Metabolic Complications in HIV-Infected Patients: Dyslipidemia & Cardiovascular Risk Management

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Preventive & Social Med., Siriraj
HAART & HIV Infection

Mortality rates and percentage of total patient-days receiving HAART\(^1\)

Persons surviving through June 2005, by years after AIDS diagnosis\(^2\)

Death in HIV-infected patients:\(^3\)
- Declining rates of HIV-related death
- Increased proportion of HIV-infected patients dying of other causes
  - Non HIV-related death increase from 19.8% to 26.3% from 1999 to 2006
  - Causes of non-HIV related death: CVD, substance abuse, non AIDS-related cancer

MI Rates in HIV-infected vs. HIV-uninfected Patients

Triant VA. et al. J Clin Endocrinol Metab 2007;92:2506-12
Relative Rate of MI According to PI Exposure

<table>
<thead>
<tr>
<th>PI exposure (yrs)</th>
<th>None</th>
<th>&lt;1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>&gt;6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/1000 person-years</td>
<td>1.5</td>
<td>2.5</td>
<td>3.0</td>
<td>4.2</td>
<td>4.7</td>
<td>5.3</td>
<td>4.4</td>
<td>6.0</td>
<td>3.7</td>
</tr>
<tr>
<td>No. of events</td>
<td>33</td>
<td>21</td>
<td>33</td>
<td>57</td>
<td>64</td>
<td>57</td>
<td>33</td>
<td>47</td>
<td>345</td>
</tr>
<tr>
<td>No. of person-years</td>
<td>21,623</td>
<td>8,410</td>
<td>10,947</td>
<td>13,616</td>
<td>13,734</td>
<td>10,734</td>
<td>7,576</td>
<td>7,821</td>
<td>94,469</td>
</tr>
</tbody>
</table>

The shown dose response equates to an adjusted* relative rate (RR) per year of exposure to PI therapy of 1.16 (95% CI 1.10 to 1.23). *Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body mass index, NNRTI exposure

Risk Factors for CVD

High risk status:
• Clinical CHD
• Symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm
• Type 2 diabetes

Traditional (non-LDL) risk factor:
• Cigarette smoking
• Hypertension (BP >140/90 or on antihypertensive drug)
• Low HDL cholesterol (<40)
• Family history of premature CHD (male <55, female <65)
• Age (men >45, women >55)

*HDL >60 counts as a “negative” risk factor
NCEP ATP III: LDL-C Goals (2004 modifications)

High Risk
CHD or CHD risk equivalents
(10-yr risk >20%)

Mod. High Risk
≥ 2 risk factors
(10-yr risk 10-20%)

Moderate Risk
≥ 2 risk factors
(10-yr risk <10%)

Lower Risk
< 2 risk factors

goal
160

Existing LDL-C goals

Proposed LDL-C goals

*Therapeutic option

Altered Risk of CVD in HIV-Infected Patients

• Increased prevalence of traditional cardiovascular risk factors unrelated to HIV or ART
  – Higher prevalence of smoking (and/or other substance abuse i.e. cocaine) compared to non-HIV infected population
• HIV or ART may affect the risk of developing a traditional cardiovascular risk factor
  – HIV or ART may worsen dyslipidemia and cause insulin resistance
• HIV or ART may cause CVD by pathophysiologic mechanisms other than the effect on traditional cardiovascular risk factor
  – Effect of HIV or ART on inflammation or endothelial function

Mechanism of ART Metabolic Toxicity

Protease Inhibitors → Adipocyte SREBP 1 → NRTIs → Lactic acidemia

- Protease Inhibitors → Hepatocyte proteasome → GLUT 4 → Peripheral lipoatrophy
- EFV → ↑ Cholesterol, ↑ Triglycerides
- ↓ mDNA
- ↓ Adiponectin, ↓ leptin, ↑ TNF
- ↑ Age → MS
- ↓ GH
- Visceral fat accumulation → Type 2 Diabetes
- ? Genetics

Carr A. Nature Reviews Drug Discovery 2003;2: 624-634
Mechanisms Involved Adipocyte Differentiation, Apoptosis/Death, & Dyslipidemia

Net Effect:

↓ Adipocyte differentiation
↑ Adipocyte apoptosis
↓ Triglyceride storage
↑ Lipid release

Tanwani LK, Mokshagundam SL.
Southern Medical Journal 2003;96:180-188
Lipid vs. CVD Risk

<table>
<thead>
<tr>
<th>Lipid Level</th>
<th>CHD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>q ↑ 10 mg</td>
</tr>
<tr>
<td>TG</td>
<td>q ↑ 89 mg</td>
</tr>
<tr>
<td>HDL-C</td>
<td>q ↓ 1 mg</td>
</tr>
</tbody>
</table>

HIV vs. Non-HIV*

- Total cholesterol: ↑ 1 mmol
  - HIV-infected – ↑ CVD risk by 26%
  - Non-HIV infected – ↑ CVD risk by 25-33%
- HDL-cholesterol: ↑ 1 mmol
  - HIV-infected – ↓ CVD risk by 28%
  - Non-HIV infected – ↓ CVD risk by 52%

## Changes in Lipid Metabolism in HIV Infection

<table>
<thead>
<tr>
<th>Treatment naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Triglyceride</td>
</tr>
<tr>
<td>↑ VLDL</td>
</tr>
<tr>
<td>↑ VLDL triglyceride production rates</td>
</tr>
<tr>
<td>↑ Small, dense LDL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI-based treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Triglyceride</td>
</tr>
<tr>
<td>↑ Total cholesterol</td>
</tr>
<tr>
<td>↑ VLDL, IDL, LDL</td>
</tr>
<tr>
<td>↑ Apo B-100</td>
</tr>
<tr>
<td>↑ Apo E</td>
</tr>
<tr>
<td>↑ Apo C-III</td>
</tr>
<tr>
<td>↑ VLDL production</td>
</tr>
<tr>
<td>↓ Postprandial delipidation</td>
</tr>
<tr>
<td>↓ VLDL to IDL/LDL transfer</td>
</tr>
<tr>
<td>↓ VLDL and LDL catabolic rates</td>
</tr>
<tr>
<td>↓ Hepatic lipase activity</td>
</tr>
<tr>
<td>↓ Lipoprotein lipase activity</td>
</tr>
</tbody>
</table>
# Effects of HIV and Its Therapy on Lipid Levels

<table>
<thead>
<tr>
<th></th>
<th>Effects of Untreated or Ineffectively Treated HIV</th>
<th>Changes Associated With Viral Suppression</th>
<th>Changes With Specific Antiretroviral Therapy</th>
<th>Role of Body Shape Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HDL-c</strong></td>
<td>Decreases early in infection</td>
<td>Increases modestly but not to premorbid levels</td>
<td>Greater increases seen with NNRTI and possibly atazanavir than other PI</td>
<td>Increased VAT and upper trunk fat associated with low HDL-C</td>
</tr>
<tr>
<td><strong>LDL-c</strong></td>
<td>Decreases later in infection</td>
<td>Increases modestly</td>
<td>No evidence of direct drug effects</td>
<td></td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td>Increases in late infection</td>
<td>Decreased in early study of AZT monotherapy</td>
<td>No decrease or even further increase with HAART regimens containing ritonavir and other (but not all) PIs; increases also may be seen with stavudine and efavirenz</td>
<td>Increased VAT and upper trunk fat but lower leg fat associated with increased TG levels</td>
</tr>
</tbody>
</table>

- Other effect: increase VLDL-c and small-dense LDL-c

Multicenter AIDS Cohort Study

The incidence of DM in HIV infected patients with HAART exposure is 4 times greater than HIV seronegative controls

- 568 HIV infected men receiving HAART
- 710 HIV negative men adjusted for age and BMI

During 4 years observation period

- Rate of DM incidence:
  HIV + : 4.7 /100 person-year
  HIV – : 1.4 / 100 person-year

% patients free from DM

Study time, yrs

Arch Inter Med 2005, 165: 1179
Mechanism of IGT/DM

- Loss of fat cells
- ↑ Muscle TG
- ↓ GLUT 4 activity
- ↑ Cytokines
- ↑ Visceral fat
- ↓ Muscle glucose uptake
- ↑ Hepatic glucose production
- ↓ Insulin secretion
- ? Impaired processing of insulin
- Metformin
- Genetic Age MS
- Tanwani LK, Mokshagundam SL. Southern Medical Journal 2003;96:180-188
Pathophysiology of Insulin Resistance

• Ectopic lipid accumulation in muscle and liver tissue
• Increased visceral adiposity associated with excess free fatty acids
• Abnormal adipocytokine physiology in HIV patients with lipodystrophy: reduced adiponectin, leptin deficiency (in mice), and increased IL-6
• Reduction in adiponectin associated with visceral obesity and predict CVD and Type 2 diabetes

Reduction of Insulin Sensitivity in HIV-treated Patients

![Box plot showing reduced insulin sensitivity in HIV-treated patients compared to controls and therapy-naive patients.](image-url)

AIDS 1998,12:F167
Insulin Resistance & Diabetes Mellitus

- Rare before HAART era
- Prevalence in HIV-infected people from recent studies:
  - IR 61%, IGT 25-35%, DM 2-7%; Metabolic syndrome 14%
- PIs (indinavir)
  - Affect glucose metabolism, independent of lipodystrophy
  - Switch from certain PIs to abacavir* restore glucose metabolism and diminish lipolysis but insulin-stimulated glucose disposal not change
  - PIs reduce glucose transport mediated by GLUT4, which may also reduce pancreatic β-cell insulin secretion
- NRTIs (cumulative exposure, especially stavudine)
  - Direct inhibition of mitochondrial function in muscles
  - May also cause insulin resistance by indirect effects via adipose tissue changes

*Exposure to abacavir and didanosine has been shown to be associated with increased risk MI and CHD, may be from direct effect on endothelium, D:A:D Study. AIDS 2008; 22:F17

Risk factors of Insulin Resistance

- Obesity
- Increasing waist circumference
- Male sex
- Non-White ethnicity
- Family history of diabetes
- Older age
- Hepatitis C co-infection
Common Effect of ART on Glucose Metabolism

• PIs
  – Increase insulin resistance: ritonavir (full dose), lopinavir/ritonavir, indinavir
  – No significant effect: nelfinavir, fosamprenavir, aquinavir, atazanavir

• NRTIs:
  – Increase insulin resistance: stavudine
  – No significant effect: zidovudine, tenofovir, abacavir, lamivudine, emtricitabine

• NNRTIs: no significant effect
Insulin Resistance & Metabolic Syndrome

Diagnostic Criteria (>3/5)*

- **Waist†**
  Asian: ≥90 cm in men, ≥80 cm in women

- **Triglyceride**
  ≥ 150,
  on drug Rx: fibrate, niacin, ω-3 fatty acid

- **HDL-c**
  <40 in men, <50 in women,
  on drug Rx: fibrate, niacin

- **Hypertension**
  SBP ≥130 or DBP ≥85,
  on drug Rx

- **Fasting plasma glucose**
  ≥100 mg/dL,
  on drug Rx

†Population- and country-specific definitions
Upper Body / Abdominal (Visceral) Obesity and Insulin Resistance

- Insulin resistance
- Constriction
- Relaxation
- Upper body / Intra-abdominal obesity
- Muscle
- Vasculature
- Liver
- Pancreas
- Insulin secretion
- Glucose release
- FFA

Upper body / Intra-abdominal obesity

Muscle

Vasculature

Liver

Pancreas

Insulin resistance

Constriction

Relaxation

FFA

Glucose release

Insulin secretion
# Dyslipidemia in Abdominal Obesity & MS

<table>
<thead>
<tr>
<th>Normal</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

**Insulin Resistance**

<table>
<thead>
<tr>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

- ↑ VLDL triglyceride
- ↑ VLDL apo B
- ↑ Number
- ↑ Size
- = LDL cholesterol
- ↑ LDL apo B
- ↑ LDL apo B/LDL cholesterol
- ↑ Number
- ↓ Size
- (small, dense)
- ↓ HDL₂ cholesterol
- ↓ Number
- ↓ Size
Is DM a “CVD Risk Equivalent” in HIV-infected Patients?

• Data from D:A:D study, using composite end point including MI, invasive coronary procedure and fatal CVD events

• Compared with patients without DM or pre-existing CVD at baseline
  – RR of a new CVD event in those with DM but no pre-existing CVD: 3.03
  – RR of a recurrent CVD event in patients with pre-existing CVD at baseline and no DM: 9.04

Treatment of Insulin Resistance & DM*

• Dietary and physical activity counseling – as for non-HIV infected population
  – Weight reduction
  – Dietary modification
  – Exercise and increase physical activity
  – Smoking cessation
  – Reduce alcohol intake

Treatment of Insulin Resistance & DM*

• Pharmacologic treatment for IR, IFG, or IGT
  – Not currently indicated, except for younger patients with a BMI >35 kg/m² with both IGT and IFG, the use of metformin may be considered along with lifestyle modifications to reduce the risk of progression to DM
  – TZDs may be useful to reduce insulin resistance and may also help to reduce central fat accumulation or induce small increases in subcutaneous fat in some insulin resistant patients, should not be used for the sole purpose of improving body composition**

Treatment of Insulin Resistance & DM*

- Pharmacologic treatment for DM – improving IR
  - Metformin reduce insulin resistance and visceral fat, may cause further reduction in subcutaneous fat and may also cause lactic acidosis
  - TZDs reduce insulin resistance, possibly via increased adiponectin level\(^1,2\) and may improve subcutaneous fat, CVD risk with TZDs is not clear (may be increased with rosiglitazone)
  - Pioglitazone improved IR and blood pressure, increased HDL without adverse effects on LDL cholesterol\(^3\)
  - Rosiglitazone vs. metformin: similar improvements in glucose metabolism but the metformin treated group had improved lipid profile and flow mediated vasodilation; rosiglitazone increased both subcutaneous and visceral fat and was associated with a subjective improvement in fat redistribution in 47% of subjects\(^4\)

Mechanisms Adversely Affect the Vasculature:

HIV infection

• Endothelial dysfunction
• Lipid disorders associated with HIV infection
• Viral protein-related endothelial cell activation
• Systemic inflammatory cytokine-chemokine dysregulation
• Direct HIV infection of endothelium and vascular smooth muscle cells
• Enhanced atheroma formation by activated macrophages
  – HIV viral load correlates with higher MCP-1/CCL2 levels, and shows an association of HIV infection and viral load status with atherosclerotic burden in the thoracic aorta
• Prothrombotic state

Mechanisms Adversely Affect the Vasculature:

ART

• Endothelial dysfunction
  – With indinavir but not with atazanavir or lopinavir
• Increased endothelial permeability
• Increased oxidative stress
• Increased mononuclear cell adhesion
• Insulin resistance
• Accelerated lipid accumulation in vessel wall
• Persistent inflammation and immune activation
• Impaired response to vascular injury
• ART-associated lipodystrophy leading to metabolic disorders, increased systemic inflammation, and reduced circulating adiponectin

Suggested Mechanisms of Accelerated Atherosclerosis in HIV

Atheroma formation and growth

- Endothelial activation
  - ↑ adhesion molecules (VCAM-1)

  - Platelet adhesion → monocyte infiltration → differentiation into macrophages → foam cells → inflammatory cytokines

  - Lymphocyte infiltration including activated CD4+ T cells → inflammatory cytokines

Plaque fibrous cap rupture and thrombosis

- Activated T cells in plaque:
  - → IFN-γ → ↓ collagen synthesis by smooth muscle cell
  - → proinflammatory cytokines (IL-1, TNF-α)
  - → breakdown of collagen and plaque extracellular matrix

  - Plaque instability and rupture

  - TF release from atheroma core
    - → contact with bloodstream coagulation factors

  - Activated T cells in plaque:
    - → CD40 ligand → macrophage → ↑ tissue factor
    - → proinflammatory cytokines (IL-1, TNF-α)
    - → ↑ tissue factor by endothelial cell

- Activated monocyte in plaque
  - Serine proteinases

- Activated endothelial and smooth muscle cells in plaque
  - PAI-1

- Thrombosis

Effects of HIV and Its Therapy on CVD Risks

Cardiovascular Disease

Dyslipidemia
- ↑ TG
- ↓ HDL
- ↑ FFA
- ↔ LDL
- ↑ Small dense LDL

Insulin resistance
- ↑ Glucose

Inflammation

Body Composition
- Lipoatrophy
- Lipohypertrophy

Predisposing Factors:
- Genetics
- Smoking
- Sedentary Lifestyle
- Diet
- Obesity
- Hypertension
- Renal Disease

HIV

HAART
- Specific ARV