Body Fat Changes and Metabolic Complications Associated with Antiretroviral Therapy

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Overview

- ➢ Definition

- ➢ Epidemiology

- ➢ Factors in the development of fat redistribution and metabolic alterations:

  - *The host*

  - *The virus*

  - *The role of drugs*

Definition

> No currently accepted definition.

> Lipoatrophy and fat accumulation.

> Patient and physician perception.

> Semiquantitative scales: LSGS-HOPS.[1]

> **Objective definition**: age, sex, duration of infection, stage, WHR, anion gap, HDL, trunk/peripheral fat ratio, % leg fat, and intra-abdominal to extra-abdominal fat ratio.[2]

[1] Lichtenstein KA, *AIDS*, 2001.
[2] Carr A., *Lancet*, 2003.

Clinical Manifestations

### Lipoatrophy

Lipohypertrophy

Epidemiology: Prevalence of LD

Legend:
- Any lipodystrophy
- Lipodystrophy with subcutaneous lipoatrophy
- Lipodystrophy with central obesity

Prevalence: 2-83%

Y-axis: Percentage (%)
X-axis: Months after starting HAART

Martinez, *Lancet*, 2001.
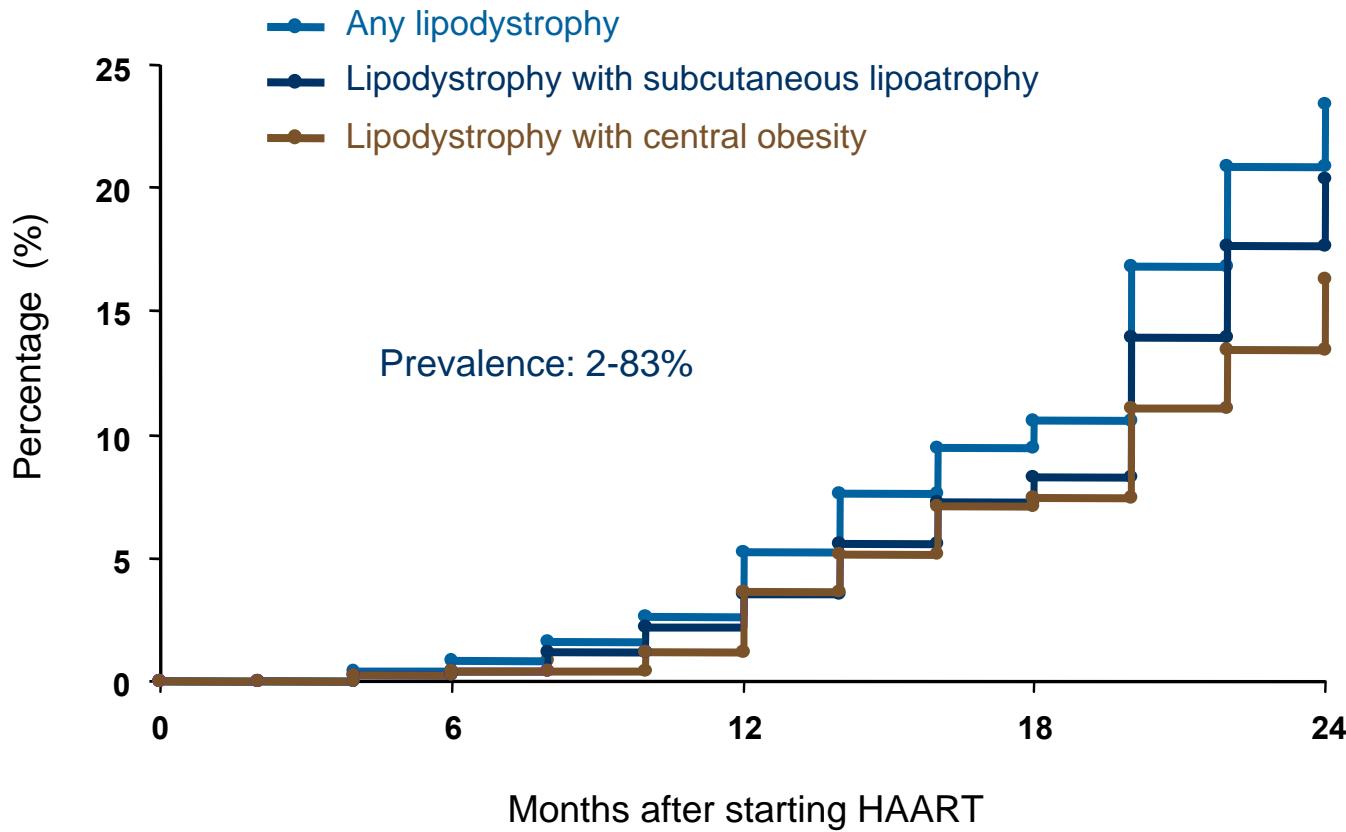
Etiology and Pathogenesis

Genetic background → ← Environmental factors

Risk Factors

Lichtenstein K *et al., JAIDS*, 2005.
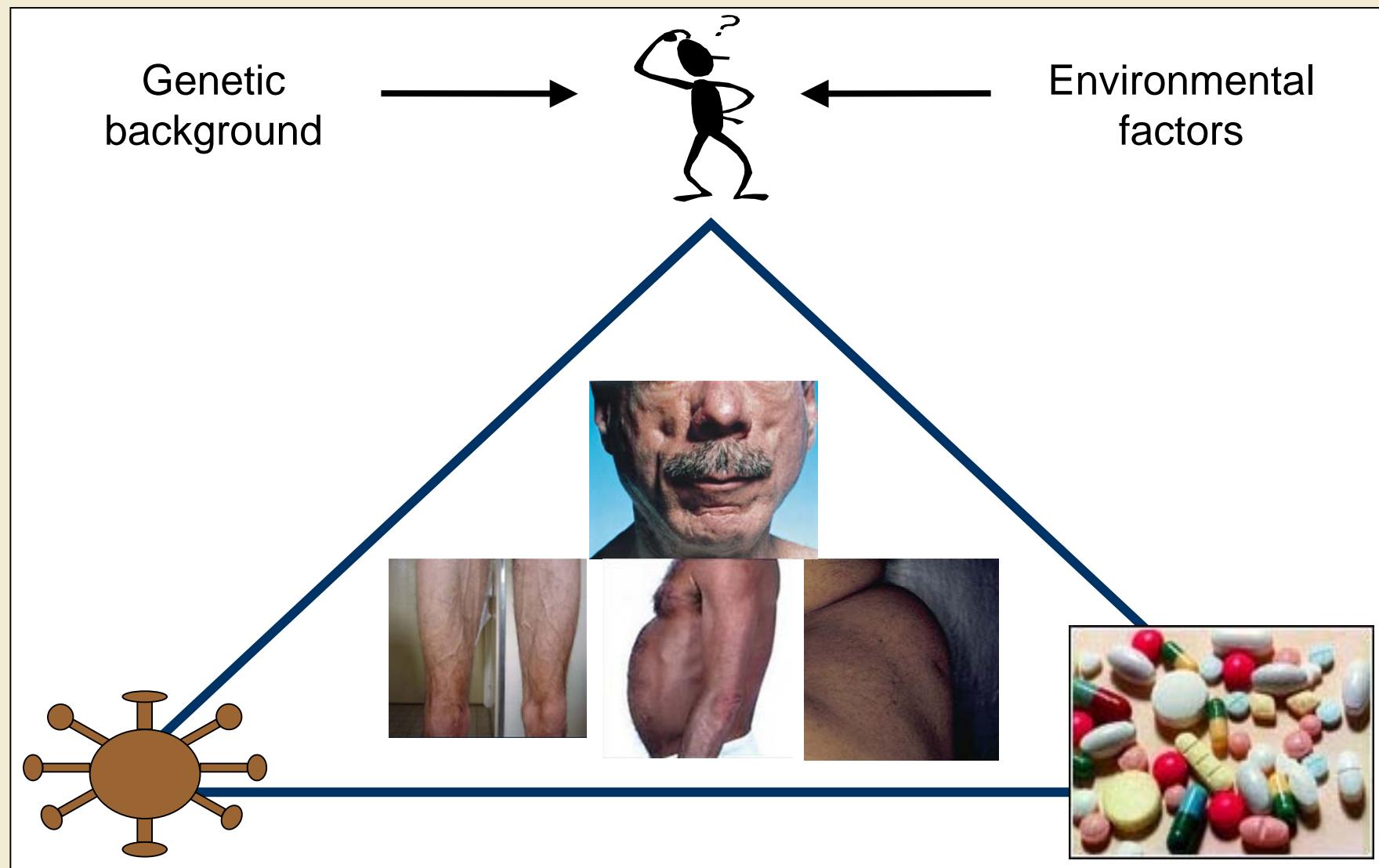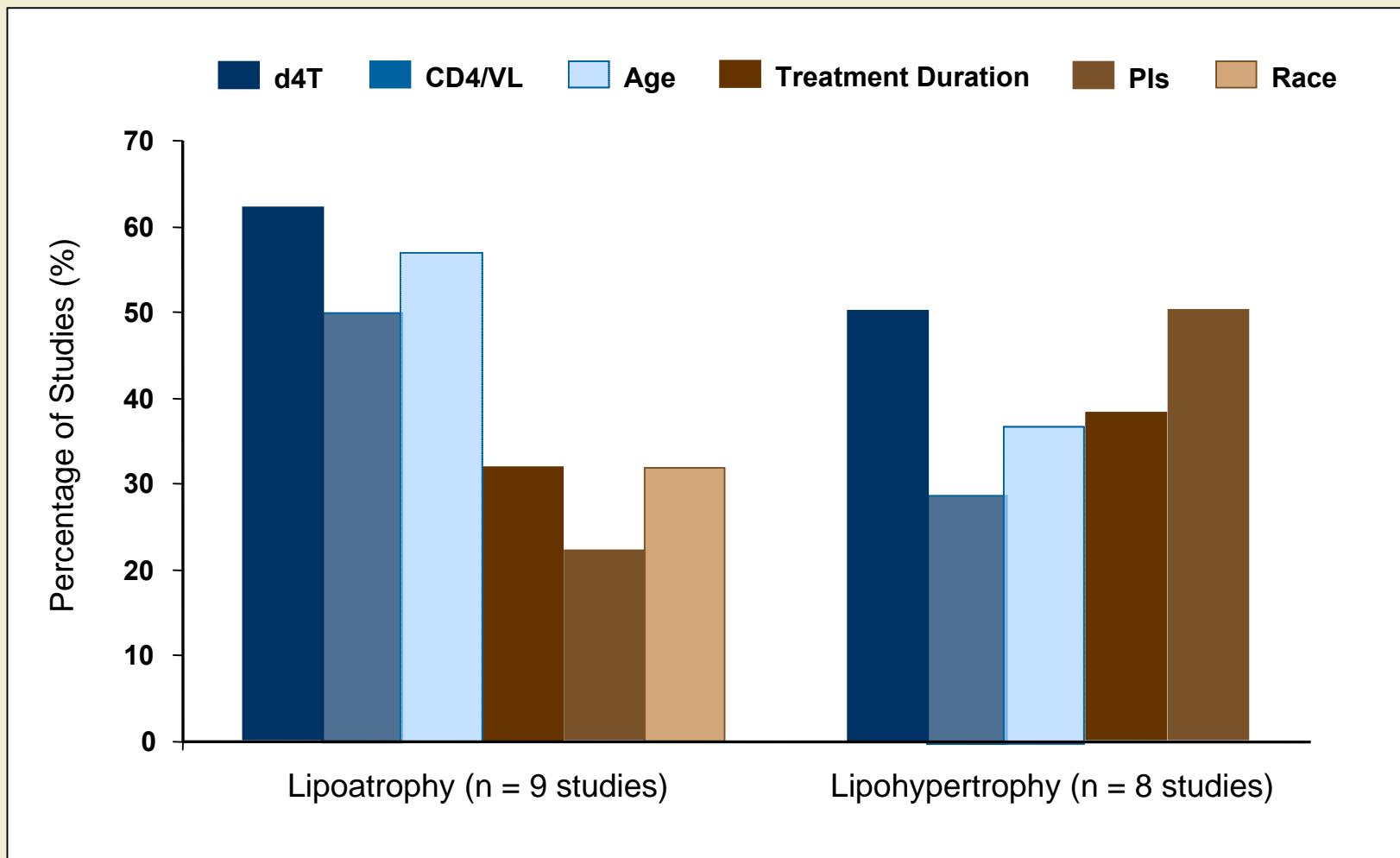
TNF-α promoter gene polymorphism and LA

Maher B. AIDS 2002, Nolan D. AIDS 2003
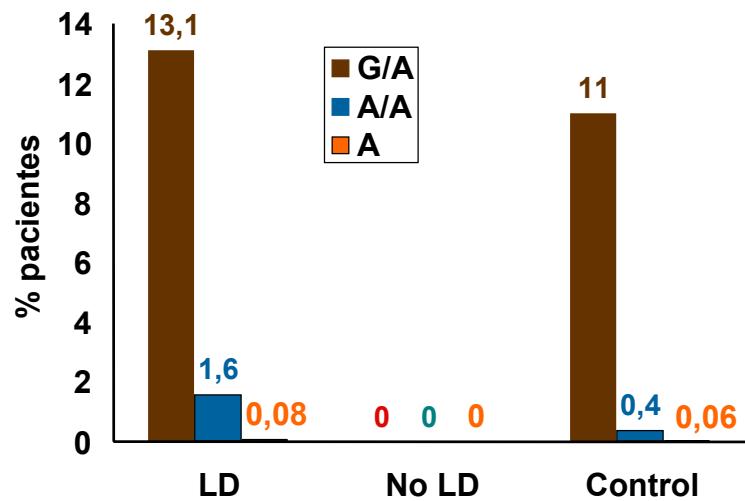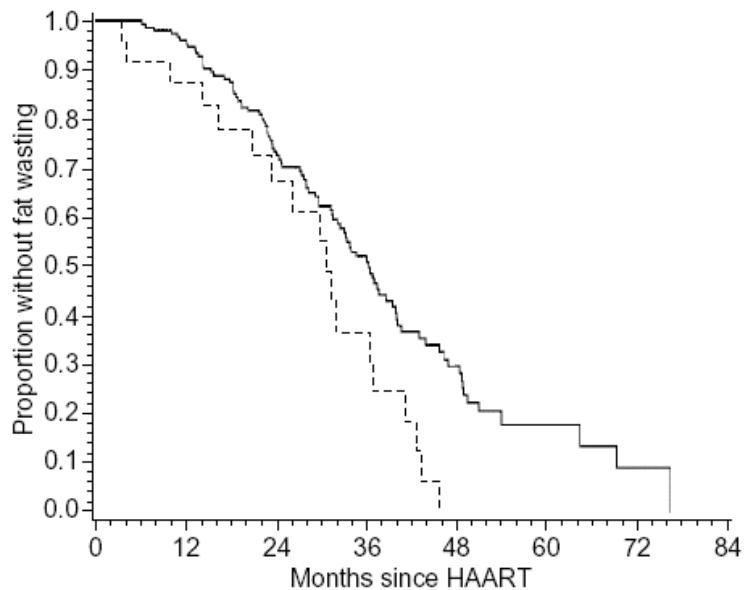
HIV-1-Induced Adipocyte Gene Expression Disturbances

Giralt M., *AVT*, 2006.
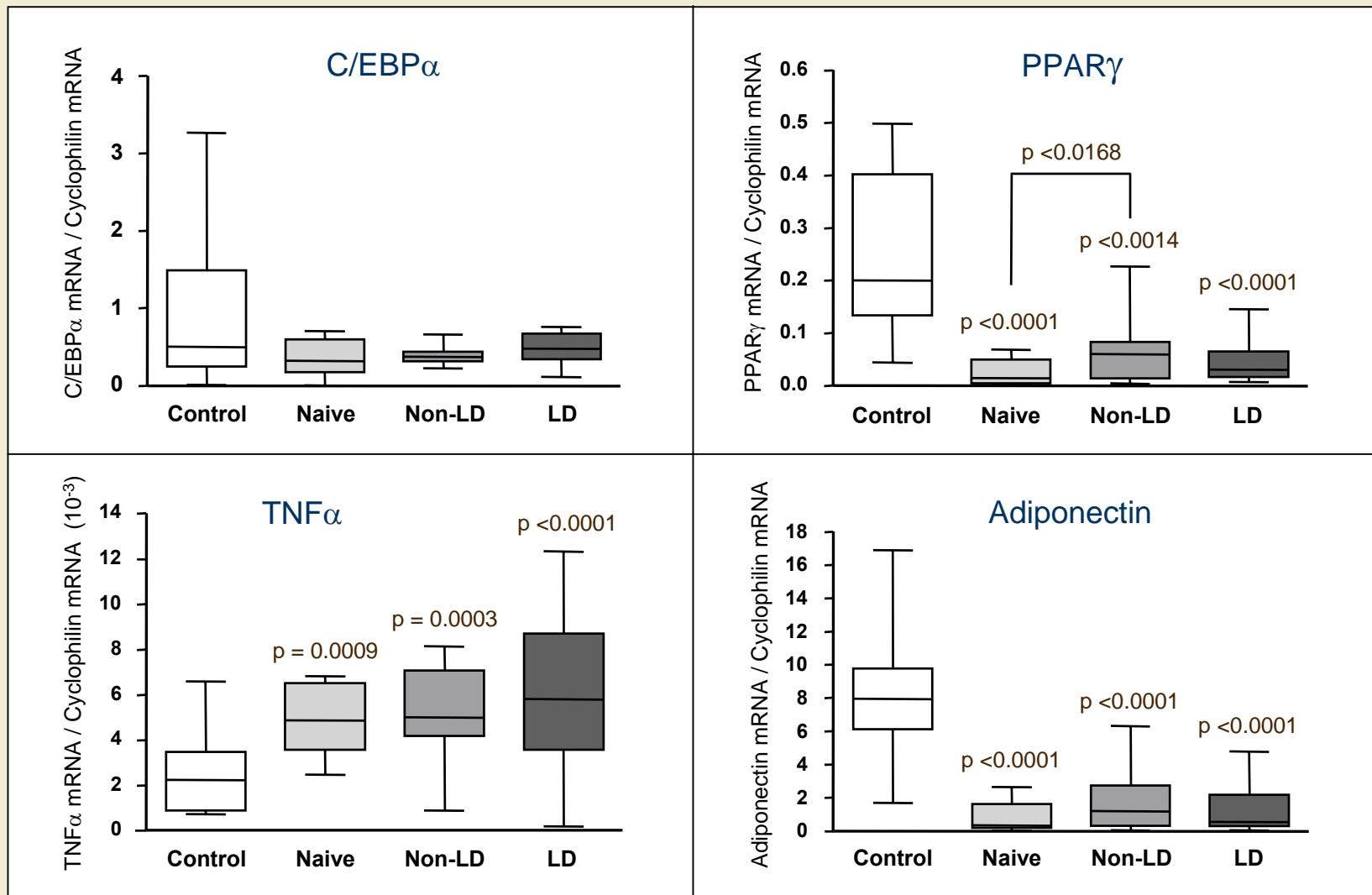
HIV-1-induced fat deficit

Tien PW. AJE 2006
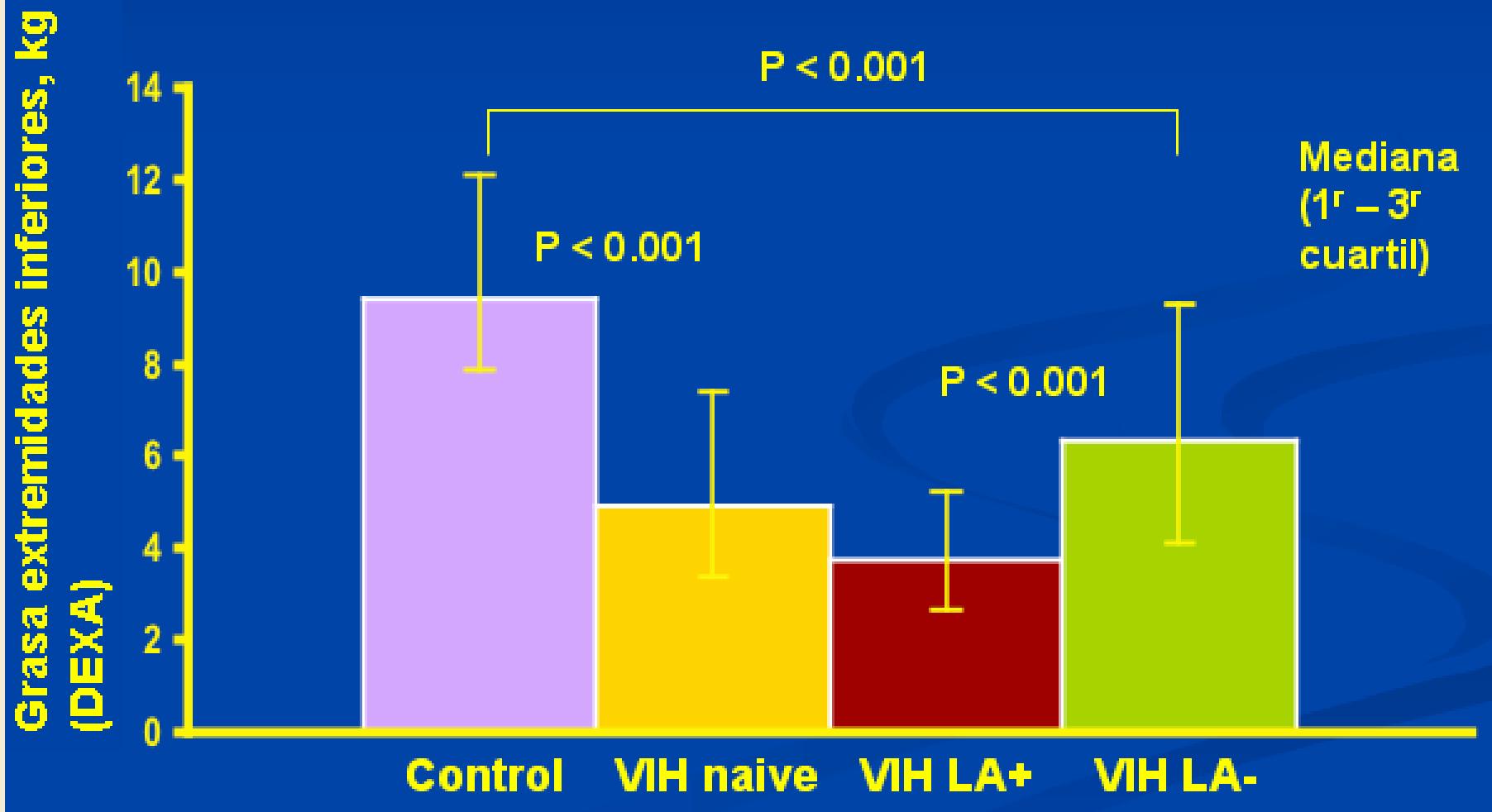
ACTG 384/5005s:
Median % change in limb fat[1]

By NRTI assignment

Median change (%)

20 — 10 — 0 — -10 — -20 — -30

Entry 16 32 48 64 80

Study week

† (at week 16, AZT-3TC)
† (at week 32, AZT-3TC)
† (at week 64, AZT-3TC)
† (at week 80, AZT-3TC)
† (at week 16, ddl-d4T)
† (at week 32, ddl-d4T)
* (at week 48)
* (at week 64)
* (at week 80)

● AZT-3TC
● ddl-d4T

By NNRTI/PI assignment

Median change (%)

20 — 10 — 0 — -10 — -20 — -30

Entry 16 32 48 64 80

Study week

† (at week 16, EFV)
† (at week 16, NFV)
† (at week 32, NFV)
† (at week 64, NFV)
† (at week 80, NFV)
* (at week 80, EFV)

● EFV
● NFV

Statistically significant differences between groups.

† *p <0.05 within groups from baseline.*

[1] Dubé M., *Personal Communication*, 2004.

Gene Disturbances in Lipohypertrophy

UCP1 mRNA

UCP1 mRNA / 18S rRNA (10^{-8})

ND — Control
ND — LA
BH

COII mRNA

COII mRNA / 18S rRNA (10^{-2})

p = 0,0004
p = 0,002

Control   LA   BH

PPARγ mRNA

PPARγ mRNA / 18S rRNA (10^{-5})

p <0,0001
p = 0,0076

Control   LA   BH

TNFα mRNA

TNFα mRNA / 18S rRNA (10^{-7})

p = 0,0052
p = 0,0015

Control   LA   BH

PCNA

VDAC / β-actin (arbitrary units)

p = 0,031
p = 0,0238

Control   LA   BH

Guallar JP, *AIDS*, 2007.
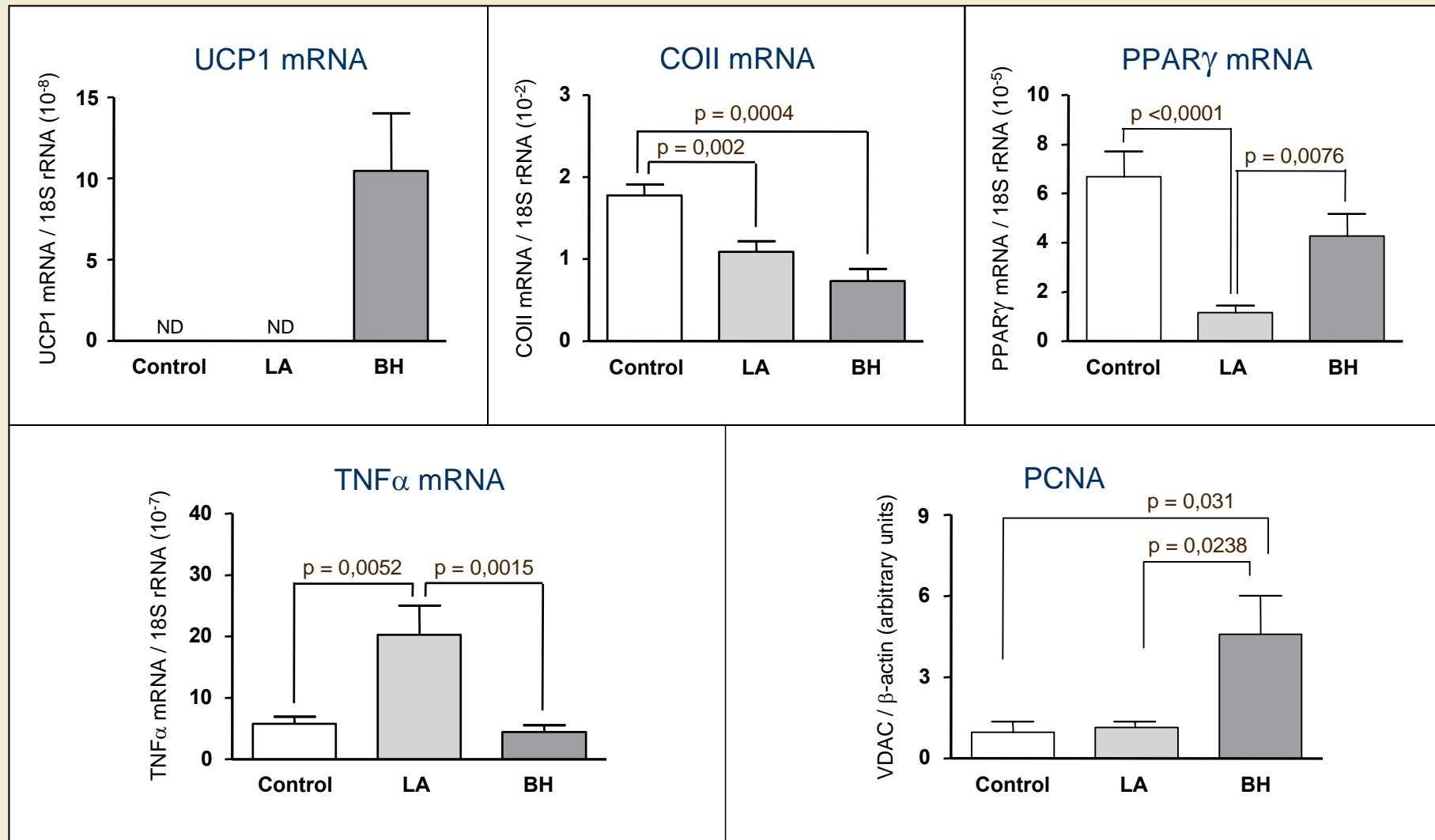
Adipocentric Theory
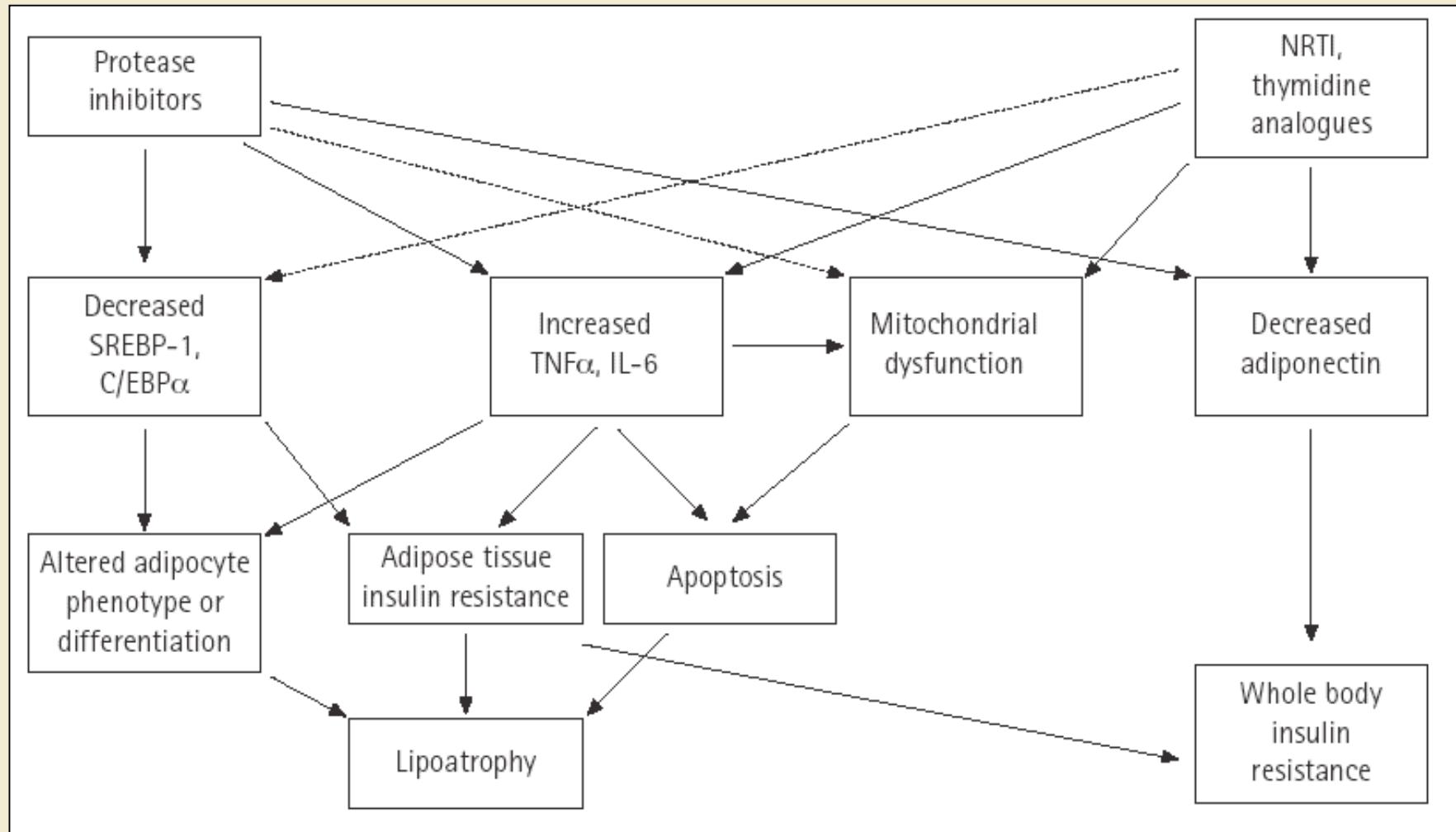
Lipohypertrophy

> Not all fat is alike.

> Plasticity of viceral depot.

  – Preadipocyte subtypes.[1]

  – Endocrine/paracrine function.[2]

  – Switch in subtypes.[3]

  – Switch in receptors.[4]

> Differential effects of drugs.[5]

[1] Tchkonia T., *AJP – Endocrinology and Metabolism*, 2005.
[2] Li X., *Int J Obes Relat Metab Disord*, 2004.
[3] Tchkonia T., *AJP – Endocrinology and Metabolism*, 2005.
[4] Hube F., *Endocrinology*, 2000.
[5] Cianflone K., *AVT*, 2006.

Pathogenesis - Metabolic Alterations: ART-Induced Glucose and Lipid Disturbances

Increased Hepatic Lipid & VLDL Production & Secretion

Hyperlipidemia
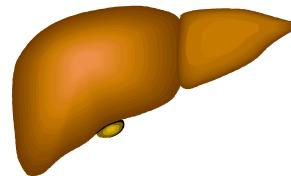
TG Synthesis, apoB, VLDL

Insulin Resistance

ARTs

Lipodystrophy

GLUT4 GLUT1

Impaired Glucose Uptake & Utilisation in Muscle & Adipose
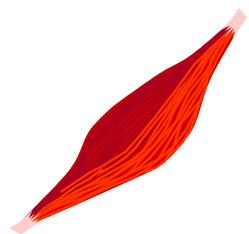
Suppressed Adipogenesis
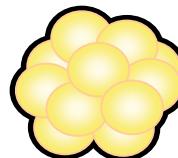
Decreased Fat Storage in Adipose (Lipoatrophy)

The host: interindividual susceptibitlity to dyslipidemia

- Apolipoprotein E2 genotype associated with hypertriglyceridemia (Grunfeld C. JCEM 1997)

- Apo C-III polymorphisms associated with hypertriglyceridemia (Rimland D. HIV Med 2005; Bonnet E. JCEM 2001)

- SREBP-1c polymorphism associated with hypercholesterolemia (Miserez AR. AIDS 2001)

HIV-1-Induced Lipid Effects

Brown T. *et al., IAC*, 2006.
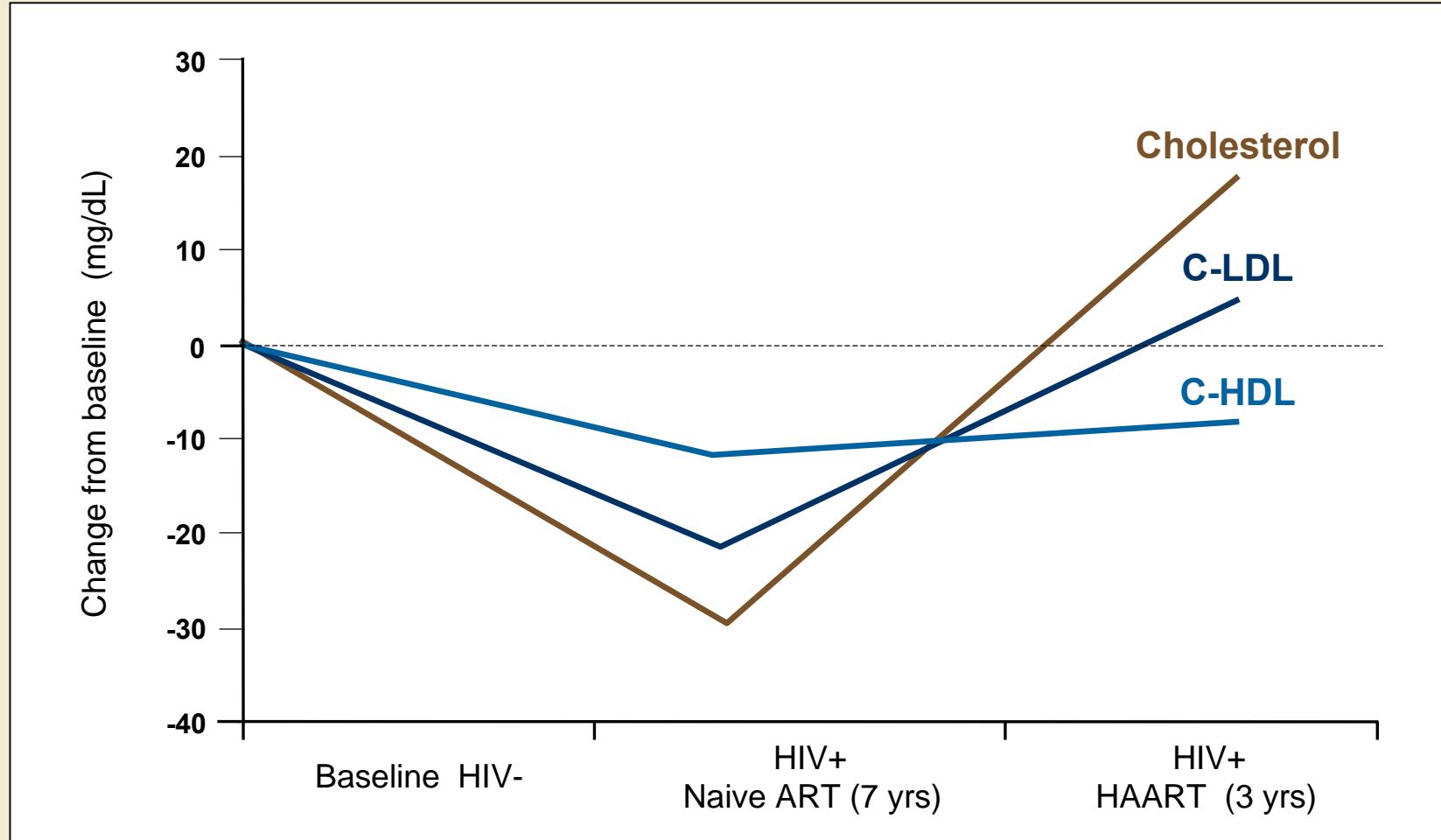
ART-Induced Lipid Abnormalities

Legend:
- ART naive (n = 2315)
- NRTI + 1 PI (n = 3444)
- NRTI + 2 PI (n = 607)
- NRTI + NNRTI (n = 1117)

Categories (mmol/L):
- TC ≥ 6.2
- HDL-C ≤ 0.9
- LDL-C ≥ 3.4
- TC:HDL-C ≥ 6.5
- TG ≥ 2.3

Fontas E. *et al., Journal of Infectious Diseases*, 2004.

d4T-Induced Lipid Effects

Gallant JE *et al., JAMA*, 2004.

PI-Induced Lipid Effects

Naïve patients receiving PI-based first-line regimen

Percentage change from baseline (%)

- Cholesterol
- Triglycerides

Drug	Cholesterol	Triglycerides
APV	35	32
NFV	28	30
ATV	2	-3
SQV	34	37
RTV	35	350
IDV	33	53
LPV/r	26	26
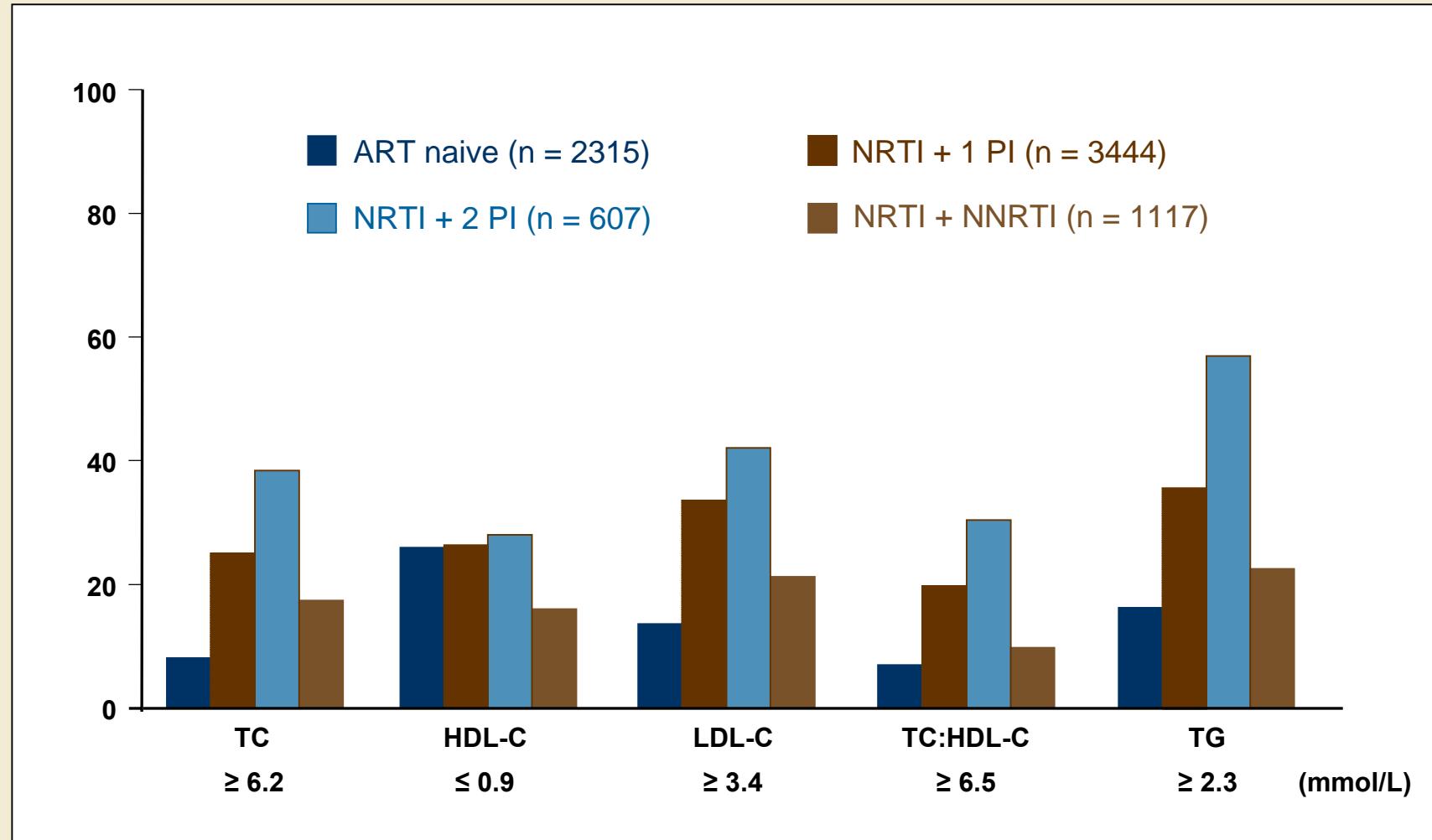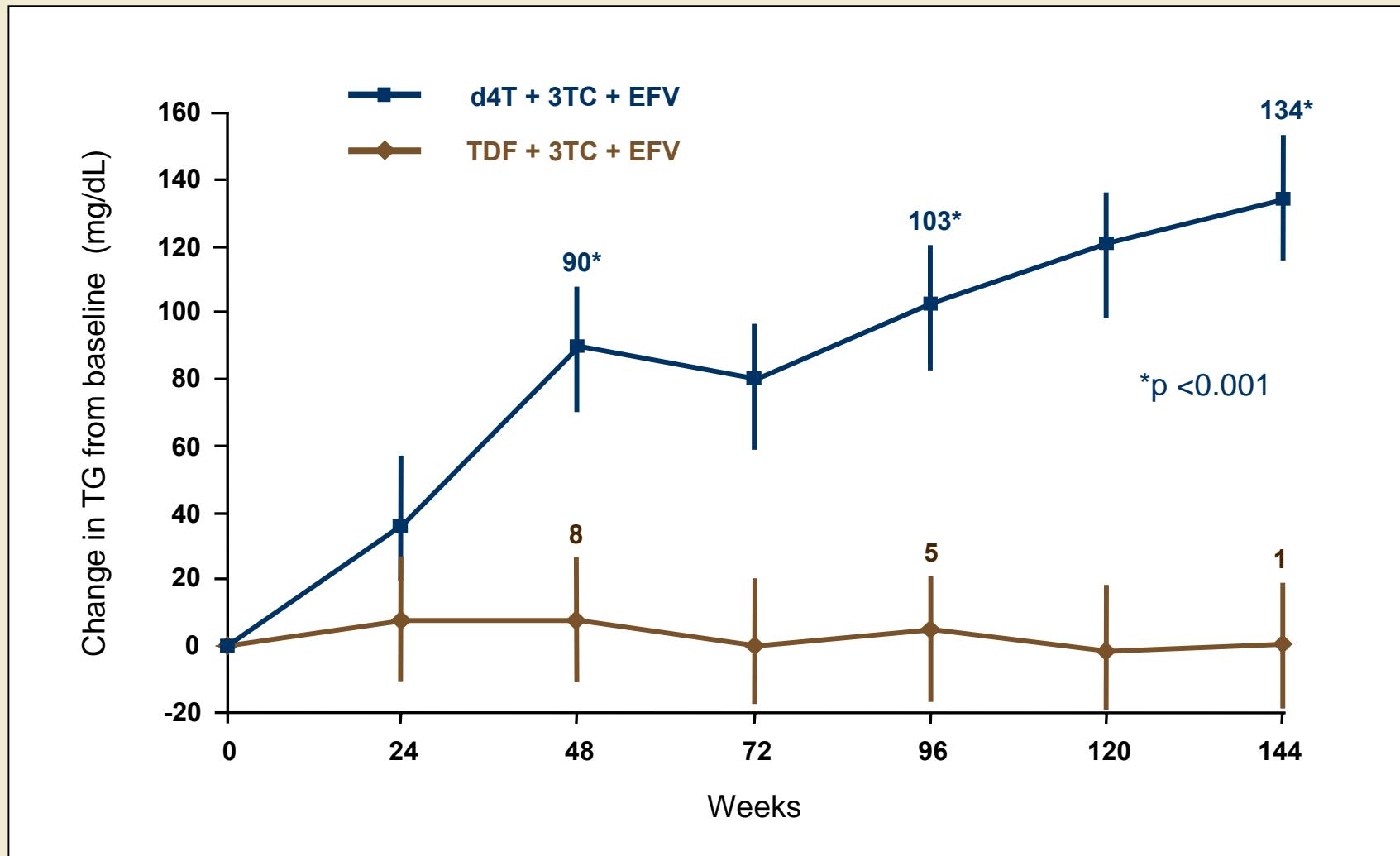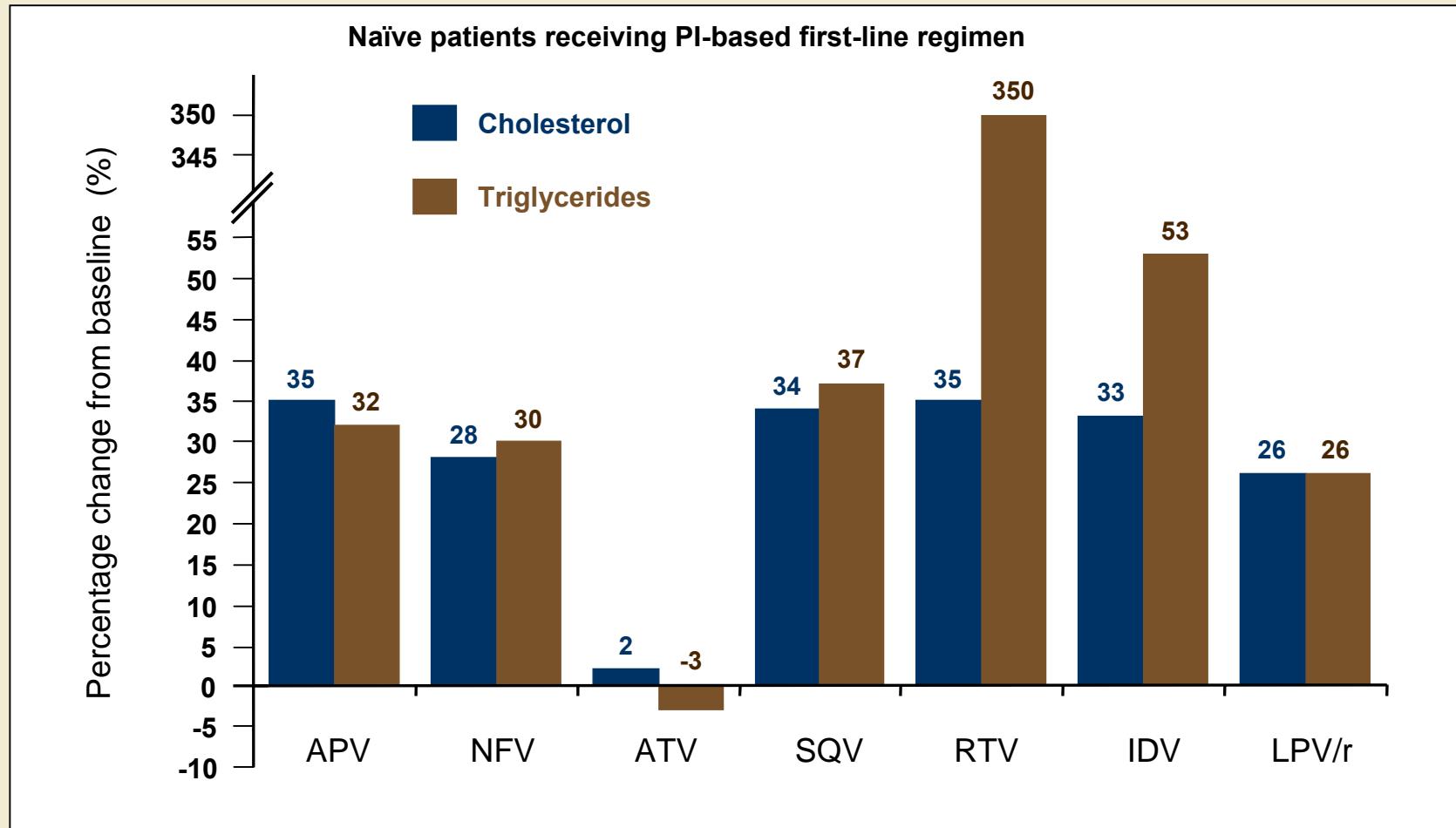
DFC 2001; Cahn P *et al.* IAS 2001; Moyle, Baldwin 1999; Danner *et al.* 1995;
Rockstroh *et al.* 2000; MicroMedEx-DrugDex.

All measurements following ≥ 4 weeks of treatment

Mechanism of Glucose Transport Through GLUT4

Bryant NJ et al. Nat Rev Mol Cell Biol. 2002.
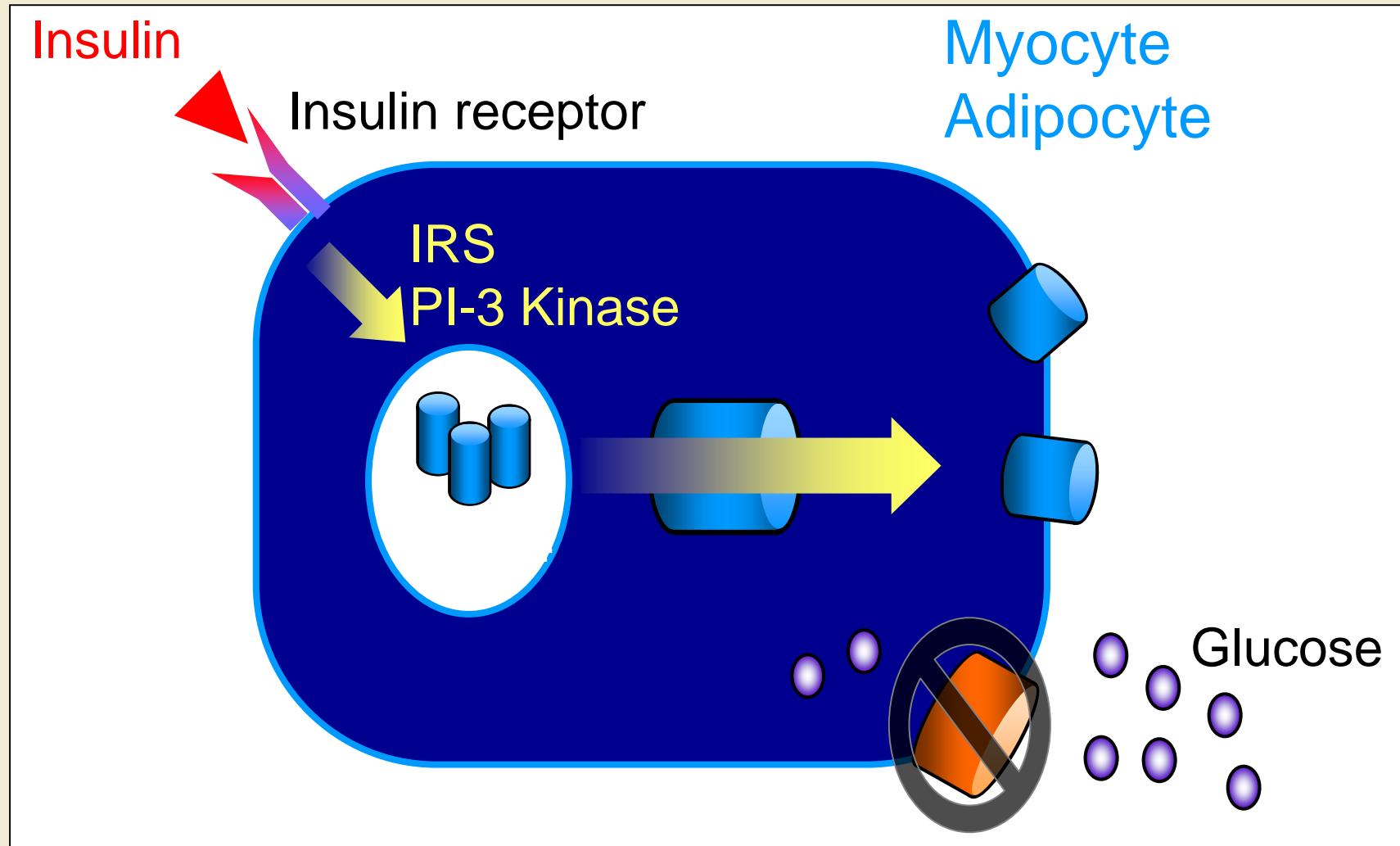
Effects Of ART On Glucose Metabolism

Lee GA, *AIDS*, 2004; Fleishman A., *CROI*, 2007; van Vonderen M., *IAS*, 2007.
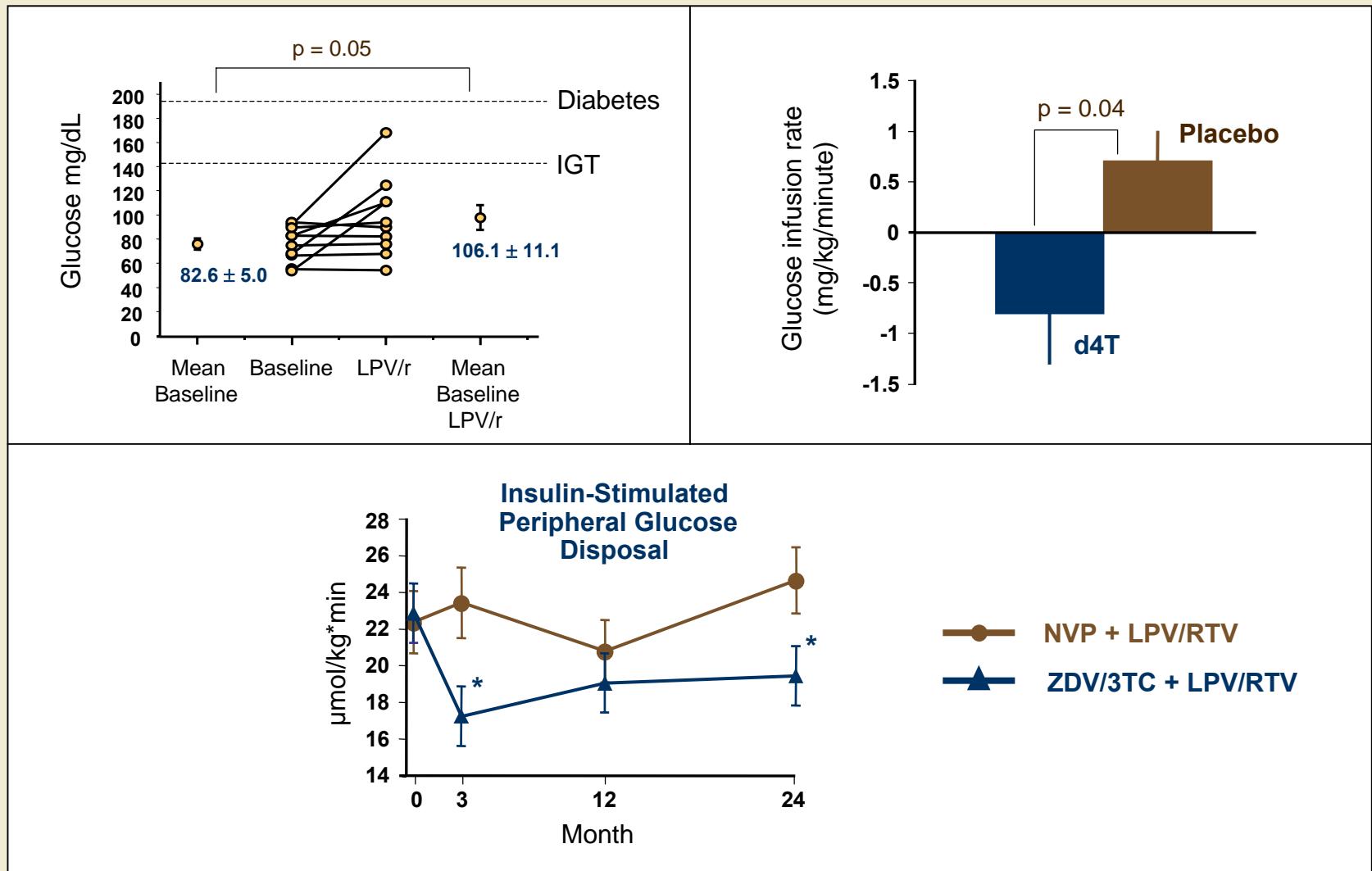
Metabolic syndrome consequences

Atherogenic dyslipidemia
$\uparrow$ TG
$\downarrow$ cHDL
cLDL«Normal» but $\uparrow$ apo B
LDL and HDL small and dense
Postprandial hyperlipidemia

Insulin resistance
Hyperinsulinemia
Hyperglycemia
Type 2 diabetes

Prothrombotic state
$\uparrow$ PAI-1
$\uparrow$ Fibrinogen

Proinflammatory state
$\uparrow$ PCR
$\uparrow$ Cytokines

ATHEROSCLEROTIC PLAQUE

Abdominal adiposity

Metabolic risk factors

$\uparrow$*Acute coronary syndrome risk*
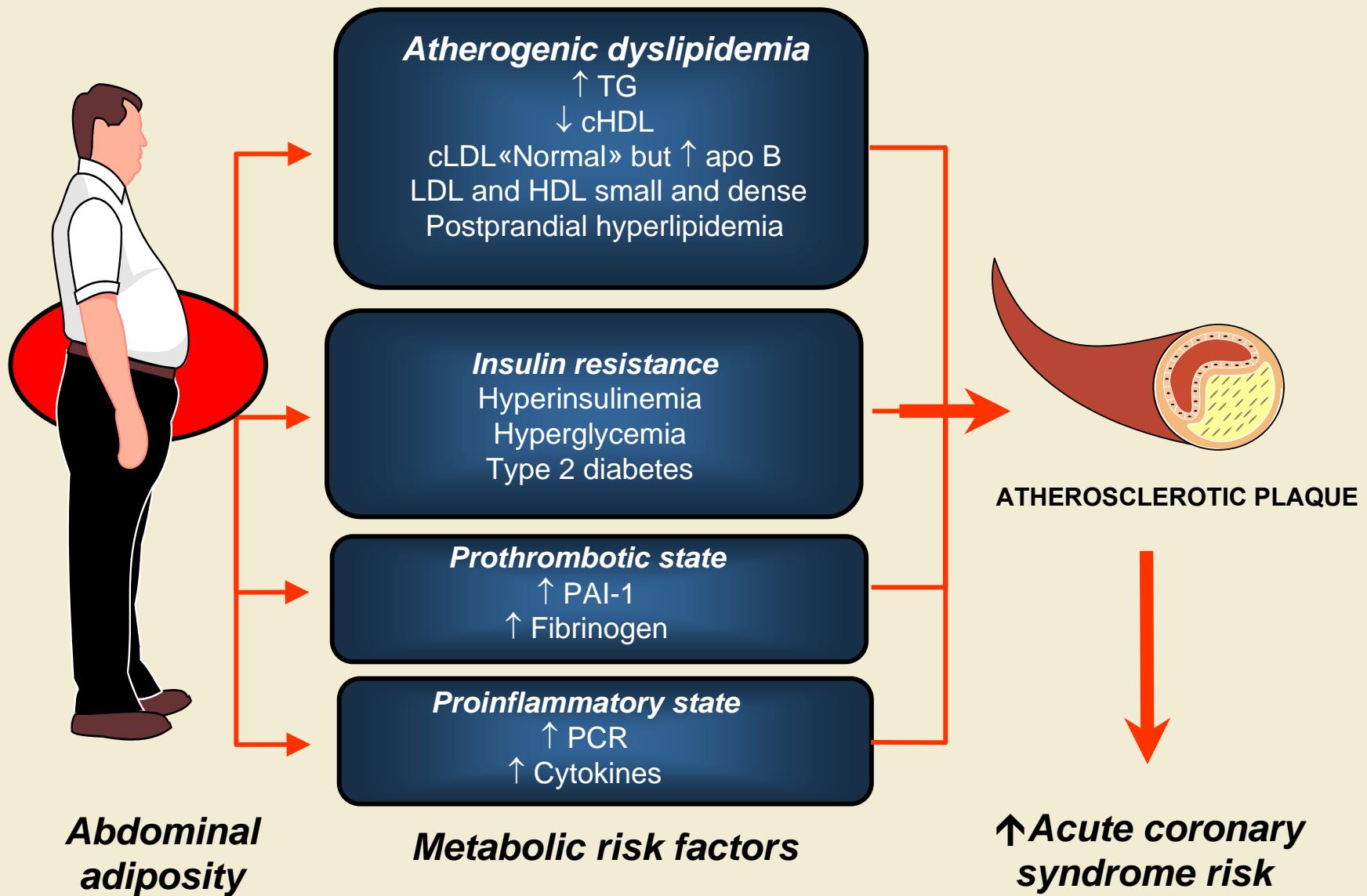
Cardiovascular Complications of cART

Relative rate per additional year of exposure to CART*: 1.16 (95% IC: 1.09-1.23)

Mls per 1000 patients-year (95% IC)

Exposure to cART (yrs.)

	None	<1	1-2	2-3	3-4	4-5	5-6	6-7	>7	Total
Episodes	16	17	20	41	61	62	51	47	30	345
Patients-year	11.815	7.105	9.027	12.098	14.892	14.394	11.351	7.935	5.853	94.469

*: Adjusted for conventional risk factors not related to cART
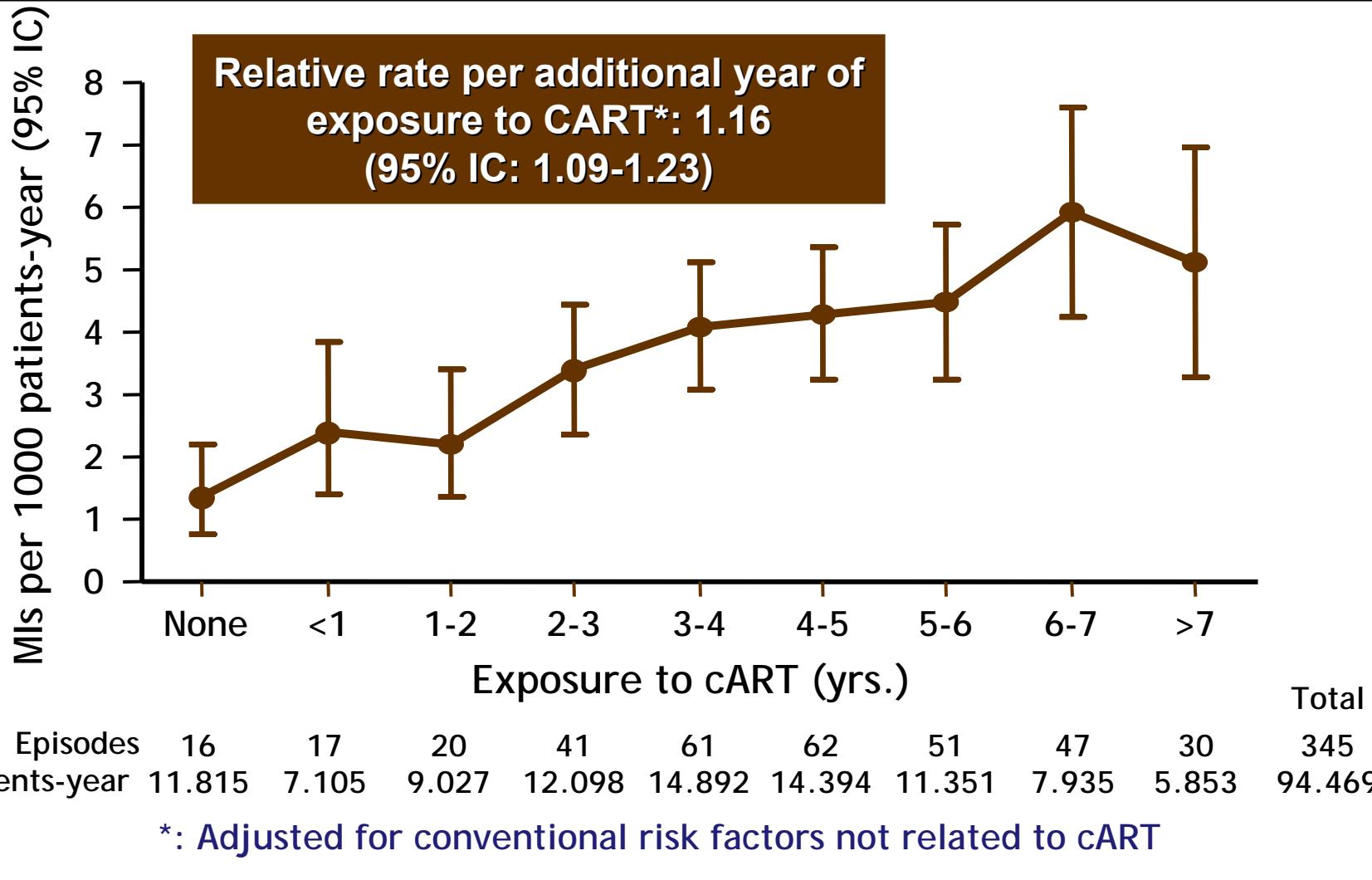
Patient Perceptions of Fat Abnormalities and Adherence

A self-report questionnaire was administered to patients receiving ART to assess patient perception of body-fat redistribution and current and future ART adherence.

n = 207

Log-rank p = 0.007

Y-axis: Clinician-Assessed Probability of Developing Fat Redistribution (0.0 – 1.0)

X-axis: Week from Date of Questionnaire (0, 8, 16, 24, 32, 40, 48, 56, 64)

Legend: Non-adherent — Adherent
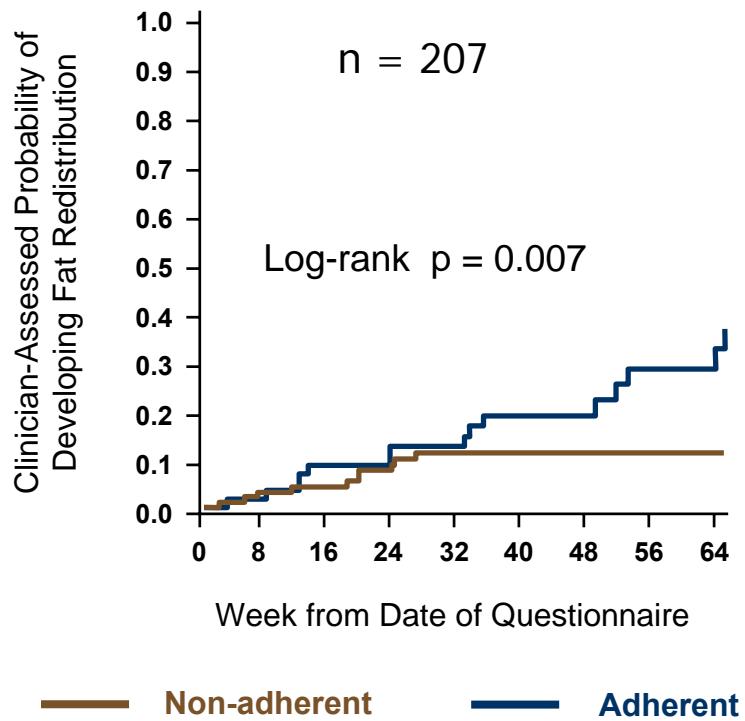
Risk of future non-adherence	OR* (95% CI)	p
Patient-perceived fat accumulation	4.67 (1.01-22.4)	0.05
Duration on ARV therapy per additional year	1.84 (1.08-3.15)	0.03

* Adjusted for patient demographics, mode of HIV transmission, prior ARV use, total duration ARV therapy.

- More adherent patients had greatest risk of fat redistribution detected by their clinician.

- Patients with self-perceived body-shape change at baseline were at greater risk of subsequent non-adherence.

Ammassari A., *JAIDS*, 2002.

Conclusions

- ➢ Metabolic and fat distribution disturbances are multifactorial: Host, HIV-1, drugs.

- ➢ Knowledge about its pathogenesis is still incomplete.

- ➢ Pathogenic mechanisms involved in lipoatrophy and lipohypertrophy seem different.

- ➢ Lipodystrophy may affect adherence to ART.

- ➢ Lipodystrophy may have a negative impact on glucose as well as lipid metabolism and lead to cardiovascular complications.

"The cause is hidden.

The effect is visible to all."

Publius Ovidius Naso (43 BC - 17 AD)