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
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

Epidemiology:
Prevalence of LD

Percentage (%)

Prevalence: 2-83%

Etiology and Pathogenesis

Genetic background

Environmental factors

[Diagram showing the relationship between genetic background and environmental factors]
Risk Factors

Lipoatrophy (n = 9 studies)

Lipohypertrophy (n = 8 studies)

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

HIV-1-Induced Adipocyte Gene Expression Disturbances

HIV-1-induced fat deficit

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

<table>
<thead>
<tr>
<th>Study week</th>
<th>AZT-3TC</th>
<th>ddl-d4T</th>
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<tbody>
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<td>Entry</td>
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<td>80</td>
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* Statistically significant differences between groups.
† p <0.05 within groups from baseline.

Gene Disturbances in Lipohypertrophy

UCP1 mRNA

Control          LA              BH

COII mRNA

Control          LA              BH

PPARγ mRNA

Control          LA                BH

TNFα mRNA

Control          LA              BH

PCNA

Control          LA              BH

Adipocentric Theory

Protease inhibitors
- Decreased SREBP-1, C/EBPα
  - Altered adipocyte phenotype or differentiation
    - Adipose tissue insulin resistance
      - Apoptosis
      - Lipoatrophy
  - Adipose tissue insulin resistance
    - Apoptosis
    - Lipoatrophy

Increased TNFα, IL-6
- Mitochondrial dysfunction
  - Decreased adiponectin
    - Whole body insulin resistance

NRTI, thymidine analogues

Lipohypertrophy

- Not all fat is alike.
- Plasticity of visceral depot.
  - Preadipocyte subtypes.\(^1\)
  - Endocrine/paracrine function.\(^2\)
  - Switch in subtypes.\(^3\)
  - Switch in receptors.\(^4\)
- Differential effects of drugs.\(^5\)

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

- Insulin Resistance
- Increased Hepatic Lipid & VLDL Production & Secretion
- Impaired Glucose Uptake & Utilisation in Muscle & Adipose
- Suppressed Adipogenesis
- Decreased Fat Storage in Adipose (Lipoatrophy)

**ARTs**

**Hyperlipidemia**

**TG Synthesis, apoB, VLDL**

**Lipodystrophy**

**GLUT4 GLUT1**
The host: interindividual susceptibility 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

ART-Induced Lipid Abnormalities

d4T-Induced Lipid Effects

PI-Induced Lipid Effects

Naïve patients receiving PI-based first-line regimen

Percentage change from baseline (%)

Cholesterol
Triglycerides

APV  NFV  ATV  SQV  RTV  IDV  LPV/r


All measurements following ≥ 4 weeks of treatment
Mechanism of Glucose Transport Through GLUT4

Insulin
Insulin receptor
IRS
PI-3 Kinase
Myocyte
Adipocyte
Glucose

Effects Of ART On Glucose Metabolism

**Diabetes**

- Baseline: 82.6 ± 5.0
- LPV/r: 106.1 ± 11.1

**IGT**

- Baseline: 82.6 ± 5.0
- LPV/r: 106.1 ± 11.1

**Glucose Infusion Rate (mg/kg/minute)**

- d4T: p = 0.04
- Placebo: p = 0.04

**Insulin-Stimulated Peripheral Glucose Disposal (µmol/kg*min)**

- NVP + LPV/RTV
- ZDV/3TC + LPV/RTV

Metabolic syndrome consequences

**Atherogenic dyslipidemia**
- ↑ TG
- ↓ cHDL
- cLDL «Normal» but ↑ apo B
- LDL and HDL small and dense
- Postprandial hyperlipidemia

**Insulin resistance**
- Hyperinsulinemia
- Hyperglycemia
- Type 2 diabetes

**Prothrombotic state**
- ↑ PAI-1
- ↑ Fibrinogen

**Proinflammatory state**
- ↑ PCR
- ↑ Cytokines

↑ Acute coronary syndrome risk

Abdominal adiposity

Metabolic risk factors

Atherosclerotic plaque
Cardiovascular Complications of cART

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

*: Adjusted for conventional risk factors not related to cART

Reiss P. 1st HIV-NAT 2007
A self-report questionnaire was administered to patients receiving ART to assess patient perception of body-fat redistribution and current and future ART adherence.

### Risk of future non-adherence

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<th>Risk Factor</th>
<th>OR* (95% CI)</th>
<th>p</th>
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<td>Patient-perceived fat accumulation</td>
<td>4.67</td>
<td>0.05</td>
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<tr>
<td>Duration on ARV therapy per additional year</td>
<td>1.84</td>
<td>0.03</td>
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* 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.

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)