Metabolic Complications of HIV

Joseph McGowan, MD, FACP, FIDSA
North Shore University Hospital
Division of Infectious Diseases
Center for AIDS Research & Treatment
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Overview

“Lipodystrophy”
Diabetes mellitus
Bone disease
Cardiovascular Disease
Wrapping it all up
Case

- 57 year old male newly diagnosed HIV+ during hospitalization for PCP. CD4 was 73 and VL was 530,000.
- He is a smoker and has a history of diabetes but he has not been taking his anti-diabetic Rx
- Also found to have:
  - Creatinine of 1.4
  - Hgb A1C of 9.5
  - LDL Cholesterol of 165
  - Co-infection with Hepatitis C
  - Symptoms of major depression

AIDS Cases, Deaths, and Persons Living With AIDS, 1985-2005 in the United States

Note: Data have been adjusted for reporting delays.

Aging HIV Population

- By 2015, estimated that 50% of the people living with HIV in the US will be aged 50 years or over
- Complications of Aging that Overlap with HIV Disease
  - Cardiovascular Disease
  - Neuro-cognitive Disease
  - Bone Mineral Loss
  - Decline in Renal Function
  - Diabetes
  - Lipodystrophy
  - Malignancies
  - Frailty

ART Cohort Collaboration: 50% of Deaths Due to Non-AIDS-Related Causes (1996-2006)

- AIDS-Related (50%)
- Non-AIDS Infections (8%)
- Cardiovascular Disease (8%)
- Liver Disease (7%)
- Violence or Drug-Related (8%)
- Other (7%)
- Non-AIDS Malignancies (12%)

n=39,272 HIV-infected patients from 13 cohort studies in Europe and North America who were treated with antiretroviral therapy.

*Causes of death were retrospectively assigned to 85% of total deaths (1597/1876).
CASCADE Collaboration: Causes of Death

- Pre-HAART (n=1424)
- HAART (n=514)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Pre-HAART (%)</th>
<th>HAART (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIs</td>
<td>31.7%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Not Specified</td>
<td>10.0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hepatitis/Liver</td>
<td>2.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2.5%</td>
<td>4.9%</td>
</tr>
<tr>
<td>AIDS-Related CVD/Diabetes</td>
<td>9.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Non-AIDS-Related</td>
<td>1.3%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

n=7680 seroconverters, of whom 1938 died (26%; 1424 pre-HAART and 514 during HAART). No change in death due to AIDS-related malignancy, other infections, organ failure, and unknown causes.


HIV and Risk of Cardiovascular Disease

- HIV has been linked to:
  - High triglycerides
  - Low HDL-C
  - Insulin resistance
  - Hyperglycemia
  - Hypertension
  - Abdominal obesity

All Increase the Risk of Cardiovascular Disease

Metabolic Dysfunction in HIV Infection and the Relationship to Cardiovascular Disease

HIV Infection

HAART

Dyslipidemia

Insulin Resistance

Body Fat Redistribution

Genetic Influences

Comorbidities

D:A:D Study: Risk Factors for CHD in an HIV+ Population

Drug class: not sufficient # of events to examine yet

<table>
<thead>
<tr>
<th>Better</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>cART Therapy</td>
<td>RR 1.17 (1.08-1.26)</td>
</tr>
<tr>
<td>Age per 5 years older</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td>Previous CVD</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (yes versus no)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (yes versus no)</td>
<td></td>
</tr>
</tbody>
</table>

Relative Rate of Myocardial Infarction (95% CI)

Multivariable Poisson regression model

Adjusted for BMI, HIV risk, cohort, calendar year and race


Copenhagen HIV Programme (D.A.D)
**D:A:D Study: NRTIs and Risk of MI**

- **Relative Risk (95% CI)**
  - **ZDV**: 1.38, 0.30-5.05
  - **ddI**: 1.74, 0.36-8.87
  - **ddC**: 1.10, 0.20-5.81
  - **d4T**: 1.11, 0.17-7.11
  - **3TC**: 0.79, 0.19-3.17
  - **ABC**: 0.85, 0.23-3.05
  - **TDF**: 0.73, 0.39-1.39

- **Cumulative Exposure: per year**
  - **ZDV**: 138.109
  - **ddI**: 74.407
  - **ddC**: 29.676
  - **d4T**: 39.157
  - **3TC**: 162.009
  - **ABC**: 53.300
  - **TDF**: 39.157

* Recent use = current or within the last 6 months. **Not shown (low number of patients currently on ddC). Lundgren JD, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 42LB.

**Meta-analysis of RCTs Assessing the association between Abacavir and MI**

- **Risk Ratio**
  - **M-H, Fixed, 95% CI**
    - **Clumeck 2001**: 0.20 [0.01, 4.08]
    - **CNA**: 3.01 [0.12, 73.60]
    - **30024**: Not estimable
    - **CNAB3005**: 3.02 [0.12, 73.87]
    - **CNAB3001**: 0.35 [0.01, 8.32]
    - **CNAB3002**: Not estimable
    - **CNAF3007**: 0.95 [0.06, 14.93]
    - **Daar 2010**: 0.57 [0.17, 1.95]
    - **ESS100327**: Not estimable
    - **ESS40002**: 5.83 [0.17, 148.50]
    - **Martin 2009**: 0.34 [0.01, 7.59]
    - **NZTA4002**: 0.34 [0.01, 8.17]
    - **Opravil 2002**: 0.14 [0.01, 1.76]
    - **Post 2010**: 0.34 [0.01, 8.17]
    - **Smith 2009**: Not estimable
    - **Vibhagool 2004**: Not estimable

- **Total (95% CI)**
  - 100.0% 0.74 [0.39, 1.42]

**Cochrane meta-analysis of MI events in ABC vs. Comparator studies suggest no association with MI**
- Included mainly naive and some switch studies
- Comparator is PI in some studies
- Follow up ranges from 24->96 weeks
- Included 6617 patients but only 26 MI events (11 ABC, 15 Control)
- Findings similar for mortality
- Findings similar if only TDF considered as comparator (RR 0.79 95% CI 0.30-2.05, P=0.63)

Cruciani M, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. WEPE0121.
D:A:D Study: PIs/NNRTIs and Risk of MI

**Approximate test for heterogeneity:** \( P = 0.02 \)

<table>
<thead>
<tr>
<th>PI* NNRTI</th>
<th>RR of MI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/r</td>
<td>1.2</td>
</tr>
<tr>
<td>Indinavir</td>
<td>1.13</td>
</tr>
</tbody>
</table>

**Primary model**
- Dyslipidemia
- Elevated blood pressure
- Diabetes mellitus
- Lipodystrophy
- Glucose
- All above + lipid-lowering and antihypertensive medication

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**Potential Mechanisms for Metabolic Abnormalities in HIV-Infected Patients Receiving HAART**

**Vesicle**
- Increased systemic VLDL and triglyceride re-esterification
- Shift to triglyceride-rich VLDL
- Increased systemic apolipoprotein
- Low and apolipoprotein E
- Increased accumulation of CD4-dependent cholesterol transfer to macrophages
- Enhanced activation of lipoprotein B
- Impaired thrombosis

**Liver**
- Increased hepatic glucose production
- Decreased mitochondrial fatty acid oxidation (with mevalonate, reverse transcriptase inhibitor)
- Increased lipid accumulation and hepatic steatosis

**Fat**
- Increased lipogenesis
- Decreased adiponectin fat differentiation and increased apoptosis
- Decreased SREBP-1 activation
- Decreased SREBP nuclear localization (with mevalonate)
- Toxic effects on mitochondria and endoplasmic RPL/mitochondrial (pathway? unclear)

**Pancreas**
- Increased pancreatic secondary lipase

**Metabolic Changes**
- Decreased glucose transporter 4-mediated glucose transport (with protease inhibitors)
- Decreased glucose phosphorylation (I) precedent to increase in free fatty acids
- Increased intracellular lipid (I) secretory to decrease in adiponectin and intracellular fatty acid inhibition

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Grinspoon; NEJM 352;1 www.nejm.org january 6, 2005
D:A:D Study: Risk Factors Associated With CVD-Related Mortality in HIV Patients

- HIV-infected patients (n=33,347)
  - Total deaths (n=2482)
  - Cardiovascular-related: 11.6%
  - Follow-up: 180,176 person-years
- Significant risk factors for cardiovascular-related mortality
  - Diabetes, hypertension, smoking, age
  - Lower CD4 counts were associated with a higher risk of death
- Need to address modifiable risk factors to further reduce cardiovascular-related mortality

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Rate Ratios for Cardiovascular Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.83 (1.29-2.59)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.04 (1.57-2.66)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.90 (1.29-2.80)</td>
</tr>
<tr>
<td>Age</td>
<td>1.46 (1.38-1.54)</td>
</tr>
</tbody>
</table>


Calculating Framingham Risk

[Image: Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)]

Observed and predicted MI rates according to ART exposure (D:A:D Study n=23,468)

Incidence of MIs is low: 345 over 94,469 patient-years follow-up (3.7/1,000 patient-years)

D:A:D Study: Is the Framingham Risk Estimation Valid in HIV-Infected Patients?

D.A.D. Risk Calculator

A Higher Percentage of HIV-infected Individuals Smoke as Compared to the General Population

HIV-infected patients entering treatment at an HIV clinic in Baltimore, Maryland between 1999 and 2003 (n=1,750)

General population of the state of Maryland; adults ages 25 to 54 years

Smoking habits reported by HIV-infected individuals who were current smokers when entering HIV treatment (69% of total):

- ≤1/2 pack/day (31%)
- 1 pack/day (41%)
- 1-2 packs/day (17%)
- ≥2 packs/day (11%)


Obesity/Overweight in HIV-infected Patients Increases Over Time After Diagnosis

72% gained weight over the course of HIV infection

Significantly more patients were obese than at time of diagnosis (63% vs 49%, P<0.001)

Increasing BMI was associated with younger age at HIV diagnosis (OR 1.10, P<0.001) and longer duration of HIV-infection (OR 1.10, P=0.02)

Categories defined in terms of Body Mass Index (BMI): wasting (<20 kg/m²), desirable weight (20.0 – 25.0 kg/m²), overweight (25.0-29.9 kg/m²), obese (>30 mg kg/m²)

Projecting CVD Risk in HIV: Cumulative Risk by Age and Over a Lifetime


Males

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>General US population</th>
<th>HIV-, high risk for HIV</th>
<th>HIV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Lifetime</td>
<td>30</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>General US population</th>
<th>HIV-, high risk for HIV</th>
<th>HIV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Lifetime</td>
<td>30</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

Competing mortality due to HIV-related causes and other non-HIV causes within the HIV-infected population results in lower overall CVD lifetime risk for HIV-infected persons.


Diabetes Mellitus Incidence is Increased in HIV-infected Patients on HAART


Diabetes Mellitus is more than 4 times higher in HIV-infected patients on HAART as compared to the general population.
Insulin Resistance
Definitions

- Insulin resistance
  - Insulin dose-response curve exhibits a rightward shift indicating reduced sensitivity (30% to 60% lower than normals)

- Impaired glucose tolerance
  - FPG (mg/dL): ≤125
  - OGTT (mg/dL): 140-199

- Impaired fasting glucose
  - FPG (mg/dL): 100-125

- Diabetes mellitus
  - FPG ≥126 mg/dL or OGTT ≥200 mg/dL; or random glucose ≥200 mg/dL plus compatible symptoms

FPG=fasting plasma glucose.
OGTT: oral glucose tolerance test (2-hour value).

Insulin Resistance in HIV Disease

- Increases the risk of cardiovascular disease, either alone or in combination with other factors

- Often associated with a cluster of metabolic abnormalities (metabolic syndrome)
  - Hypertension, hypertriglyceridemia, hypercholesterolemia, low HDL-C levels, and truncal adiposity

- Risk factors for diabetes and insulin resistance
  - Exposure to some PIs and NRTIs
    - PIs: indinavir, lopinavir/ritonavir; perhaps less often ATV, ATV/ritonavir, DRV/ritonavir, TPV/ritonavir
    - NRTIs: didanosine, stavudine, zidovudine
  - Increasing age
  - Visceral adiposity
  - Dorsocervical fat accumulation
  - Lipoatrophy

Epidemiology of DM in HIV-Infected Patients

- Prevalence varies by population
- Genetics, obesity, HCV, type of ART, ascertainment
- Definition of DM varies by cohort study
- Evidence that it varies by HIV status is conflicting


Multiple Factors May Contribute to Diabetes in HIV

- Lipoatrophy/Visceral Fat Accumulation
- Genetic Factors
- Protease inhibitors/NRTIs
  - Age
  - Cytokines
  - Liver disease (HCV, steatosis)
  - HIV?
  - Insulin Resistance
  - β-cell Dysfunction
  - Lower testosterone?
  - Obesity
  - Meds/Opiates
  - Free fatty acids
% Meeting ADA Goals

- Adherence rates to ADA guidelines: 47% for retinopathy screening and 19% for nephropathy screening

Recommended Approaches: Insulin Resistance, Glucose Intolerance, and Diabetes Mellitus in HIV

- Avoidance
  - Avoid starting with stavudine in patients with impaired glucose tolerance or diabetes mellitus
- Lifestyle modification
  - Diabetic education, self-monitoring of blood glucose, aerobic and resistance training
- Metformin
  - Monitor for lactic acidosis during first months of therapy
  - Contraindicated in patients with renal failure
- Thiazolidinediones
  - Monitor liver function every 2 months for first 12 months of therapy
  - Avoid using if AST and ALT are >2.5x the upper limit of normal
- Switching therapy
  - Switch PI-based HAART to include NNRTI
  - Switch from thymidine NRTI in the presence of diabetes or glucose intolerance


**Study 613: Glucose Tolerance of Lopinavir/Ritonavir Versus Efavirenz**

- Treatment-naïve patients (n=155)
  - Zidovudine/lamivudine + lopinavir/r
    - Switch to lopinavir/r monotherapy after week 24
  - Zidovudine/lamivudine + EFV
- No change in glucose tolerance in both arms
- NRTI discontinuation
  - Did not impact fasting glucose, fasting insulin, or HOMA index
- After >4 weeks exposure, no measurable impact on glucose tolerance was seen in either arm


**Morphologic Abnormalities Associated With HIV and ART**

- **Lipoatrophy**
  - Fat loss face (buccal fat pads), extremities, buttocks, and subcutaneous abdominal fat
  - Prominent veins because surrounding fat is absent
- **Lipohypertrophy**
  - Fat accumulation neck, visceral abdominal fat, dorsal cervical fat pad, parotid area, development of lipomata, enlargement of breasts in women
- **Mixed lipodystrophy**
  - Combination of visceral adiposity with peripheral fat atrophy

Lichtenstein KA. JAIDS. 2005;39:395-400.*
FRAM Cohort (2000-2002): Cross-Sectional Analysis of Fat Redistribution

- Lipoatrophy or lipohypertrophy
  - Subject report plus clinical examination
  - Whole-body MRI
- Subjects 33 to 45 years of age
  - HIV-infected subjects
  - HIV-negative controls
    - From the CARDIA cohort
- Peripheral lipoatrophy was not linked to central lipohypertrophy
  - Odds ratio (95% CI)
    - Men: 0.71 (0.47-1.06); P=0.1
    - Women: 0.39 (0.20-0.75); P=0.006

Prevalence

<table>
<thead>
<tr>
<th></th>
<th>HIV positive</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>38%*</td>
<td>6%</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>(n=425/152)</td>
<td>(n=183/142)</td>
</tr>
<tr>
<td>Central Lipohypertrophy</td>
<td>56%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>28%*</td>
<td>4%</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>(n=183/142)</td>
<td>(n=183/142)</td>
</tr>
<tr>
<td>Central Lipohypertrophy</td>
<td>62%</td>
<td>63%</td>
</tr>
</tbody>
</table>

FRAM. JAIDS. 2006;42:562-571.

HIV Lipodystrophy: Comparison of 1998 and 2010 Cohorts

- Cross-sectional study in HIV positive men receiving ART with no previous cardiovascular disease
  - 1998 cohort (n=144)
  - 2010 cohort (n=100)
  - Lipodystrophy: NCHECR major and minor criteria
  - Metabolic syndrome: NCEP ATP III criteria
- 2010 cohort versus 1998 cohort
  - Significantly older, longer duration of HIV therapy, better HIV RNA suppression and immunologic status

Characteristics

<table>
<thead>
<tr>
<th></th>
<th>1998 (n=144)</th>
<th>2010 (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42</td>
<td>52*</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>51</td>
<td>36*</td>
</tr>
<tr>
<td>HIV duration (months)</td>
<td>86</td>
<td>165*</td>
</tr>
<tr>
<td>ART duration (months)</td>
<td>36</td>
<td>129*</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>320</td>
<td>585*</td>
</tr>
<tr>
<td>HIV RNA Mean (copies/mL)</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Undetectable (%)</td>
<td>57</td>
<td>90*</td>
</tr>
</tbody>
</table>

*P<0.0001 versus 1998.

NCHECR: National Centre HIV Epidemiology and Clinical Research. 
HIV Lipodystrophy: Comparison of 1998 and 2010 Cohorts

- Prevalence of NCHECR-defined lipodystrophy significantly declined
  - Interestingly, patients perception of lipodystrophy and lipoatrophy significantly increased
- Predictors of lipodystrophy (2010 cohort)
  - Increase: HIV duration and LDL-C
  - Decrease: tenofovir DF, abacavir


HIV Lipodystrophy: Associated Factors

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Lipoatrophy</th>
<th>Lipohypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increasing age</td>
<td>Increasing age</td>
</tr>
<tr>
<td></td>
<td>White race</td>
<td>Prior obesity</td>
</tr>
<tr>
<td></td>
<td>Low body fat</td>
<td>Genetic susceptibility</td>
</tr>
<tr>
<td></td>
<td>Prior malnutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic susceptibility</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease factors</th>
<th>Lipoatrophy</th>
<th>Lipohypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CD4 cell counts</td>
<td>Prior diagnosis of AIDS</td>
<td>Low CD4 cell counts</td>
</tr>
<tr>
<td>Prior diagnosis of AIDS</td>
<td>Chronic inflammation</td>
<td>Prior diagnosis of AIDS</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td></td>
<td>Chronic inflammation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug factors</th>
<th>Lipoatrophy</th>
<th>Lipohypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain NRTIs</td>
<td>Certain PIs*</td>
<td>Duration of treatment</td>
</tr>
<tr>
<td>Certain PIs*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Limited data.
**Associations of HIV Lipodystrophy**

### Lipoatrophy
- Insulin resistance
- Glucose metabolism disorders
- Hyperlactatemia
- Dyslipidemia
- Negative impact on physical and psychosocial well-being
- Cosmetic/aesthetic effects
- Other long-term complications?

### Lipohypertrophy
- Respiratory abnormalities
- Coronary heart disease
- Insulin resistance
- Metabolic syndrome
- Dyslipidemia
- Cosmetic/aesthetic effects
- Negative impact on physical and psychosocial well-being

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**HIV Lipodystrophy: Associations With Dyslipidemia, Diabetes, and Impaired Glucose Tolerance**

- **Total Cholesterol (>200 mg/dL)**: 57.1%*
- **LDL-C (>100 mg/dL)**: 16.7%*
- **HDL-C (<35 mg/dL)**: 21.8%
- **Triglycerides (>200 mg/dL)**: 45.7%
- **2-Hour Glucose (>200 mg/dL)**: 13.3%
- **Diabetes Mellitus**: 5.6%

**HIV-infected patients**
- Lipodystrophy
- No lipodystrophy

- **57.1%**
- **21.8%**
- **45.7%**
- **13.3%**
- **5.6%**

*Adjusted for waist-hip ratio.
*P*=0.005; †P=0.002; and ‡P<0.04 versus no lipodystrophy.

Potential Etiologies of HIV Lipodystrophy

- Lipoatrophy
  - Adipose cell loss
  - Adipocyte dysfunction
  - Multiple injury hypothesis
    - HIV, antiretroviral therapy, host factors

- Lipohypertrophy
  - Adipocyte hypertrophy
  - Increase in cell numbers
  - Multiple contributing factors
    - HIV, antiretroviral therapy, host factors

Mitochondrial Dysfunction Hypothesis

- Certain NRTIs inhibit mitochondrial DNA polymerase \( \gamma \)
- Mitochondrial dysfunction
  - Result of NRTI toxicity
    - Intra-class differences among the NRTIs
- Differential toxicity in tissues is related to local factors
  - Mitochondrial toxicity
    - Adipose tissue: may promote lipoatrophy
    - Hepatic cells: may promote lactic acidosis
- Mitochondrial toxicity has clinical consequences
Impact of HIV and Treatment on Mitochondrial DNA Levels

mtDNA:nDNA Ratio

<table>
<thead>
<tr>
<th>HIV Positive</th>
<th>No ART</th>
<th>Symptomatic* ART</th>
<th>Discontinued ART</th>
<th>Restarted ART No Stavudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Negative</td>
<td>1.28</td>
<td>0.72</td>
<td>0.41</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Symptomatic hyperlactatemia.

Model of NRTI-Induced Lipoatrophy

<table>
<thead>
<tr>
<th></th>
<th>Adipocyte mtDNA Content (copies/mL)</th>
<th>Leg Fat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV negative</td>
<td>1586</td>
<td>24</td>
</tr>
<tr>
<td>HIV positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI-naïve</td>
<td>1564</td>
<td>24</td>
</tr>
<tr>
<td>Tenofovir DF and/or abacavir (n=25)</td>
<td>1707</td>
<td>24</td>
</tr>
<tr>
<td>Stavudine (n=35)</td>
<td>275</td>
<td>11</td>
</tr>
<tr>
<td>Zidovudine (n=41)</td>
<td>771</td>
<td>17</td>
</tr>
</tbody>
</table>

Note: BMI for patients in each group was adjusted to 24 kg/m².
Model of NRTI-Induced Lipoatrophy: Adipocyte Integrity

HIV-Negative ART-Naïve HIV-Patients
HIV-Patients Receiving Abacavir and/or Tenofovir DF
Normal
Fine membrane structure of adipocytes
Large non-staining lipid droplet
Small numbers of blue-staining nuclei

HIV Patients Receiving Zidovudine
Abnormal Adipocytes
Less spherical
Smaller volume
Increased intercellular space
Up-regulated mitochondrial protein expression (yellow label)
Nuclei are more frequent and large in size

HIV Patients Receiving Stavudine

RAVE Study: Switch to Either Tenofovir DF or Abacavir

- Open-label switch study
  - 105 patients with self-defined lipoatrophy on NRTI
    - HIV RNA <50 copies/mL
    - Switch to tenofovir DF or abacavir
  - Median weight/limb fat prior to switch
    - Tenofovir DF arm: 74/3.0 kg
    - Abacavir arm: 72/2.9 kg
- Results at 48 weeks
  - Total limb fat increased to similar extent in both arms over 48 weeks (by DEXA)

Abdominal MRI Scans

Control subject  
Increased VAT

Courtesy of Ellen Engelson, Donald Kotler

Case

- 58 y.o. former competitive body builder dx with HIV in 1990 (nadir CD4 ~100)
- Initiated AZT monotx in 1990 and multiple regimens since then including d4T, every available PI
- Currently on TDF/FTC/ATV/r
- HIV RNA < 20; CD4 345
- On pioglitazone for diabetes (HgA1c = 6.4)
Rationale for Treatment of Visceral Obesity

- Reduce cardiovascular risk
  - Direct, indirect effects
  - General population: effects of liposuction\(^1\) and omentectomy\(^2\) on metabolic parameters
- Reduce risk of diabetes mellitus
- Improve quality of life
  - Maximize adherence to antiretrovirals
- \(?\) Reduce risk of hepatic fibrosis (NASH)
- \(?\) Improve bone mineral density

FRAM: Low Limb Muscle Mass and Central Adiposity Associated with 5 Year Mortality


ACTG 5224s: Visceral Fat Change by Regimen in A5202

Nocturnal Pulse Secretion of GH is Reduced in HIV Lipodystrophy

~40% of men with LD have reduced peak GH response to GHRH-arginine (18% deficient using stringent criterion)

Lifestyle Interventions

- Mostly small studies of exercise interventions
- RCT of supervised home-based aerobic & progressive resistance training x 16 w in 40 women with WHR ≥ 0.85 & fat redistribution
  - WC ↓ 1.0 cm but NS change in VAT, lipids
- Single arm study of individualized light aerobic training x 4 m in 17 “lipodystrophic” pts (15 w/ lipohypertrophy)
  - VAT ↓ 12%, TC 23%, TG 43%, HDL ↑ 6%
- RCT of intensive lifestyle intervention (weekly sessions w/dietician) x 6 m in 34 pts w/ metabolic syndrome
  - WC ↓ 2.6 cm but NS change in lipids, HOMA-IR

1Reitschel et al, JCEM, 2001;86:504-10. 2Koutkia et al JCEM, 2005;90:32-8

37 women with abdominal obesity (16 on ATV) randomized to immediate or delayed (wk 24) switch to RAL

Lake JE et al, AIDS Patient Care STDs. 2012 Jul 23. [Epub ahead of print]

Metformin 500 mg bid Decreases Abdominal Fat But Non-Selectively

- Elevated WHR, fat gain/loss in at least 1 area, IGT &/or insulin > 15 μIU/ml

Phase III Trial of Tesamorelin

- N = 404 randomized 2:1 to tesamorelin x 26 w then re-randomized (T to T or P x 26 w; P to T x 26 w)

Falutz J et al, JAIDS 2010;53:311-22

Metabolic & Adverse Effects of Tesamorelin

- IGF-1 ↑ 86%
- Trends for modest ↓ TG, TC:HDL
  - Original phase III trial: significant ↓ TG, TC, TC:HDL
- Minimal adverse effects on glucose (8% FBG ≥ 125 at baseline)
- Injection site erythema (14%), pruritus (10%), hypersensitivity skin reaction (3%)
- 49% with IgG to tesamorelin at week 26
  - NS difference in IGF-1 or VAT by presence of Ab

## Morphologic Complications: Other Pharmacologic Approaches

<table>
<thead>
<tr>
<th></th>
<th>Lipoatrophy</th>
<th>Central Fat Accumulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uridine</strong></td>
<td>Improves(^1)</td>
<td>Increased(^1)</td>
<td>HDL-C decreased</td>
</tr>
<tr>
<td></td>
<td>(0.7 kg limb fat gain at 12 weeks)</td>
<td></td>
<td>Unlicensed “dietary” supplement</td>
</tr>
<tr>
<td></td>
<td>No improvement(^2)</td>
<td>No change(^2)</td>
<td>Expensive</td>
</tr>
<tr>
<td><strong>Statins</strong> (pravastatin)</td>
<td>Improves(^1)</td>
<td>No change(^1)</td>
<td>Total cholesterol and LDL-C decrease by (~25%)</td>
</tr>
<tr>
<td></td>
<td>(0.5 kg limb fat gain at 12 weeks)</td>
<td></td>
<td>No change in insulin resistance or triglycerides</td>
</tr>
<tr>
<td></td>
<td>No improvement(^2)</td>
<td>No change(^1)</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrate</strong></td>
<td>No change(^1)</td>
<td>No change(^1)</td>
<td>Triglycerides: 20%-25% decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improves HDL-C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimal impact on insulin resistance</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Intervention</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polylactic acid\textsuperscript{1,2}</td>
<td>Rapidly effective</td>
<td>Multiple injections</td>
</tr>
<tr>
<td></td>
<td>Effects last 96 weeks</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Small office procedure</td>
<td></td>
</tr>
<tr>
<td>Autologous fat transfer\textsuperscript{3}</td>
<td>Effective</td>
<td>No fat to transfer in 40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fat hypertrophy in 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retouch in 16%</td>
</tr>
<tr>
<td>Buffalo hump liposuction\textsuperscript{4,6}</td>
<td>Rapid reduction</td>
<td>Requires surgery</td>
</tr>
<tr>
<td></td>
<td>No proven pharmacologic alternatives</td>
<td>May recur</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not effective for ant neck</td>
</tr>
</tbody>
</table>

\textsuperscript{2}Valantin MA, et al. AIDS. 2003;17:2471-2477.
\textsuperscript{5}Gervasoni C, et al. AIDS. 2004;18:574-578.
Limitations of Current Approaches

- Challenge to selectively reduce visceral fat without worsening lipoatrophy that may co-exist
- Safety profile, especially with prolonged use; cost
- Reaccumulation of fat with cessation of interventions (rhGH, tesamorelin)
  - Intermittent therapy? Induction-maintenance?
- What is the minimal amount of reduction for clinical benefit?

Both HIV Infection and HAART Impact Lipid Parameters

- Seroconversion associated with:
  - ↓ in TC, LDL-C, and HDL-C
- HAART associated with:
  - ↑ TC above normal
  - ↑ LDL-C to normal
  - HDL-C remained subnormal
- Early LDL changes may represent, in part, a return to health rather than toxicity

Treatment-Associated Hyperlipidemia: Hierarchy of Risk (Highest to Lowest Risk)

- **NRTIs**
  - Stavudine > zidovudine > abacavir = tenofovir DF
  - Combinations
    - Stavudine + lamivudine > tenofovir DF + lamivudine
    - Zidovudine/lamivudine > emtricitabine/tenofovir DF
    - Stavudine + didanosine > emtricitabine + didanosine
    - Stavudine + didanosine > abacavir + lamivudine

- **Ritonavir-boosted PIs**
  - Indinavir, lopinavir, tipranavir > atazanavir, darunavir, fosamprenavir, saquinavir
  - Ritonavir: full dose > boosting dose

- **NNRTIs**
  - Efavirenz > nevirapine (both increase HDL-C)

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**STARTMRK:**

Lipid Changes at 5 Years

Fasting Lipid Levels at Baseline and Week 240 as Compared with NCEP Goals

[Graph showing lipid levels over time and comparison with NCEP goals.]

Sponsor: Merck

SPIRIT: Changes from Baseline to Week 24 in Fasting Lipids

Conclusion: Switching to FTC/RPV/TDF resulted in a greater improvement in 10-year Framingham Risk Score at Week 24 compared to PI + RTV + 2 NRTIs ($P=0.001$)

Sponsor: Tibotec

TDF/FTC/EVG/c vs. EFV and vs. ATV/r: Lipid changes

Conclusion: While some lipid fractions better with Quad than EFV or ATV/r, overall differences were modest and unlikely to be of clinical significance.
Dolutegravir versus Efavirenz: Spring -1

Figure 2: Changes in lipid variables to week 48
Individual lipids are expressed in mg/dL. Cholesterol-HDL is a unitless ratio.


Treatment of Hyperlipidemia in HIV Infected Patients

Check Fasting Lipid Panel
Before initiating ART
4 to 6 weeks after starting ART

Calculate Framingham 10-Year Risk Score
Meet criteria for treatment of LDL-C using ATP III guidelines?

Taking a PI?

First-Line Therapy
Per NCEP ATP III guidelines

Triglycerides <500 mg/dL

First-Line Therapy
Atorvastatin 10-40 mg/day
Pravastatin 20-40 mg/day
Rosuvastatin 10 mg/day

Second-Line Therapy
Fluvastatin 20-40 mg/day
Switch PI to atazanavir

Triglycerides >500 mg/dL

First-Line Therapy
Gemfibrozil 600 mg bid
Fenofibrate 54-160 mg/day

**HOPS Cohort: Incidence of MI and Lipid-Lowering Agent Use by Year**

- **MI incidence per 1000 Patient-Years by Year**
- **Percentage of Patients on LLAs by Year**

<table>
<thead>
<tr>
<th>Effect</th>
<th>HR adj</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLAs</td>
<td>0.34</td>
<td>0.14-0.85</td>
<td>0.021</td>
</tr>
<tr>
<td>Age &gt;40 years</td>
<td>2.38</td>
<td>0.88-6.43</td>
<td>0.087</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.45</td>
<td>0.99-6.05</td>
<td>0.052</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.22</td>
<td>0.98-5.05</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Use of lipid-lowering agents was associated with reduced risk for CVD among HIV-infected patients with hyperlipidemia.

**INTERHEART Study: In the General Population, Multiple Traditional Risk Factors Confer Synergistic Increases in the Risk of MI**

Evaluated factors associated with MI in 15,000 (MI) patients versus 15,000 case controls

- **Risk Factor (Adjusted for All Others)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smk (1)</td>
<td>2.9 (2.6-3.2)</td>
</tr>
<tr>
<td>DM (2)</td>
<td>2.4 (2.1-2.7)</td>
</tr>
<tr>
<td>HTN (3)</td>
<td>1.9 (1.7-2.1)</td>
</tr>
<tr>
<td>ApoB/A1 (4)</td>
<td>3.3 (2.8-3.8)</td>
</tr>
<tr>
<td>1+2+3</td>
<td>13.0 (10.7-15.8)</td>
</tr>
<tr>
<td>All (4)</td>
<td>42.3 (33.2-54.6)</td>
</tr>
<tr>
<td>+Ab</td>
<td>68.5 (53.0-88.6)</td>
</tr>
<tr>
<td>Obes</td>
<td>182.9 (132.6-252.2)</td>
</tr>
<tr>
<td>All RFs</td>
<td>333.7 (230.2-483.9)</td>
</tr>
</tbody>
</table>

>90% of total risk can be attributed to these factors

VA Study Results

Among never smokers, HIV infection was still associated with an increased risk of AMI (HR=2.42, 95% CI=1.31-4.50)

Baseline classes of ART, HIV-1RNA, and CD4 count were not associated with AMI risk.

HIV infection was associated with the same risk of AMI as diabetes and ever smoking

### HIV is an Independent Risk Factor for Cardiovascular Disease

- X-sectional study: HIV infection is characterized by more severe atherosclerosis as measured by carotid IMT even after adjusting for common CVD risk factors (age, gender, race, smoking, Diabetes, HTN, and Lipids)¹

- Endothelium dependent vasodilation in young, untreated HIV+ men was markedly lower than HIV- controls and similar to HIV-men 25 years older. HIV is associated with accelerated vascular aging.²

---

Independent Predictors of Carotid Intimal Thickness (CIMT)

- CIMT predicts cardiovascular disease and helps risk-stratify patients for cardiovascular events
- Prospective cohort of HIV-positive (n=179) and HIV-negative patients (n=128)
  - HIV positive (CD4 609 cells/mm³, HIV RNA <200 copies/mL [91%])
    - Calculated heart age was 6.7 years older than HIV negative
    - Overall lower lipid values
- Factors not predictive of CIMT at either CCA or ICA
  - Use of abacavir, lopinavir/ritonavir, indinavir; duration of HIV infection, T-cell nadir

**Significant Predictors of CIMT**

<table>
<thead>
<tr>
<th>CCA</th>
<th>HIV Positive</th>
<th>HIV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart age</td>
<td>Age</td>
</tr>
<tr>
<td>ICA</td>
<td>IL-6</td>
<td>Hypertensive medications</td>
</tr>
<tr>
<td></td>
<td>- Diabetics</td>
<td>History of MI/stroke</td>
</tr>
<tr>
<td></td>
<td>- Hypertensive medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- CVD risk calculator</td>
<td></td>
</tr>
</tbody>
</table>


SMART Study: Treatment Interruption Associated With Higher Rates of AIDS-related OI or Death (Any Cause)

- Hazard ratio, 2.6; 95% CI, 1.9-3.7; P<0.001
- Treatment Interruption (DC group)
- Continuous Treatment (VS group)

Adapted with permission from New England Journal of Medicine. © 2006.
Treatment Interruption Associated With Higher Rates of Major Cardiovascular, Hepatic, and Renal Disease

- No apparent reductions in rates of major cardiovascular, hepatic, and renal disease associated with deferred ART or periodic ART-sparing regimens

<table>
<thead>
<tr>
<th>End Point</th>
<th>Hazard Ratio (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, any cause</td>
<td>1.8 (1.2-2.9)</td>
</tr>
<tr>
<td>Major cardiovascular, renal, or hepatic disease</td>
<td>1.7 (1.1-2.5)</td>
</tr>
<tr>
<td>Serious opportunistic disease</td>
<td>6.6 (1.5-29.1)</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>1.2 (1.0-1.5)</td>
</tr>
</tbody>
</table>

*Treatment Interruption vs Continuous Treatment


Inflammatory Markers in Treatment Interruption Studies

- INSIGHT/SMART study group: nested case-control study of pts who died from any cause classified as early deaths (≤ 2 yrs after randomization, n = 95) or late deaths (> 2 yrs, n = 71)
- Elevated BL hsCRP, IL-6, and D-dimer associated with increased risk of both early and late death

Change in D-Dimer (μg/mL) from Baseline to 1 Month after Stopping HAART

Kuller, et al, PLoS Medicine, October 2008

Immune Activation and Disease Progression

- The role of Immune Activation in HIV disease progression is becoming more clear.
- Activated CD4 cells are preferentially targeted for HIV infection.
- Immune activation in HIV is often non-specific which leads to accelerated turnover and death of CD4 T cells and potential exhaustion of immune regeneration.
- Most CD4 loss is in non-infected cells (bystander cell death).
- Impairment of the gut mucosa can lead to microbial translocation and elevated circulating LPS.
HIV Causes Disruption of the Gastrointestinal Tract

- Loss of CD4+ T cells
- Enterocyte apoptosis
- Loss of tight junctions
- Microbial translocation

Pathogenesis: Immunology

What is the mechanism for ongoing CD4+ destruction in HIV disease?

- HIV replication
- Immune activation
- Microbial translocation
- Gut mucosal damage
- Immune deficiency
Emerging Concept of Cardiovascular Disease and HIV Pathophysiology

- Relationship of HIV, ART, and vascular pathogenesis
- Persistent immune activation, inflammation, and microbial translocation
- CD4 < 500 cells/mm³ is an independent risk factor for incident CVD
- Role of
  - T cell dysfunction
  - Other infections (i.e., CMV)


Effects of Life-style Modification and Metformin on Coronary Calcium in HIV+ Patients with Metabolic Syndrome

![Graph showing the effects of lifestyle modification and metformin on coronary calcium score.](image)

Conclusion: Metformin use associated with reduced coronary calcium progression

Fitch K, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 119.
Low Dose ASA Reduces Platelet Activity and Immune Activation

- Platelet aggregation (PA) study in 25 HIV+ pts on ART and 29 HIV- controls
  - Response to stimuli w/ ADP, AA, and w/o stimuli
  - Repeat after 1 week low dose ASA
  - HLADR+CD38+CD8 cells measured

- Results
  - Greater PA in HIV+ vs. HIV- (P<0.05 for each)
  - Significant reduction after low dose ASA (P<0.01 for each)
  - Sig decline in HIV+ pts in CD38+ cells, not in HIV-


CVD Risk Management in HIV Patients

- In HIV+ patients, as in the general population, lifestyle modification should be the first approach.
  - Smoking cessation
  - Diet modification
  - Increase in exercise

- Lipid-lowering therapy or switching should be individualized.

- Impact of smoking cessation is greatest intervention.
Thank you!

Joseph McGowan, MD
JMcGowan@NSHS.edu