Fat redistribution on ARVs: dogma versus data

Gary Maartens
“Half of what we are going to teach you is wrong, and half of it is right. Our problem is that we don’t know which half is which.”

GP Berry, Dean Harvard Medical School 1949-1965
Lipohypertrophy – fat accumulation
Lipoatrophy – fat loss
Fat redistribution

- Seen progressively more commonly with duration on ART
- Fat loss & fat accumulation may occur together or separately
  - Term “lipodystrophy” not clinically useful
- Assessed subjectively or on imaging (DEXA, CT, MRI)
Fat redistribution patterns

• Fat loss:
  – Subcutaneous fat everywhere
  – Most noticed face, buttocks, limbs

• Fat accumulation
  – Subcutaneous & visceral fat
  – Buffalo hump
  – Breasts
Lipodystrophy questions

- What is the pathogenesis?
- Are fat changes linked to specific ARVs?
- Does switching ARVs help?
Lipoatrophy - pathogenesis

• Biopsy of affected adipose tissue:
  – Mitochondrial depletion
  – Infiltration with macrophages
  – Pro-inflammatory cytokines
  – ↑ apoptosis

• Associated with NRTIs that are most toxic to mitochondria (d4T, ddI, AZT)
Lipoatrophy – genetic predisposition

Hemochromatosis Gene Polymorphisms, Mitochondrial Haplogroups, and Peripheral Lipoatrophy during Antiretroviral Therapy

Todd Hulgan, Pablo Tebas, Jeffrey A. Canter, Kathleen Mulligan, David W. Haas, Michael Dubé, Steven Grinspoon, Gregory K. Robbins, Alison A. Motsinger, and Asha R. Kallianpur, for the AIDS Clinical Trials Group 384 and A5005s Study Teams

Mitochondrial DNA Haplogroups Influence Lipoatrophy After Highly Active Antiretroviral Therapy

Sher L. Hendrickson, PhD, Lawrence A. Kingsley, DrPh, Eduardo Ruiz-Pesini, PhD, Jason C. Poole, PhD, Lisa P. Jacobson, ScD, Frank J. Palella, MD, Jay H. Bream, PhD, Douglas C. Wallace, PhD, and Stephen J. O’Brien, PhD*
Fat loss: RCTs of NRTIs

TDF vs d4T @ 96 weeks: total limb fat 7.9 kg vs 5.0 kg (P.001)
TDF vs AZT @ 48 weeks: total limb fat 8.9 kg vs 6.9 kg (P.03)
Fat loss: NRTIs ACTG5142 (fat loss >20% limbs from baseline)
Fat loss limbs >20% from baseline RCT: LPV/r vs EFV (+2 NRTIs) vs LPV/r + EFV

P Values at week 96
- Efavirenz vs lopinavir: 0.003
- Efavirenz vs lopinavir-efavirenz: < 0.001
- Lopinavir vs lopinavir-efavirenz: 0.023
Increase in limb fat after switching d4T/AZT
Fat loss - summary

• Pathogenesis is mitochondrial depletion and inflammation – genetic component
• Caused by NRTIs that are toxic to mitochondria
• PIs less associated than NNRTIs (?due to PI’s anti-apoptotic properties)
• Switch to less toxic NRTIs results in very slow improvement
Which ARVs cause fat accumulation?

Protease inhibitors implicated in initial studies
Metabolic sub-study FIRST trial:
PI or NNRTI + 2NRTIs; or PI+NNRTI

• Anthropometry & bio-impedance used to measure fat redistribution

• 70% of PIs unboosted

• NNRTIs 63% EFV 37% NVP

• NRTIs about 50% AZT, 40% d4T
FIRST study – regional fat

No significant difference by strategy
Body fat EFV vs LPV with AZT+3TC (LPV alone if VL suppressed on 3 consecutive months)
Fat accumulation:
LPV/r vs EFV (+2 NRTIs) vs LPV/r + EFV

• Trunk fat increased from a median of 8.2 kg (IQR 5.0–12.2) at entry to 10.4 kg (IQR 6.8–14.4) at week 96.

• There were no significant differences at weeks 48 or 96 by randomized treatment or NRTI selection.
What about raltegravir & atazanavir?
RCT ATV vs EFV (+AZT + 3TC)

VAT: visceral adipose tissue
SAT: subcutaneous adipose tissue
TAT: total adipose tissue

CID 2006;42:273
ATV/r vs EFV ACTG5224S

- Metabolic sub-study of RCT:
  - TDF+FTC vs ABC+3TC (no difference in fat changes)
  - ATV/r vs EFV

- Subcutaneous limb & abdominal fat gain greater with ATV/r

- No difference in increases in visceral fat
ATV/r vs ATV (d4T + 3TC)

≥20% limb fat loss @ 96 wk: ATV/r 29% vs ATV 49% P<0.05
Switch boosted PI to ATV/r

• ReAL study:
  – On boosted PI regimen; n=200
  – VL <400
  – waist >90cm

• Randomised to continue vs switch to ATV/r

• No change in fat distribution on DEXA or fat gain at week 48 & 96

Moyle 17th IAC 2008
http://clinicaltrials.gov/ct2/show/results/NCT00135356
Switch boosted PI to raltegravir

• Sub-study of SPIRAL
  – RCT switch to RAL or stay on PI/r
  – All VL suppressed at baseline
• N=73 (39 switch RAL, 34 stay on PI/r)
• “No differences were seen between treatment groups in the DXA-scan regarding body fat after 48 weeks”

Curran CROI 2011
Switching ARVs for fat accumulation

“we do not recommend switching antiretrovirals to combat lipohypertrophy”

“substitution of HIV medications to reduce regional fat accumulation cannot be advocated”
Effect of ART on pro-inflammatory cytokines causing wasting
Fat accumulation - summary

- All ART regimens, even ARVs with minimal metabolic effects, cause fat gain
- No regimen switch effective
- Is fat accumulation a consequence of treating HIV, which reduces immune activation?
Epidemiology of fat redistribution by HIV status

• FRAM studies HIV pos (on ART about 5 years at baseline) vs controls (from CARDIA cohort)
• Fat measured by MRI baseline & 5 years
• Ages well matched, ethnicity reasonable match, HIV+ men mostly MSM (unknown in CARDIA)
Fat distribution HIV+ vs control: women
Fat distribution HIV+ vs control: men

Buffalo hump
Change in fat - legs

$P = 0.63 \quad P = 0.23 \quad P = 0.0028 \quad P < 0.0001$

Baseline quartile of leg subcutaneous adipose tissue
Change in fat - visceral

Change in visceral adipose tissue (L)

Control
HIV+

Baseline quartile of visceral adipose tissue

n = 96  n = 54  n = 56  n = 55  n = 69  n = 51  n = 73  n = 54

P = 0.13  P = 0.93  P = 0.79  P = 0.19
FRAM 1 & 2 studies: summary

- Subcutaneous fat loss more common in HIV+
- HIV+ patients with fat loss at baseline worsened over time
- Visceral fat accumulation over time no difference by HIV status
- Fat accumulation similar in women irrespective of HIV status, but lower in HIV+ men than control men (?MSM factor)
MACS – change in waist circumference MSM
Loss of subcutaneous fat (from some NRTIs) together with fat accumulation (due to ageing & lifestyle) results in unusual appearance.
Lipodystrophy and anti-retroviral therapy as predictors of sub-clinical atherosclerosis in human immunodeficiency virus infected subjects

Giovanni Guaraldi\textsuperscript{a}, Chiara Stentarelli\textsuperscript{a}, Stefano Zona\textsuperscript{a}, Gabriella Orlando\textsuperscript{a}, Federica Carli\textsuperscript{a}, Guido Ligabue\textsuperscript{b}, Antonella Lattanzi\textsuperscript{c}, Giacomo Zaccherini\textsuperscript{a}, Rosario Rossi\textsuperscript{c}, Maria Grazia Modena\textsuperscript{c}, Nikolaos Alexopoulos\textsuperscript{d}, Frank Palella\textsuperscript{e}, Paolo Raggi\textsuperscript{d,4}

Adjusted ORs for presence of coronary artery calcium

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoatrophy alone</td>
<td>3.82</td>
<td>(1.11, 13.1)</td>
</tr>
<tr>
<td>Fat accumulation alone</td>
<td>7.65</td>
<td>(1.71, 37.17)</td>
</tr>
<tr>
<td>Mixed lipodystrophy</td>
<td>4.36</td>
<td>(1.26, 15.01)</td>
</tr>
</tbody>
</table>
Lipodystrophy and mortality

- FRAM study
- Lipoatrophy not associated with ↑mortality
- Visceral fat accumulation increased population attributable risk of mortality by 6.5%

Scherzer CROI 2011
Visceral fat & mortality HIV-
HIV MAN GROWS BOOBS
Condition a side-effect of ARVs – medical experts
Efavirenz and didanosine treatment are associated with the emergence of gynaecomastia. An underlying hypo-androgenism seems to contribute to the emergence of this disorder in these patients.
SHORT COMMUNICATION

Efavirenz directly modulates the oestrogen receptor and induces breast cancer cell growth

MJ Sikora,1 JM Rae,1,2 MD Johnson3 and Z Desta4

1Department of Pharmacology, 2Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA, 3Lombardi Cancer Center and Department of Oncology, Georgetown University Medical Center, Washington, DC, USA and 4Division of Clinical Pharmacology, Department of Medicine, Indiana University, Indianapolis, IN, USA
Conclusions

• Fat loss pathogenesis well understood

• Fat loss improves on switching to NRTIs that are less toxic to mitochondria

• Fat gain not linked to any ARV & not increased compared with controls

• Switching ARVs does not improve fat gain

• Check vascular risk factors with fat gain