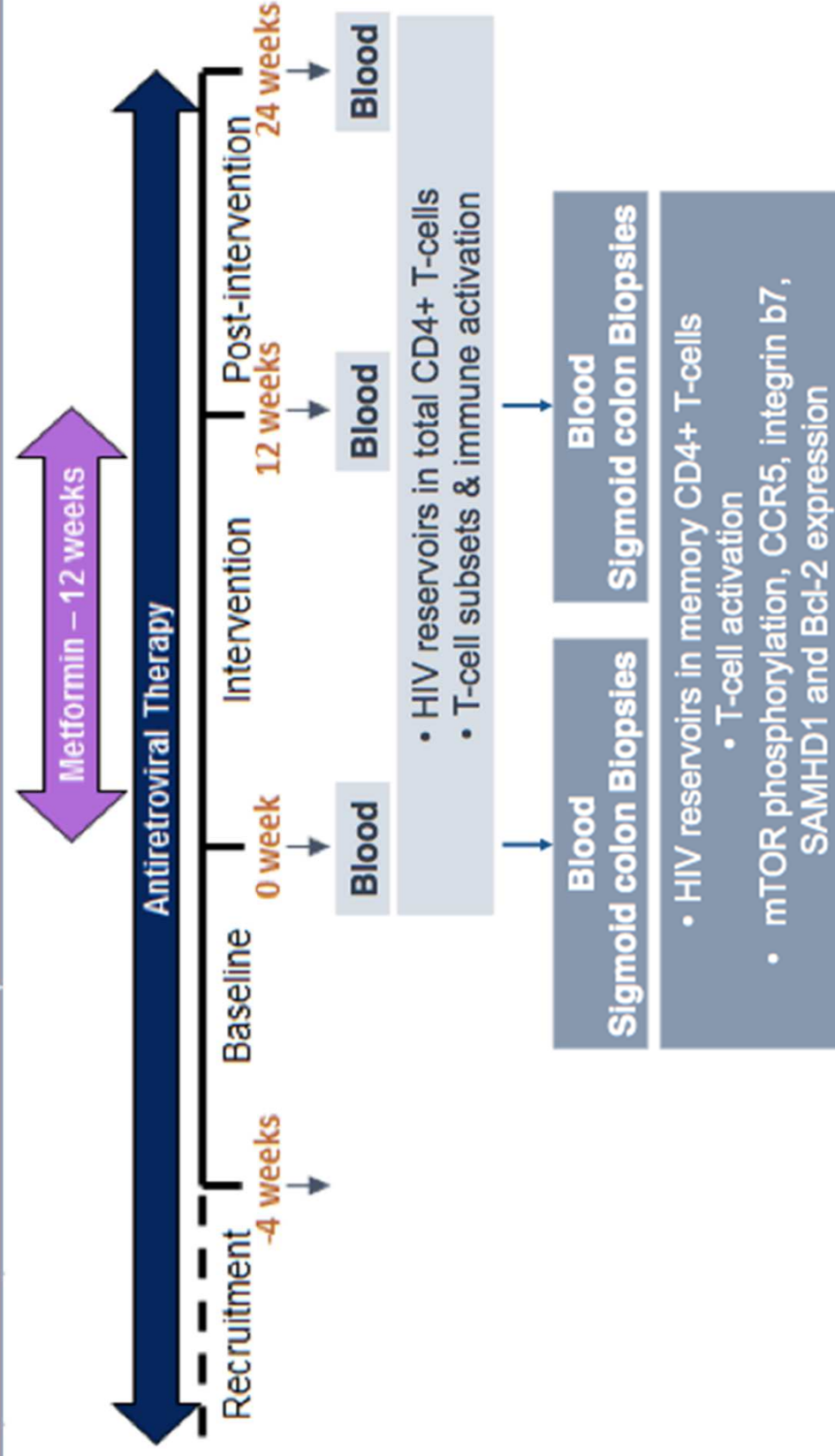
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**Conclusions:** TCZ therapy alters lipid profiles in HIV+ individuals on ART. The concentrations of multiple lipid classes increased during TCZ treatment, however, the SaFA/UFA ratio was improved for some classes. IL-6 blockade may reduce some indices of inflammation in HIV+ individuals, but also exacerbates lipid levels, potentially limiting benefits in this population. Further study is needed to determine the consequences of TCZ-mediated lipidome alterations on CVD risk.

Delphine Planas<sup>1,2</sup>, Rosalie Ponte<sup>3</sup>, Amélie Pagliuzza<sup>2</sup>, Augustine Fert<sup>1,2</sup>, Laurence Marchand Raymond<sup>2</sup>, Annie Gosselin<sup>2</sup>, Franck Dupuy<sup>3</sup>, Vikram Mehraj<sup>3</sup>,  
Sylvie Lesage<sup>1,4</sup>, Maged Peter Ghail<sup>5</sup>, Jonathan B. Angel<sup>6,7</sup>, Eric A. Cohen<sup>1,8</sup>, Nicolas Chomont<sup>1,2</sup>, Jean-Pierre Routy<sup>3\*</sup> and Petronela Ancuta<sup>1,2\*</sup>

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Delphine Planas<sup>1,2</sup>, Rosalie Ponte<sup>3</sup>, Amélie Pagliuzza<sup>2</sup>, Augustine Fert<sup>1,2</sup>, Laurence Marchand Raymond<sup>2</sup>, Annie Gosselin<sup>2</sup>, Franck Dupuy<sup>3</sup>, Vikram Mehraj<sup>3</sup>, Sylvie Lesage<sup>1,4</sup>, Maged Peter Ghail<sup>5</sup>, Jonathan B. Angel<sup>6,7</sup>, Eric A. Cohen<sup>1,8</sup>, Nicolas Chomont<sup>1,2</sup>, Jean-Pierre Routy<sup>3\*</sup> and Petronela Ancuta<sup>1,2\*</sup>

<sup>1</sup>Département de microbiologie, infectiologie et immunologie, Faculté de médecine, Université de Montréal, Montréal, QC, Canada; <sup>2</sup>CRCHUM-Research Centre, Montréal, QC, Canada; <sup>3</sup>McGill University Health Centre-Gen site, Montréal, QC, Canada; <sup>4</sup>HMR Research Centre, Montréal, QC, Canada; <sup>5</sup>Division of Gastroenterology and Hepatology, McGill University, Montréal, QC, Canada; <sup>6</sup>Ottawa Hospital Research Institute, Ottawa, ON, Canada; <sup>7</sup>Department of Medicine, The Ottawa Hospital, Ottawa, ON, Canada; <sup>8</sup>Institut de Recherches Cliniques de Montréal, Montréal, QC, Canada. \*equal contribution

**Results:** Metformin was well tolerated. Total HIV-DNA levels in blood/colon CD4<sup>+</sup> T-cells and the frequency of blood CD4<sup>+</sup> T-cells carrying replication-competent HIV was stable between Visits 1-3. However, investigations on matched blood/colon samples revealed a positive effect of metformin as reflected by *i*) decreased infiltration of CD4<sup>+</sup> T-cells in the colon (median: 7.3% vs. 4.7%, Visit 1 vs. 2; p=0.019), indicative of reduced colon inflammation; *ii*) decreased mTOR phosphorylation in colon CCR6<sup>+</sup>CD4<sup>+</sup> T-cells (median: 13.0% vs. 7.9%, Visit 1 vs. 2; p=0.0087); *iii*) a tendency for decreased expression of the HIV co-receptors CCR5 and integrin  $\beta$ 7, and increased expression of the HIV restriction factor SAMHD1 in colon CCR6<sup>+</sup>CD4<sup>+</sup> T-cells; and *iv*) decreased sCD14 plasma levels (mean: 1,893 vs. 1,519 ng/ml; Visit 1 vs. 3; p=0.02).

**Conclusion:** This pilot study reveals metformin-mediated benefits in controlling inflammation, in part *via* mTOR regulation, and prompts us to further investigate the immunological/virological benefits of long-term metformin supplementation in HIV+ART individuals.

# Visceral fat reduction with tesamorelin is associated with improved liver enzymes in HIV

Visceral fat reduction and improved liver enzymes Fourman *et al.*

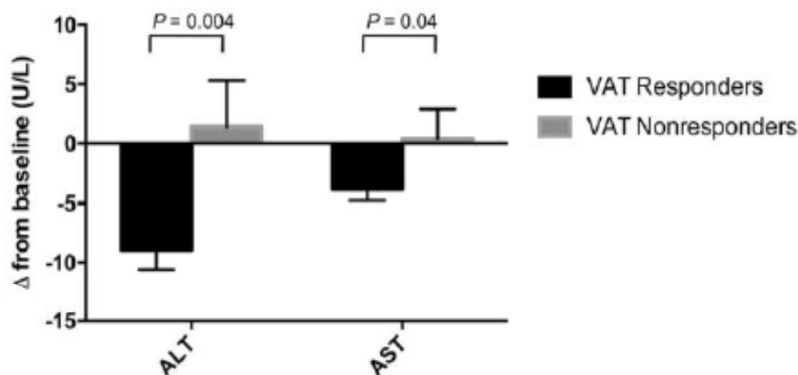


Fig. 2. Changes in ALT and AST among tesamorelin VAT responders and nonresponders with baseline ALT or AST more than 30 U/l at week 26. ALT, alanine aminotransferase; AST, aspartate aminotransferase; VAT, visceral adipose tissue. *P* values are based on comparisons of responders and nonresponders adjusting for baseline ALT or AST, clinical trial, and viral hepatitis status. Responder × hepatitis and responder × trial interactions were not significant. Error bars represent the standard error of the mean.

Liver enzymes at the conclusion of the main study were available for analysis in 176 responders and 79 non-

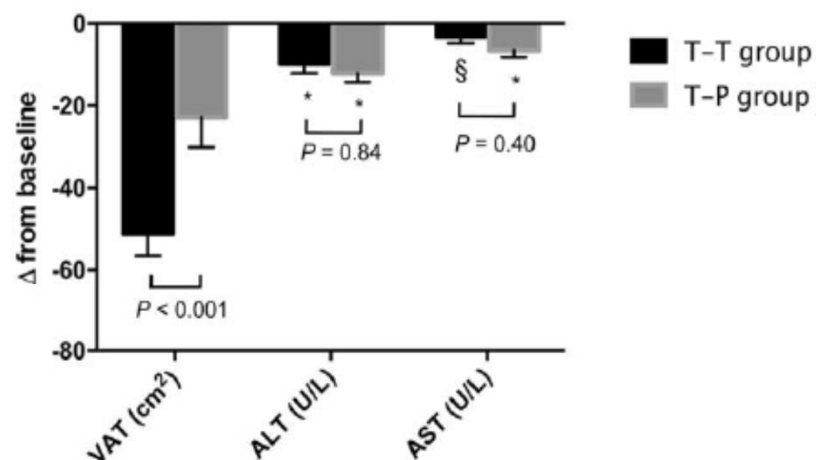


Fig. 3. Changes among initial tesamorelin VAT responders with baseline ALT or AST more than 30 U/l following rerandomization to tesamorelin (T-T) or placebo (T-P) at week 52. ALT, alanine aminotransferase; AST, aspartate aminotransferase; VAT, visceral adipose tissue. *P* values shown reflect comparisons of T-T and T-P groups controlling for baseline value, change from baseline to week 26, and clinical trial. Results of within-group comparisons of liver enzymes between week 52 and baseline are designated as \**P* value less than 0.001, §*P* value less than 0.05. Error bars represent the standard error of the mean.

# Metreleptin-mediated improvements in insulin sensitivity are independent of food intake in humans with lipodystrophy

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**BACKGROUND.** Recombinant leptin (metreleptin) ameliorates hyperphagia and metabolic abnormalities in leptin-deficient humans with lipodystrophy. We aimed to determine whether metreleptin improves glucose and lipid metabolism in humans when food intake is held constant.

**METHODS.** Patients with lipodystrophy were hospitalized for 19 days, with food intake held constant by a controlled diet in an inpatient metabolic ward. In a nonrandomized, crossover design, patients previously treated with metreleptin ( $n = 8$ ) were continued on metreleptin for 5 days and then taken off metreleptin for the next 14 days (withdrawal cohort). This order was reversed in metreleptin-naïve patients ( $n = 14$ ), who were reevaluated after 6 months of metreleptin treatment on an ad libitum diet (initiation cohort). Outcome measurements included insulin sensitivity by hyperinsulinemic-euglycemic clamp, fasting glucose and triglyceride levels, lipolysis measured using isotopic tracers, and liver fat by magnetic resonance spectroscopy.

**RESULTS.** With food intake constant, peripheral insulin sensitivity decreased by 41% after stopping metreleptin for 14 days (withdrawal cohort) and increased by 32% after treatment with metreleptin for 14 days (initiation cohort). In the initiation cohort only, metreleptin decreased fasting glucose by 11% and triglycerides by 41% and increased hepatic insulin sensitivity. Liver fat decreased from 21.8% to 18.7%. In the initiation cohort, changes in lipolysis were not independent of food intake, but after 6 months of metreleptin treatment on an ad libitum diet, lipolysis decreased by 30% (palmitate turnover) to 35% (glycerol turnover).

**CONCLUSION.** Using lipodystrophy as a human model of leptin deficiency and replacement, we show that metreleptin improves insulin sensitivity and decreases hepatic and circulating triglycerides and that these improvements are independent of its effects on food intake.

**TRIAL REGISTRATION.** ClinicalTrials.gov NCT01778556

**FUNDING.** This research was supported by the intramural research program of the NIDDK.



*Ogni difficoltà su cui si sorvola diventa un fantasma che turba il nostro sonno*

*F. Chopin*

## “I don’t want to look like an AIDS victim”: A New Zealand case study of facial lipoatrophy

Gillian Abel DPH MPH PhD  | Lee Thompson BA MA PhD

**Photo 1**



**Photo 2**



**Photo 3**



**Photo 4**

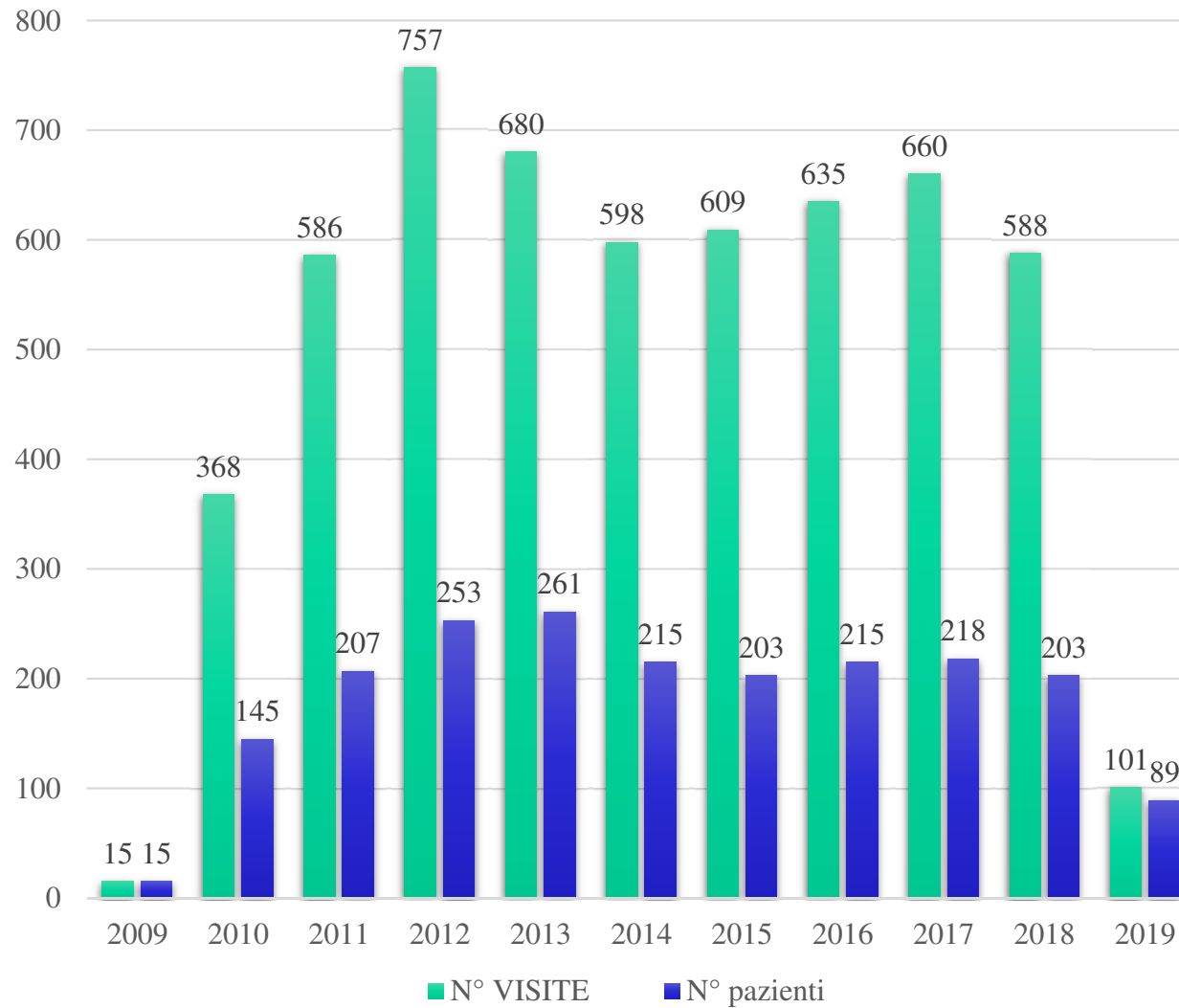


**Photo 5**



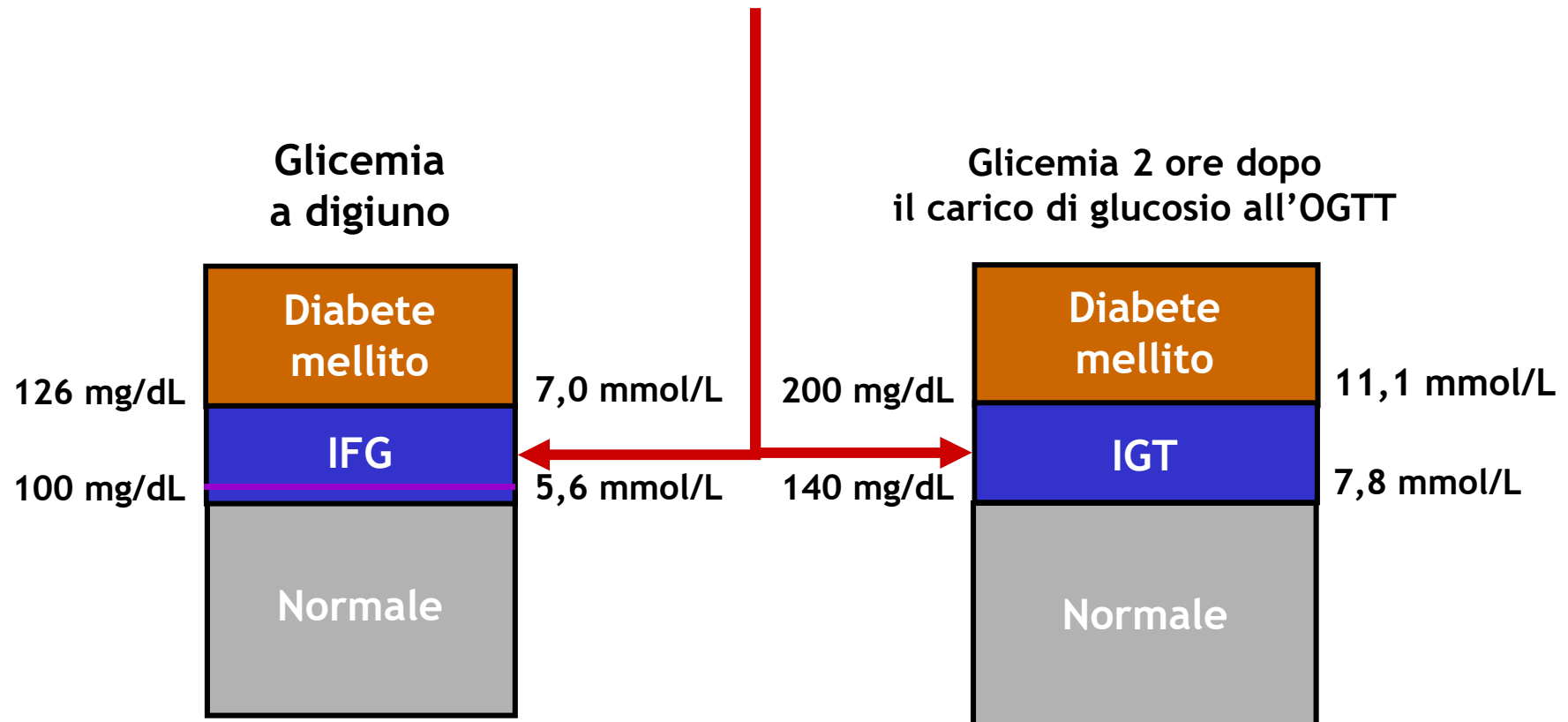
Tom’s Selfies

# Accessi al servizio di chirurgia plastica \_ Data on File\_ 180319\_OS





# PRE-DIABETE



**About 50% of cases convert from NFG/NGT to diabetes in less than 5 years**

Adattamento dal rapporto di follow-up di The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;26:3160-3167

RESEARCH ARTICLE

Open Access



# A pilot study of brisk walking in sedentary combination antiretroviral treatment (cART)- treated patients: benefit on soluble and cell inflammatory markers

Matteo Bonato<sup>1\*</sup>, Laura Galli<sup>2</sup>, Laura Passeri<sup>2</sup>, Valeria Longo<sup>2</sup>, Gaspare Pavei<sup>3</sup>, Simona Bossolasco<sup>2</sup>, Cecilia Bertocchi<sup>4</sup>, Massimo Cernuschi<sup>2</sup>, Giuseppe Balconi<sup>4</sup>, Giampiero Merati<sup>1</sup>, Adriano Lazzarin<sup>2</sup>, Antonio La Torre<sup>1</sup> and Paola Cinque<sup>2</sup>

## Abstract

**Background:** Chronic HIV infection is associated with low-level inflammation and increased risk of chronic diseases and mortality. The objective was to assess the effects of moderate intensity exercise on metabolic and inflammatory markers in HIV-infected treated persons.

**Methods:** This was a pilot study enrolling cART-treated, sedentary persons with metabolic complications in a 12-week protocol, consisting of three sessions per week of 60 min brisk walking with (strength-walk group) or without (walk group) 30 min circuit-training. Assessments at baseline and week 12 (W12) included body morphometrics and total body dual-energy X-ray absorptiometry; lipid and glucose blood profile; plasma level of high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), D-dimer, interleukin-18 (IL-18), soluble CD14, and CD38 and HLA-DR expression on CD4+ and CD8+ T-cells.

**Results:** Forty-nine patients were included and 35 (71%) completed the program: 21 in the walk and 14 in the strength-walk group. At W12, significant improvements were observed of body mass index, waist and hip circumference, and total cholesterol both overall and in the walk group, and of LDL cholesterol in both training groups. In the whole group, significant reductions were observed in hsCRP, IL-6, D-dimer, IL-18, and of CD8+/CD38+/HLA-DR+ cell frequencies. hsCRP and CD8+/CD38+/HLA-DR+ frequency decreased significantly in both training groups when examined separately whereas IL-6 and D-dimer in the walk group only.

**Conclusions:** Brisk walking, with or without strength exercise, could improve lipid profile and inflammatory markers in chronic HIV infection.

**Trial registration:** ACTRN12615001258549, registered 17 November 2015, "retrospectively registered" Web address of trial: <http://www.ANZCTR.org.au/ACTRN12615001258549.aspx>

**Keywords:** cART, Immune activation, Inflammatory markers, Exercise, Physical activity

**“Sono una persona  
con infezione da HIV,  
fumare è l'ultimo dei miei problemi”**

**FALSO**

**2 GIORNI**

I sensi del gusto e del tatto migliorano: alito, dita, denti e capelli sono più puliti. Il catarro segnala che i polmoni stanno reagendo al cambiamento

**15 ANNI**

Il rischio di malattie cardiache coronariche è lo stesso di un non fumatore

**5 ANNI**

Il rischio di mortalità per tumore polmonare si riduce quasi della metà. Diminuiscono anche il pericolo di cancro all'esofago, al cavo orale, alla vescica

**3 SETTIMANE**

Migliorano circolazione sanguigna e capacità polmonare

**24 ORE**

Il monossido di carbonio viene eliminato dal corpo

**20 MINUTI**

La pressione e il ritmo cardiaco tornano ai valori normali

**1 MESE**

Le ciglia delle vie respiratorie si ricostruiscono, il muco è rimosso dai bronchi. Calano il rischio d'infezioni respiratorie e di ictus (-33 per cento)

**12 ORE**

I polmoni respirano meglio

**3 MESI**

Diminuisce la tosse cronica

“Una persona con infezione da HIV che fuma riduce la propria aspettativa di vita di quasi il doppio di quanto faccia da solo l'HIV. Nel caso dei fumatori con HIV, infatti, si sommano due processi infiammatori deleteri per l'insorgenza dei tumori, uno provocato dal virus e l'altro dalla combustione della sigaretta. Il risultato è che oggi una delle principali cause di morte per una persona con infezione da HIV sono il cancro del polmone e quello della gola. Smettere di fumare, però, può cambiare la tua prognosi in maniera significativa: una persona con infezione da HIV che smette di fumare ha un'aspettativa di vita simile a chi non è affetto dal virus”. I trattamenti integrati per smettere di fumare (sostegno psicologico e farmaci specifici) hanno dimostrato una maggior percentuale di successo”



**I.R.C.C.S. Ospedale  
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