# Fat redistribution on ARVs: dogma versus data

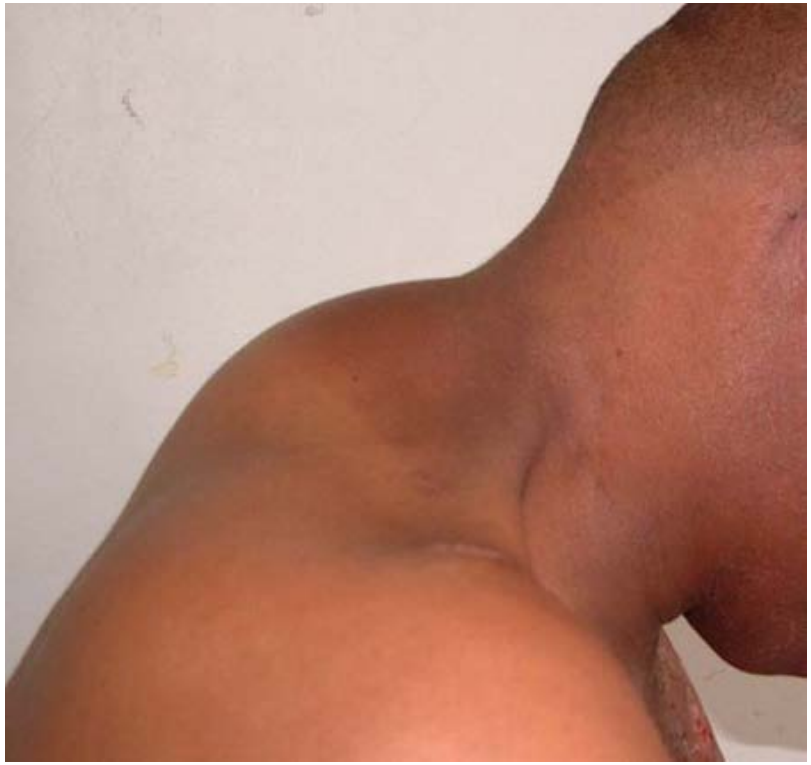
Gary Maartens

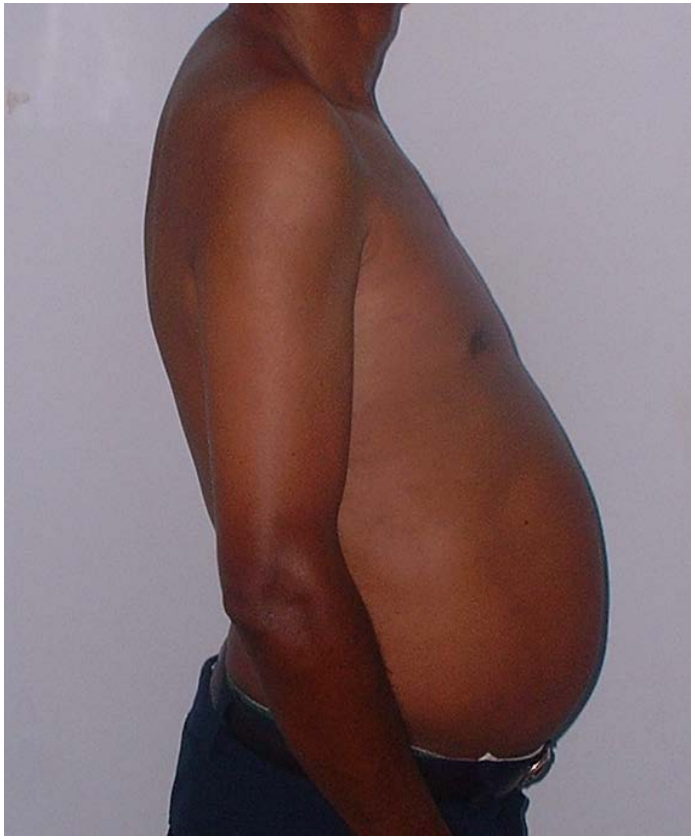
Division of Clinical Pharmacology
UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

“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.”

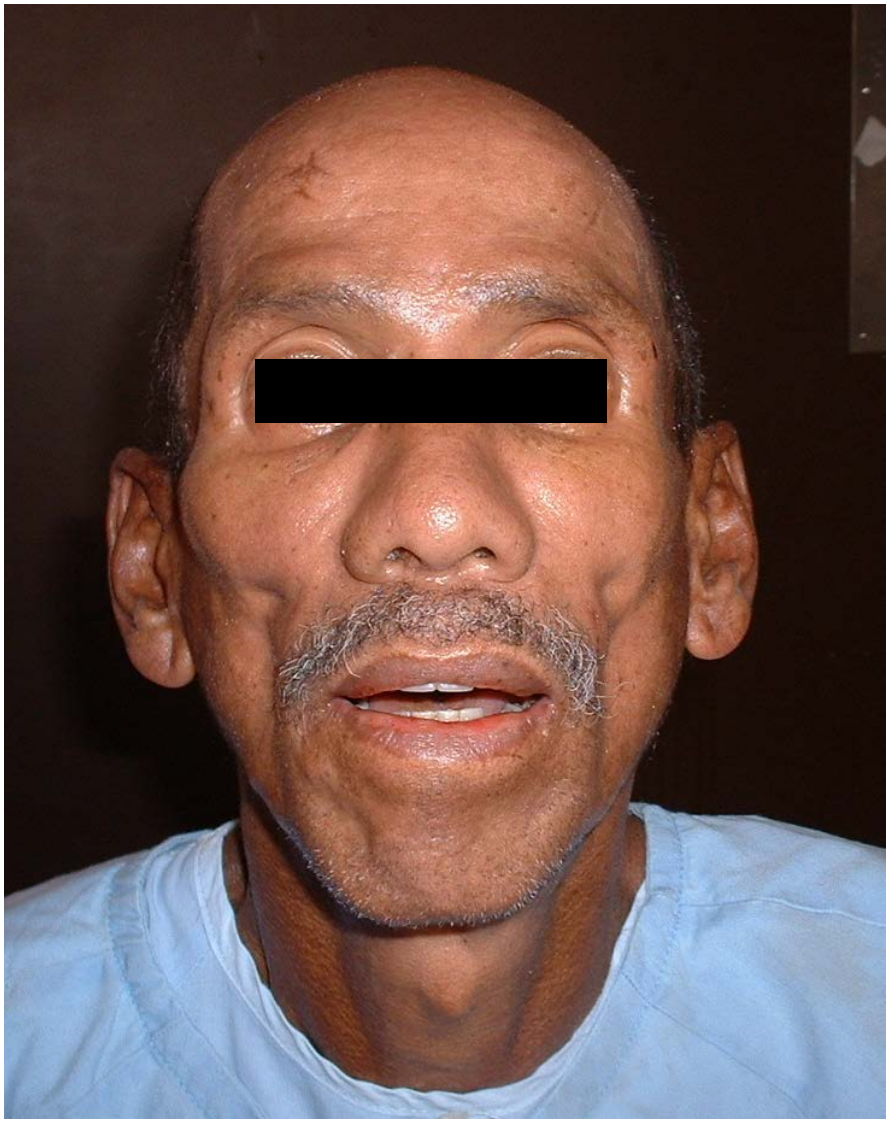
GP Berry, Dean Harvard Medical School 1949-1965

# 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)

JID 2009;200:252
CID 2010; 51:591

# Lipoatrophy – genetic predisposition

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

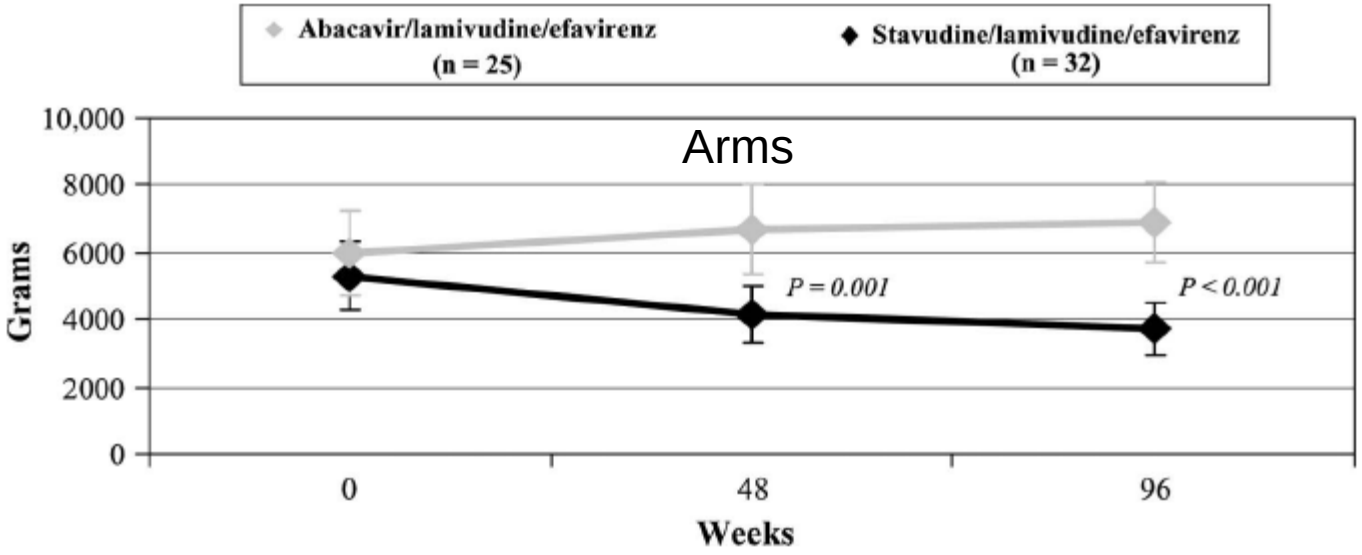
**Todd Hulgan,[1] Pablo Tebas,[2] Jeffrey A. Canter,[1] Kathleen Mulligan,[3,a] David W. Haas,[1] Michael Dubé,[4] Steven Grinspoon,[5] Gregory K. Robbins,[5] Alison A. Motsinger,[1] and Asha R. Kallianpur,[1] for the AIDS Clinical Trials Group 384 and A5005s Study Teams**

## 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**

JID 2008;197:858
JAIDS 2009;51:111

# Fat loss: RCTs of NRTIs

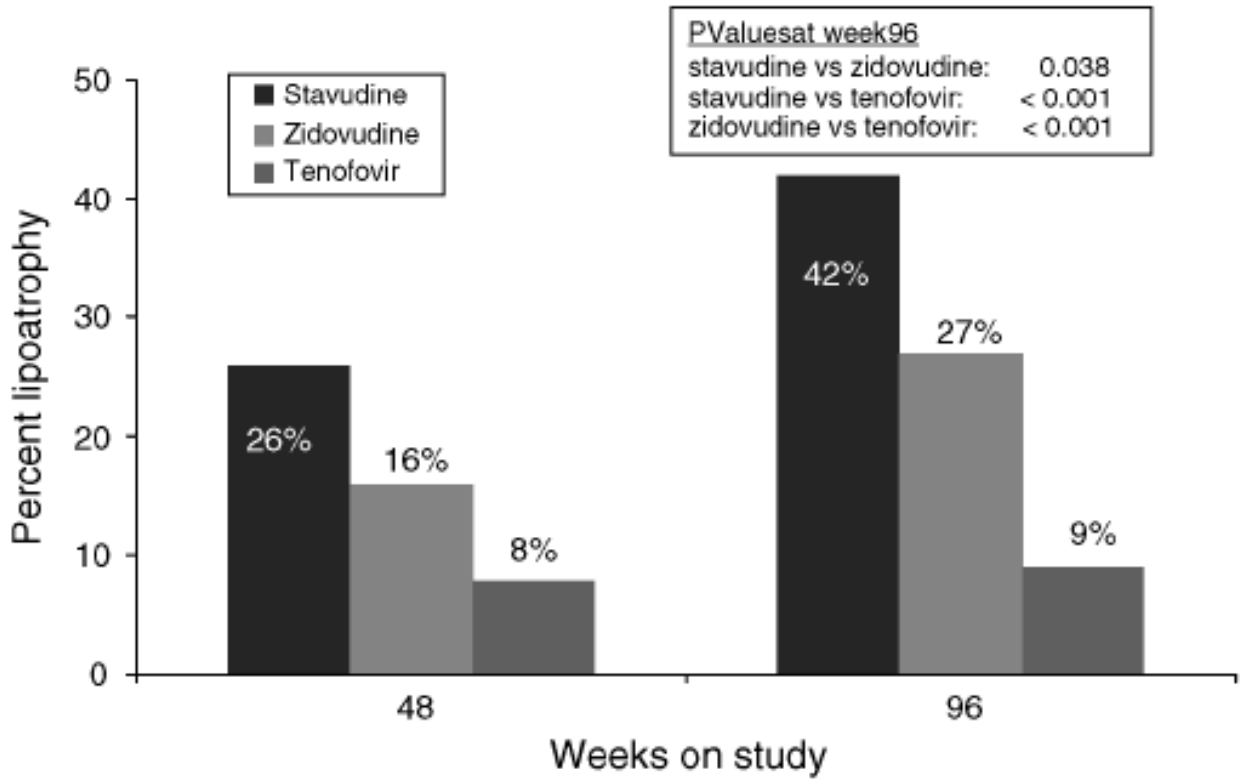



TDF vs d4T @ 96 weeks: total limb fat 7.9 kg vs 5.0 kg (P.001)

TDF vs AZT @ 48 weeks: total limb fat 8.9 kg vs 6.9 kg (P.03)

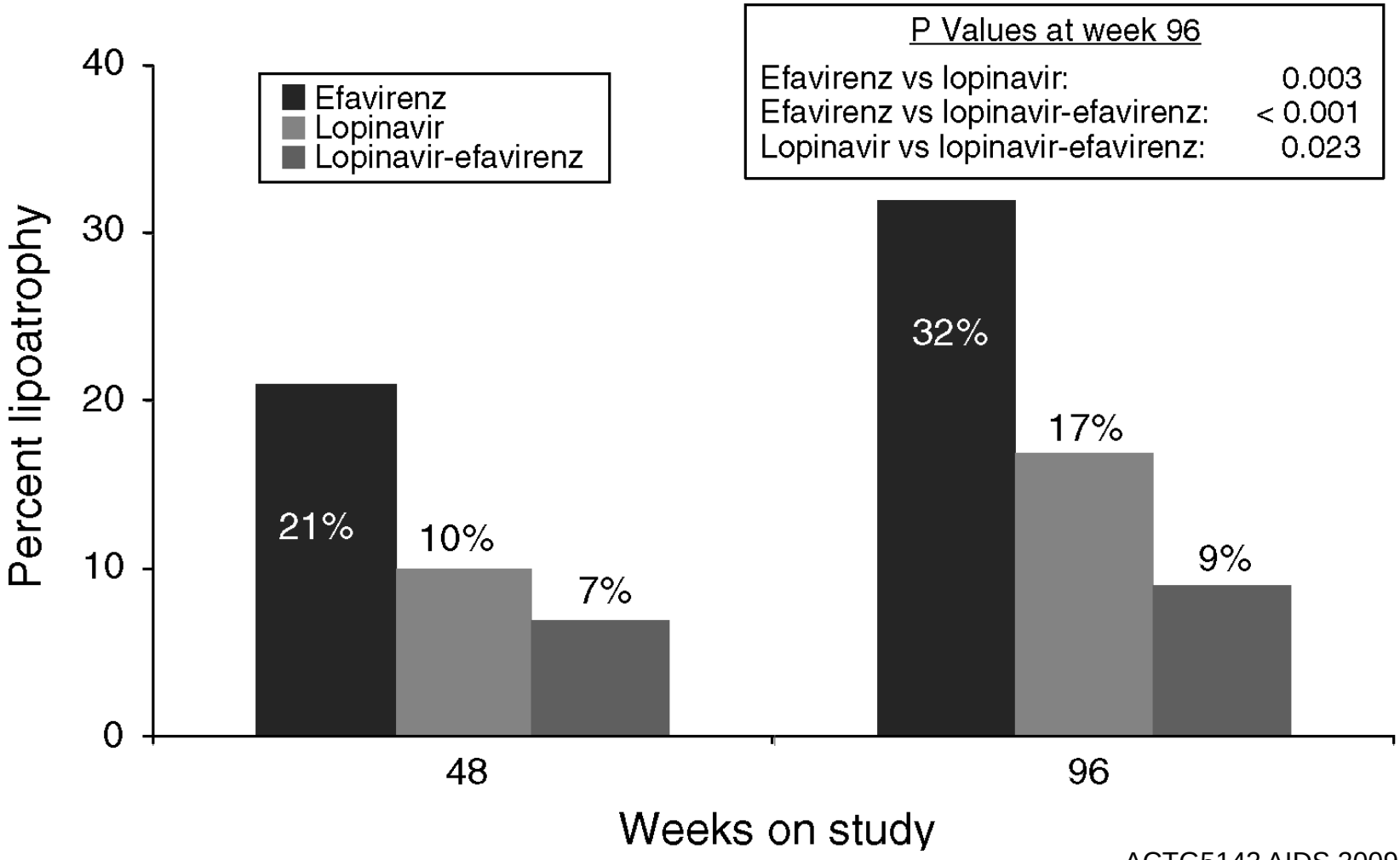
JAMA 2004;:292:191
JAIDS 2007;44:139
NEJM 2006;354:251

# Fat loss: NRTIs ACTG5142 (fat loss >20% limbs from baseline)



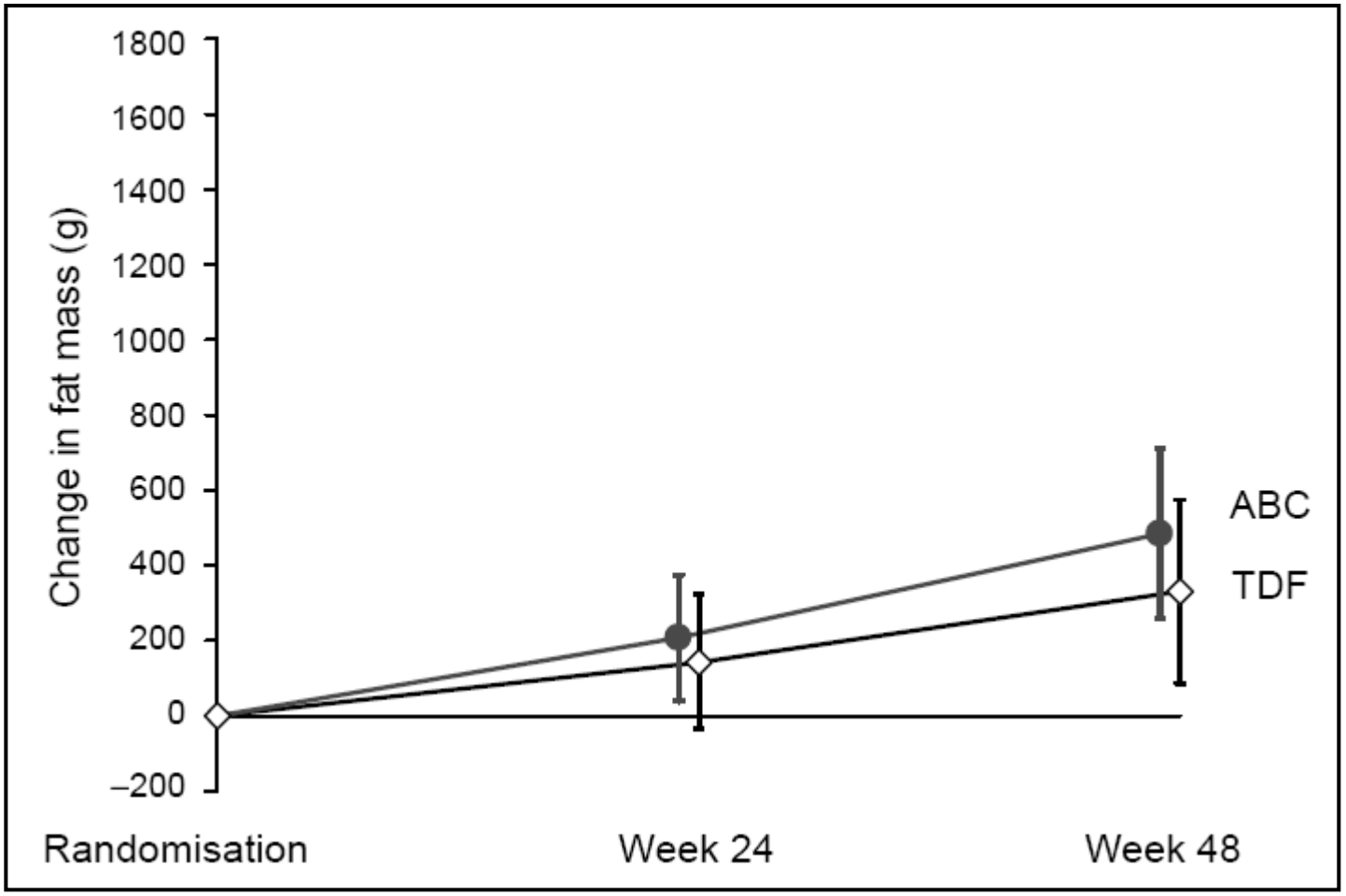

ACTG5142 AIDS 2009;23:1109

# Fat loss limbs >20% from baseline RCT: LPV/r vs EFV (+2 NRTIs) vs LPV/r + EFV




ACTG5142 AIDS 2009;23:1109

# Increase in limb fat after switching d4T/AZT




AIDS 2006;20:2043

# 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

CPT 2007;82:248

# Which ARVs cause fat accumulation?

Protease inhibitors implicated in initial studies

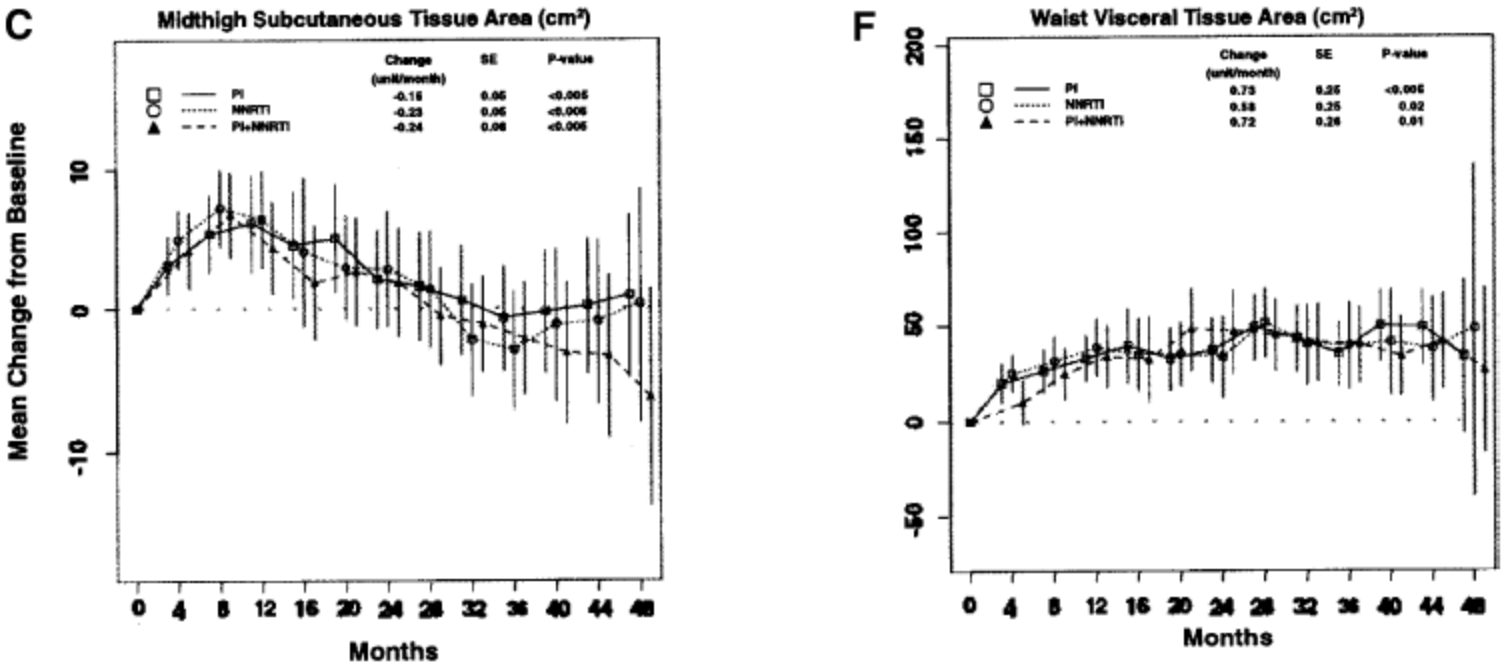
# Metabolic sub-study FIRST trial:

## 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

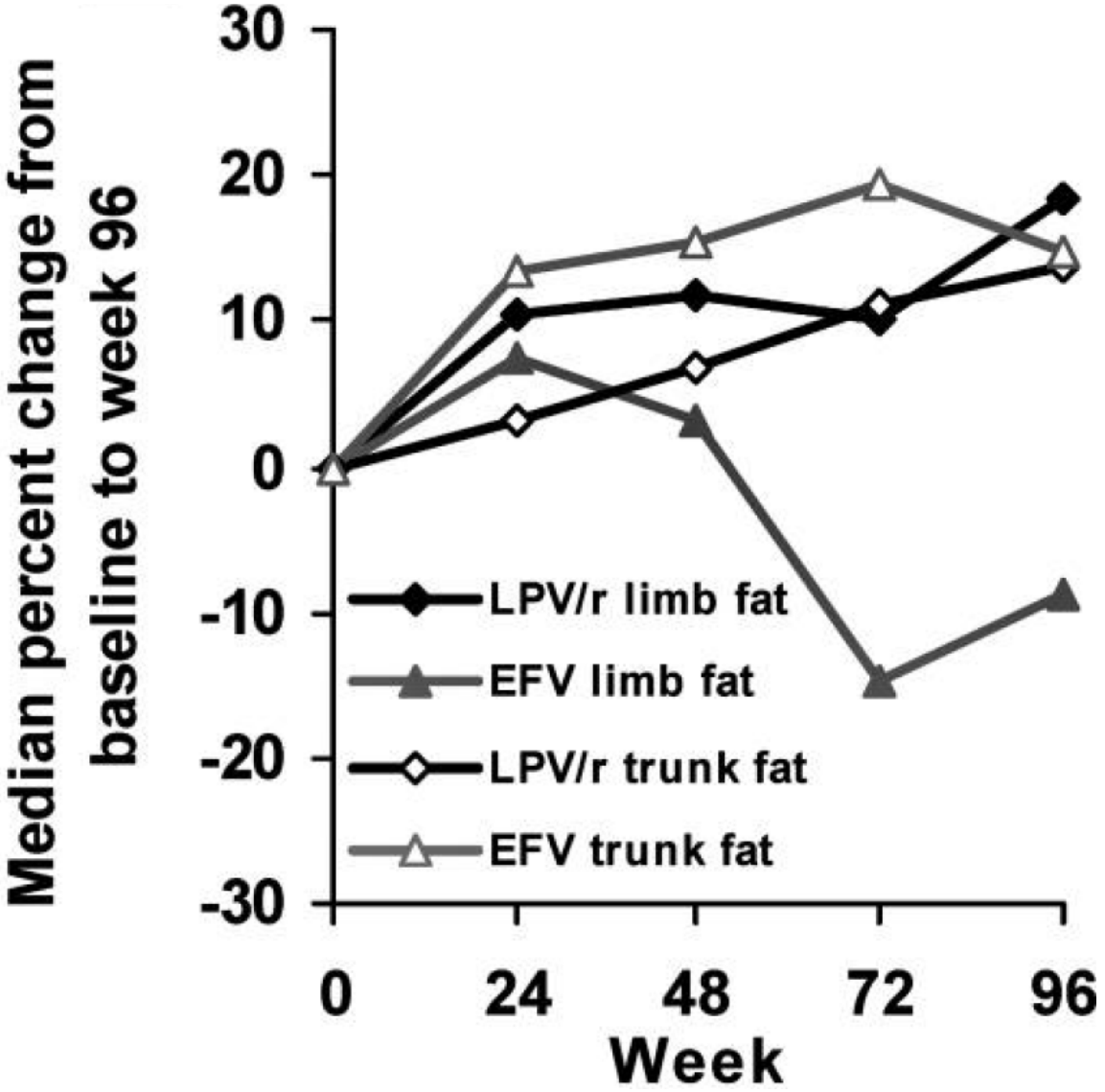
J Acquir Immune Defic Syndr 2007;44:506–517

# 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)



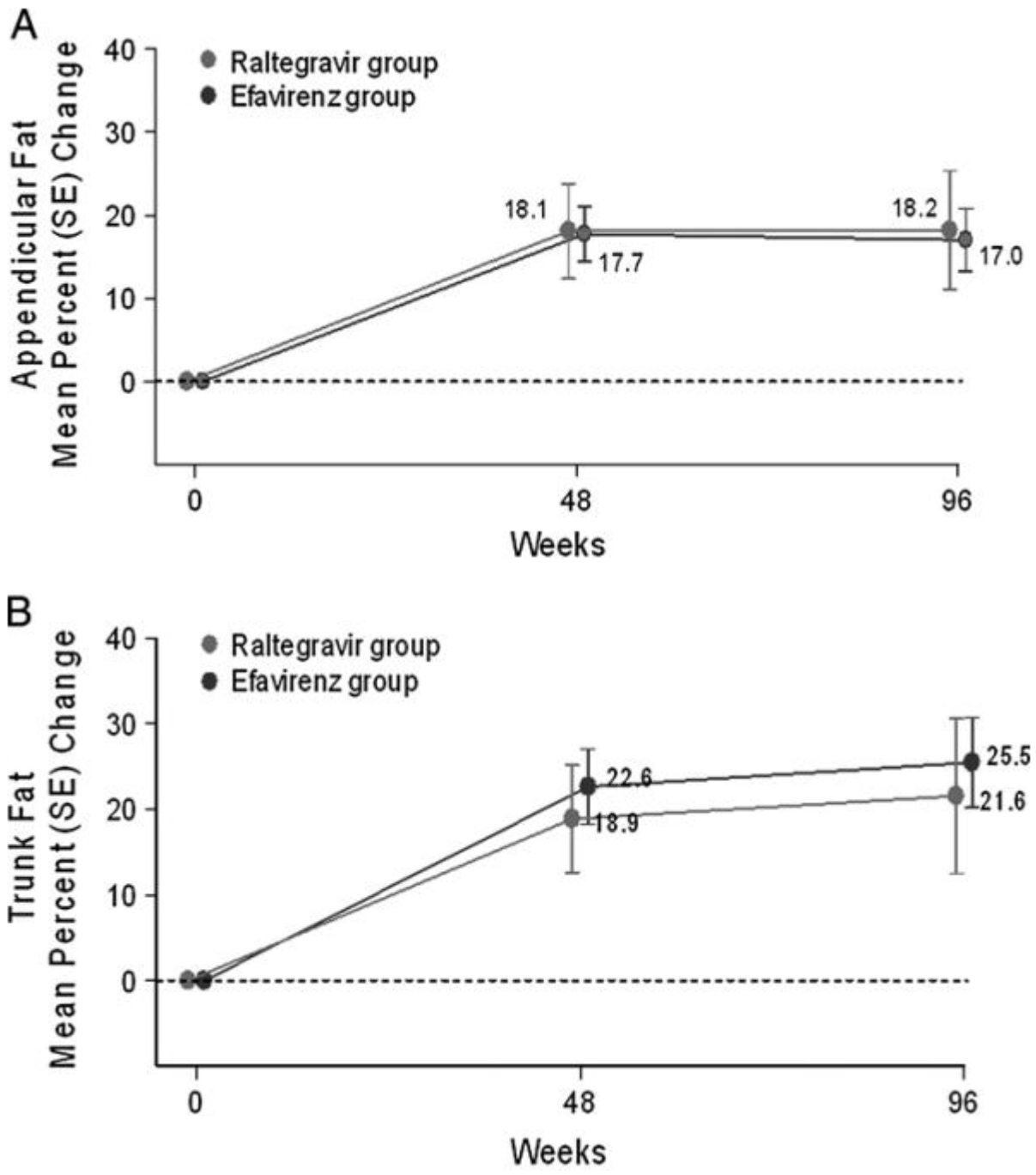

JID 2008;198:234

# Fat accumulation: LPV/r vs EFV (+2 NRTIs) vs LPV/r + EFV

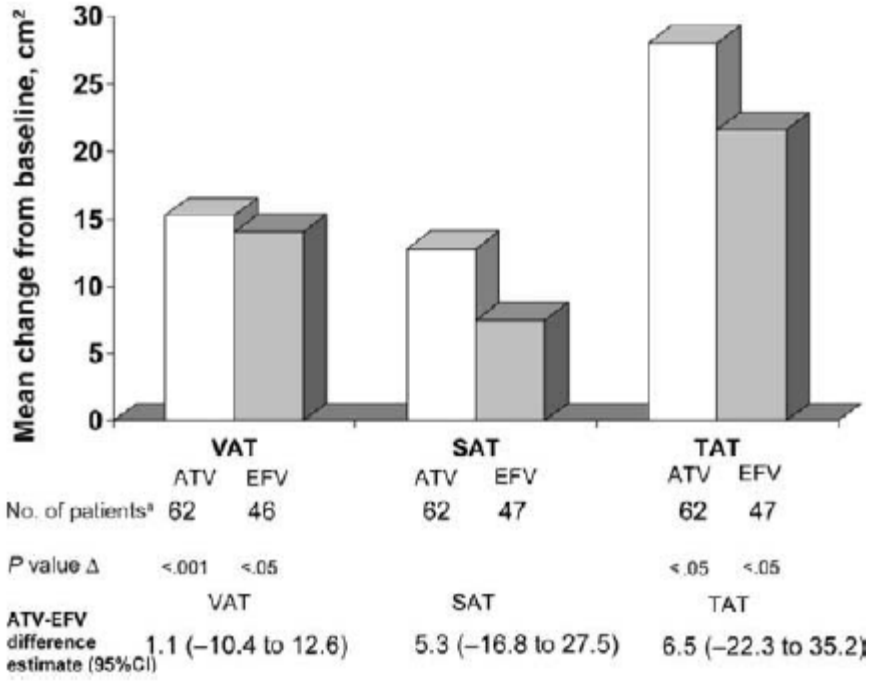
- Trunk fat increased from a median of 8.2 kg (IQR 5.0–12.2) at entry to 10.4 kg (IQR 6.8–14.4) at week 96.
- There were no significant differences at weeks 48 or 96 by randomized treatment or NRTI selection

ACTG5142 AIDS 2009;23:1109

What about raltegravir & atazanavir?


A
Appendicular Fat
Mean Percent (SE) Change
Raltegravir group
Efavirenz group
40
30
20
10
0
18.1
17.7
18.2
17.0
0
48
96
Weeks
B
Trunk Fat
Mean Percent (SE) Change
Raltegravir group
Efavirenz group
40
30
20
10
0
22.6
18.9
25.5
21.6
0
48
96
Weeks

# RCT ATV vs EFV (+AZT + 3TC)



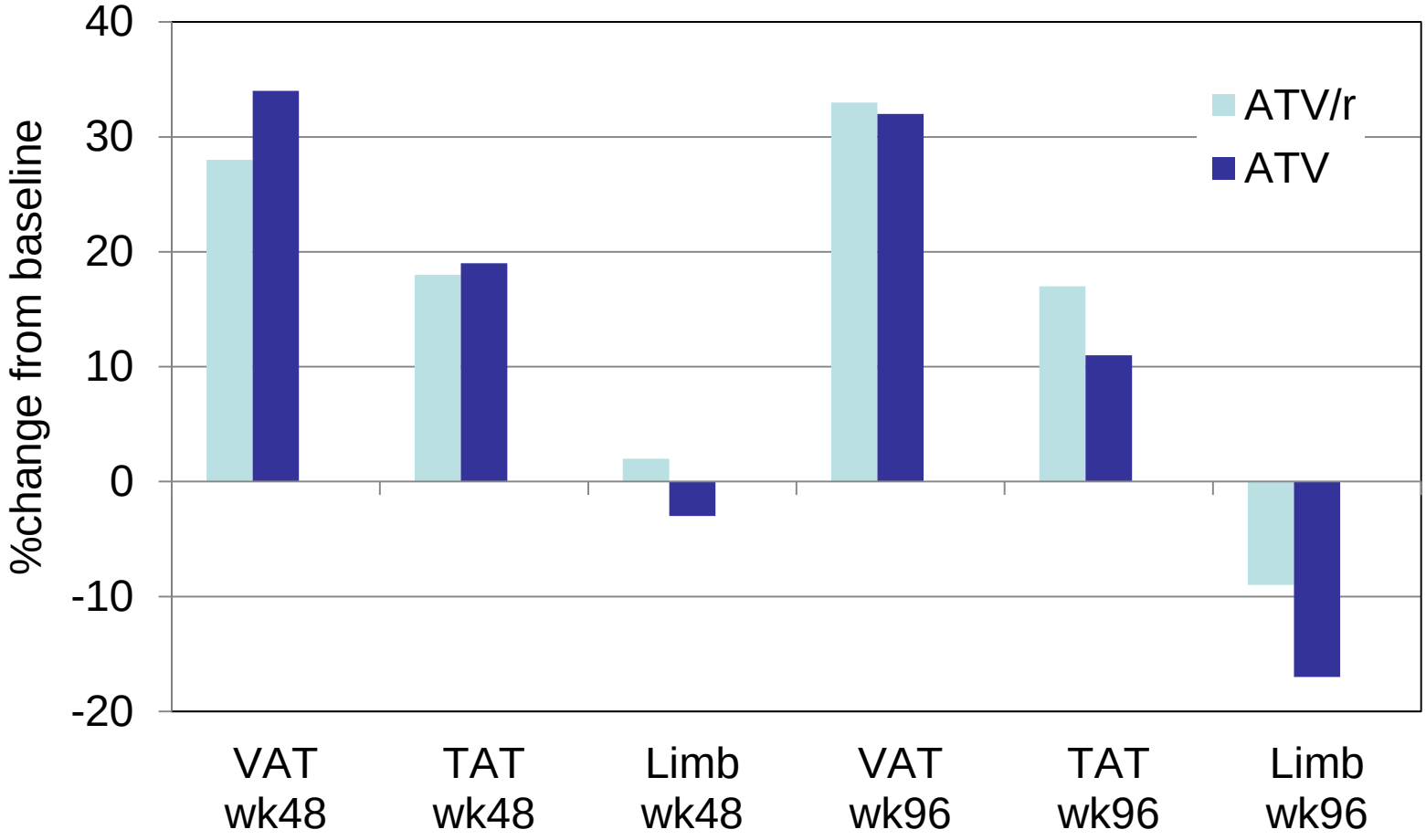

| | |
|---|---|
| VAT | visceral adipose tissue |
| SAT | subcutaneous adipose tissue |
| TAT | total adipose tissue |

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

CID 2009;48:1323

# 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://ctr.bms.com/pdf//AI424131.pdf
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”

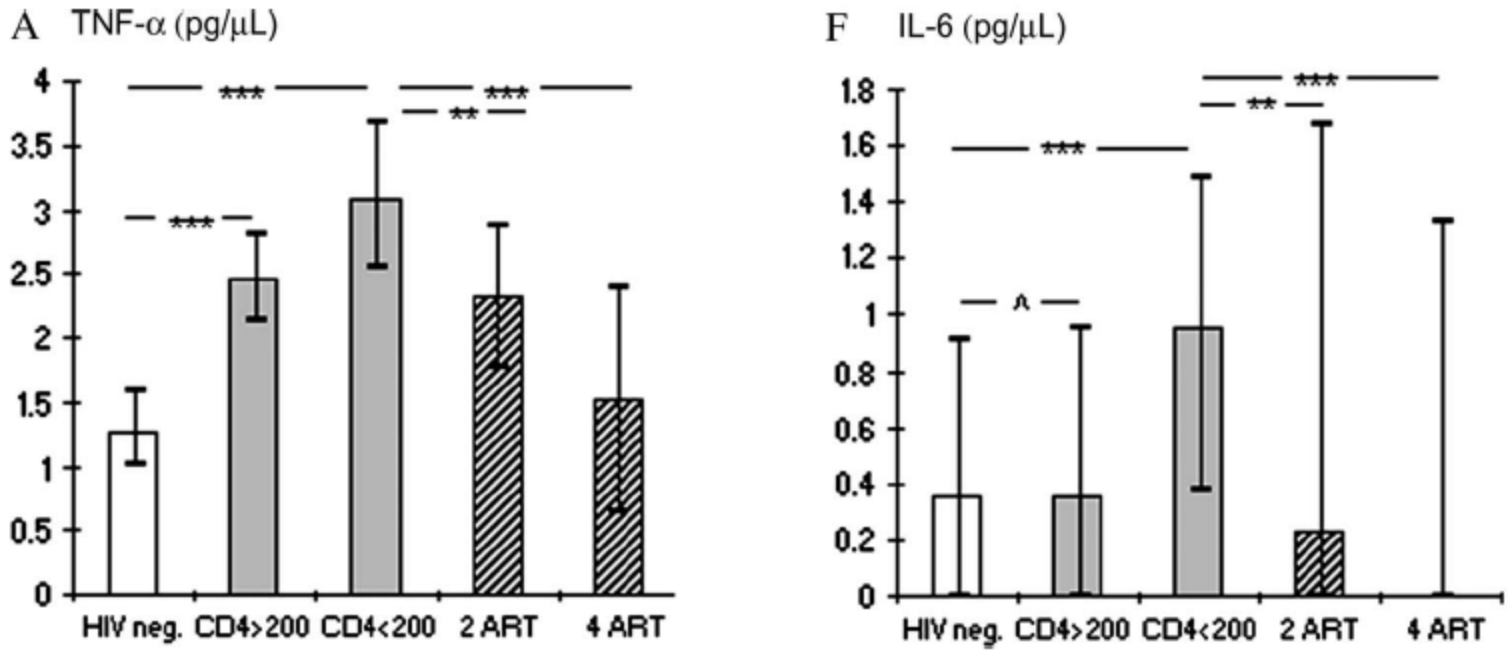
# Switching ARVs for fat accumulation

"we do not recommend switching antiretrovirals to combat lipohypertrophy"

"substitution of HIV medications to reduce regional fat accumulation cannot be advocated"

JAIDS 2008;49(S2):S93
Curr Opin Infect Dis 2011;24:43

# Effect of ART on pro-inflammatory cytokines causing wasting




JAIDS 2009;52:493

# Fat accumulation - summary

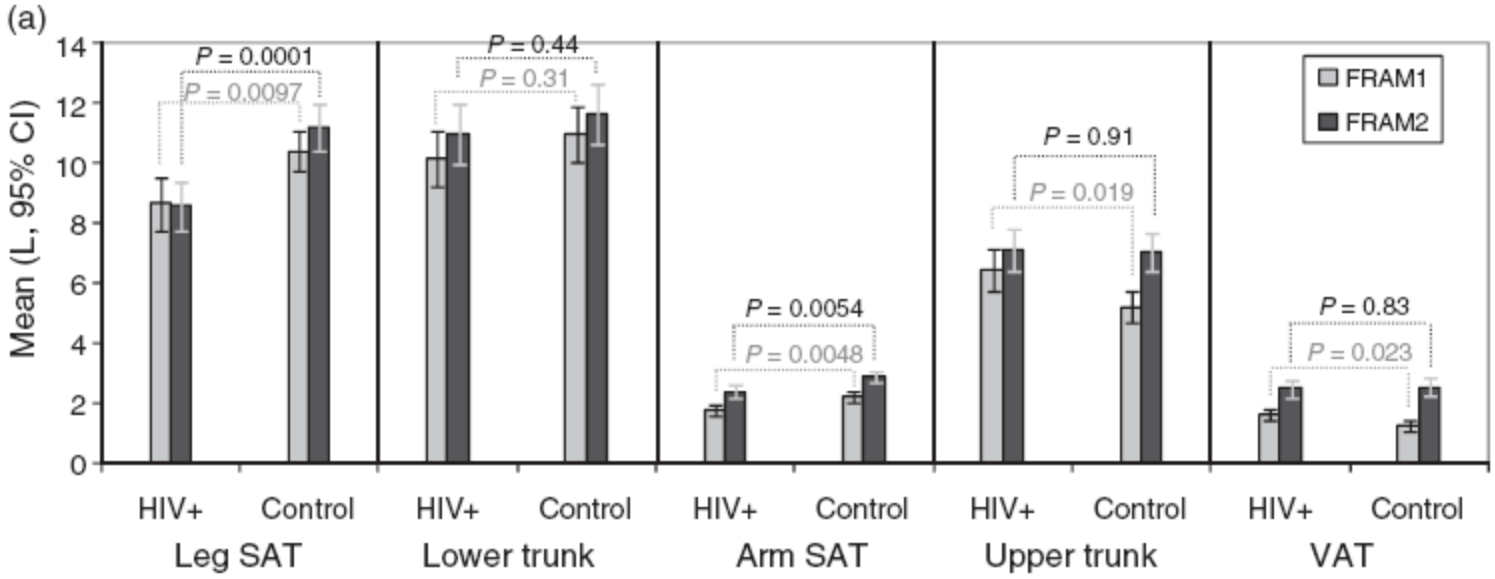
- All ART regimens, even ARVs with minimal metabolic effects, cause fat gain
- No regimen switch effective
- Is fat accumulation a consequence of treating HIV, which reduces immune activation?

# Epidemiology of fat redistribution by HIV status

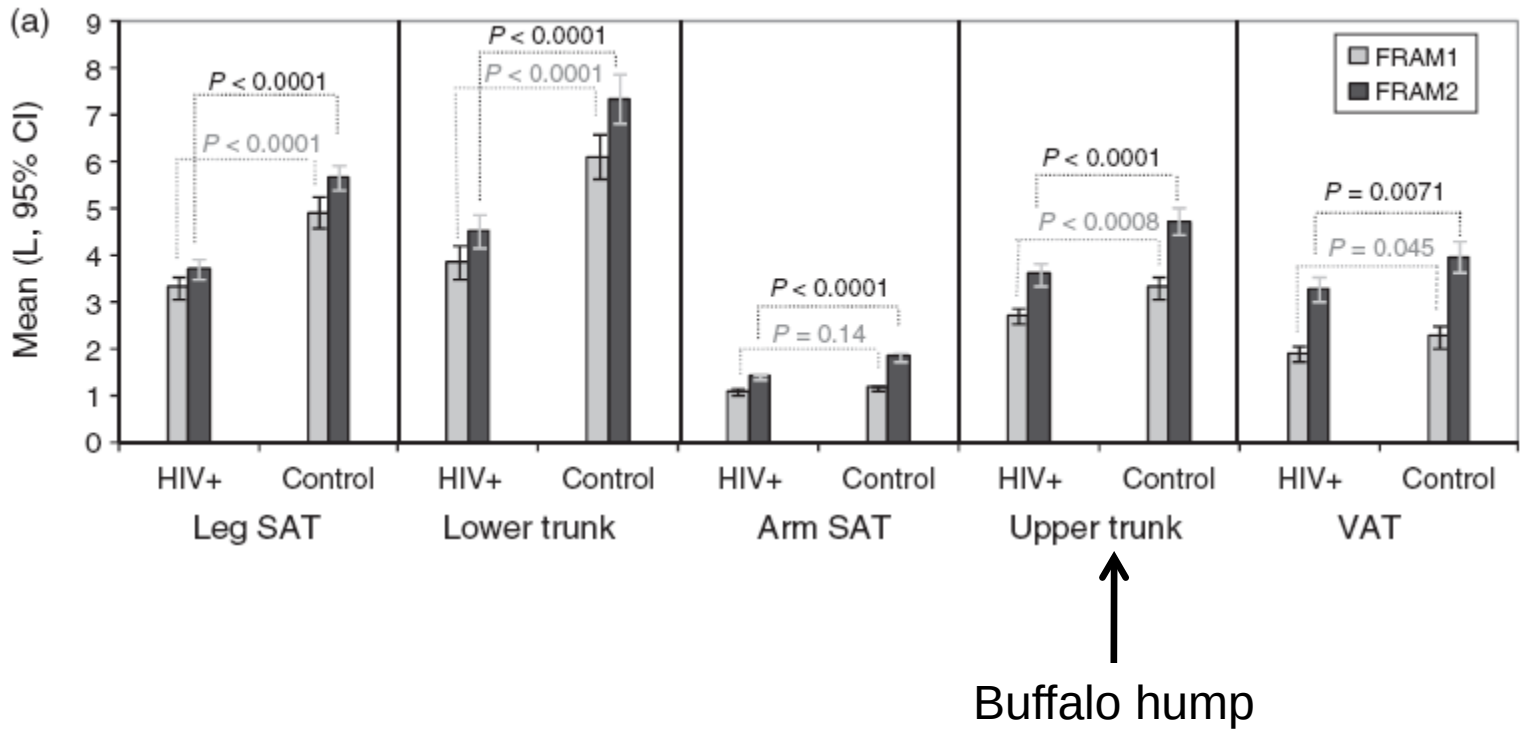
- FRAM studies HIV pos (on ART about 5 years at baseline) vs controls (from CARDIA cohort)
- Fat measured by MRI baseline & 5 years
- Ages well matched, ethnicity reasonable match, HIV+ men mostly MSM (unknown in CARDIA)

AIDS 2010;24:1717

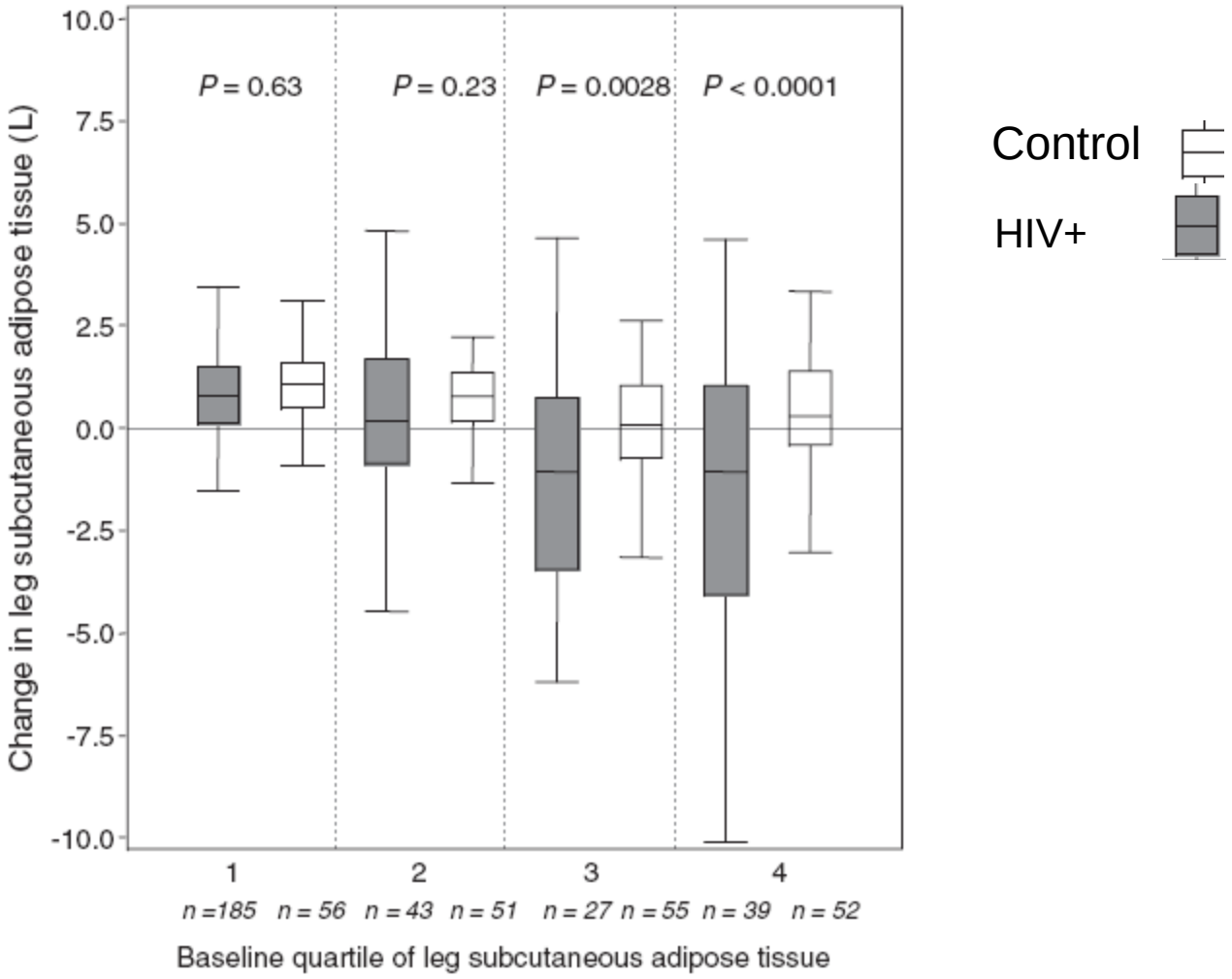
# Fat distribution HIV+ vs control: women



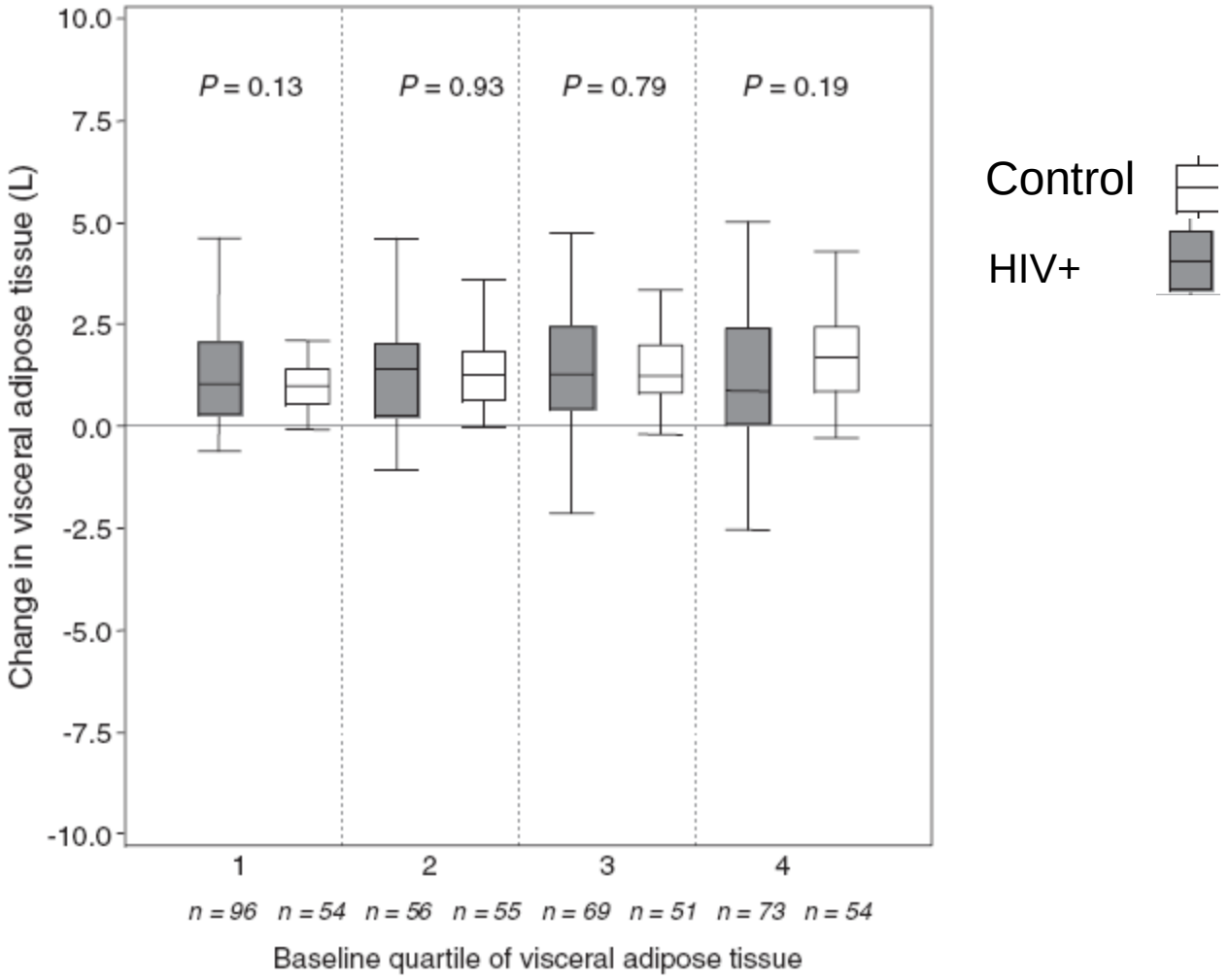
# Fat distribution HIV+ vs control: men



# Change in fat - legs



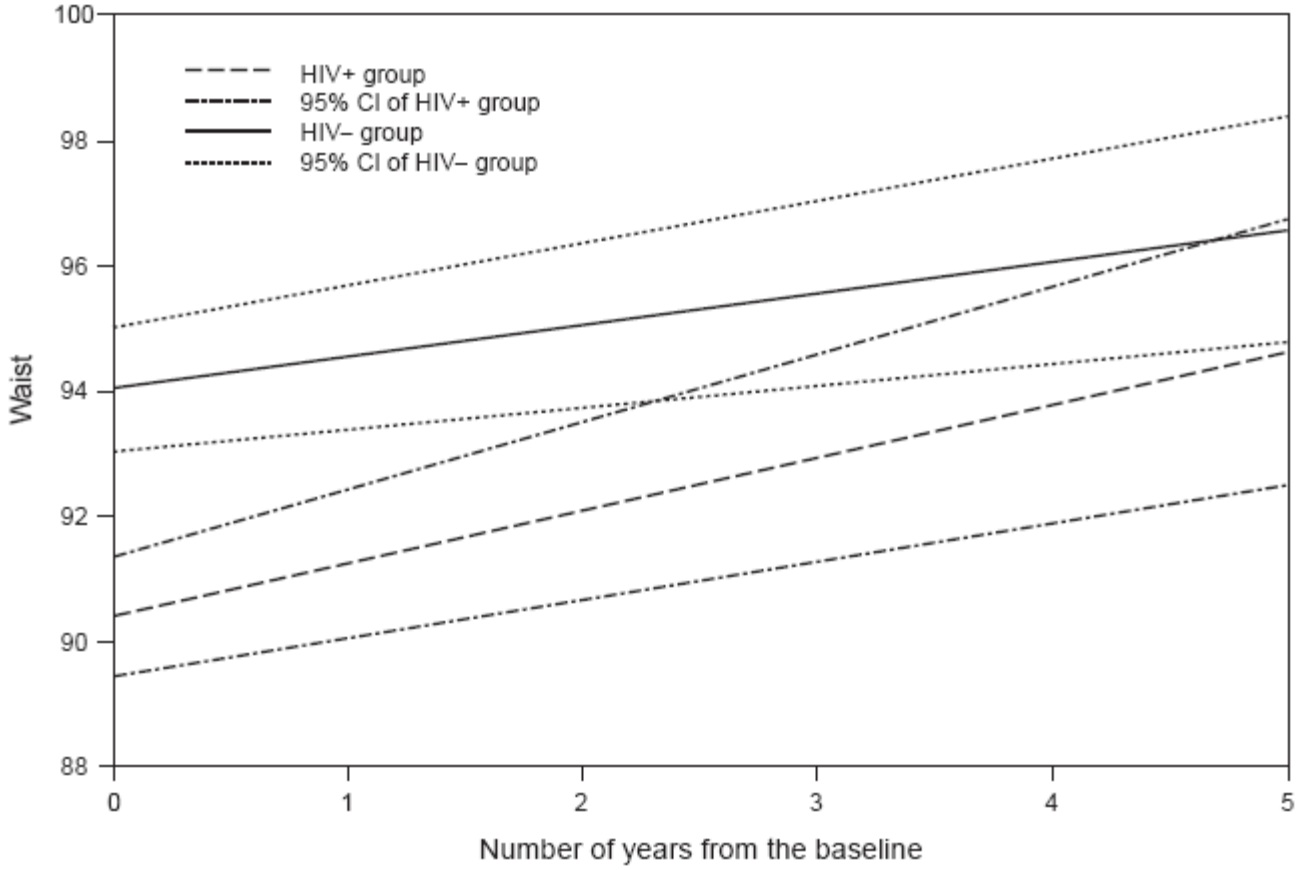
# Change in fat - visceral



# 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




AIDS 2007;21:1731

Loss of subcutaneous fat (from some NRTIs) together with fat accumulation (due to ageing & lifestyle) results in unusual appearance

Atherosclerosis 208 (2010) 222–227

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# Lipodystrophy and anti-retroviral therapy as predictors of sub-clinical atherosclerosis in human immunodeficiency virus infected subjects

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

Adjusted ORs for presence of coronary artery calcium

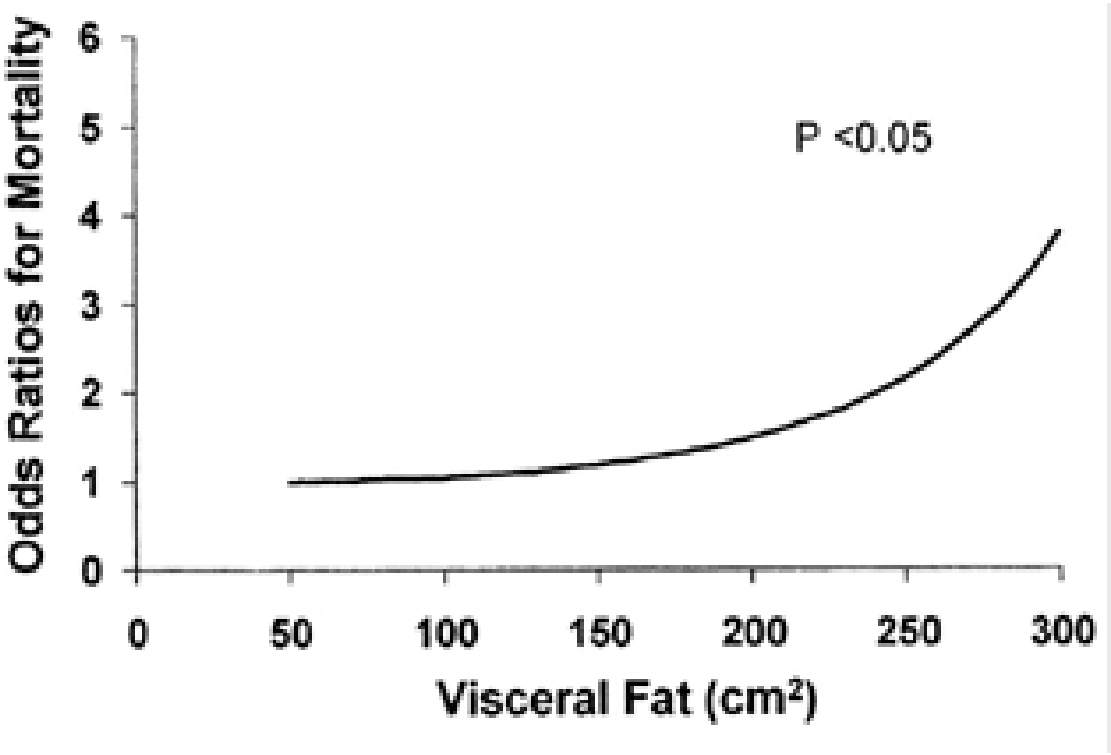
| | |
|---|---|
| Lipoatrophy alone | 3.82 (95% CI: 1.11, 13.1) |
| Fat accumulation alone | 7.65 (95% CI: 1.71, 37.17) |
| Mixed lipodystrophy | 4.36 (95% CI: 1.26, 15.01) |

# 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-




Kuk Obesity 2006;14:336–341

Wednesday October 31 2007 Late Final

# Sowetan

THE SOUL TRUTH www.sowetan.co.za R3.80

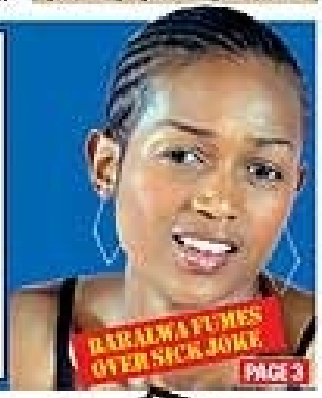


## R70m BONUS FOR PSL BOSSES

PAGE 39

## BAFANA NAME CHANGE POLL RESULTS

PAGE 4



BARALWA FUMES OVER SICK JOKE

PAGE 3

EXCLUSIVE

# HIV MAN GROWS BOOBS

Condition a side-effect of ARVs – medical experts

PAGE 5

Antiviral Therapy 9:511-517

# Gynaecomastia in HIV-infected men on highly active antiretroviral therapy: association with efavirenz and didanosine treatment

*José A Mira[1], Fernando Lozano[2], Jesús Santos[3], Emilia Ramayo[4], Alberto Terrón[5], Rosario Palacios[3], Eva M León[2], Manuel Márquez[3], Juan Macías[1,2], Ana Fernández-Palacín[6], Jesús Gómez-Mateos[2] and Juan A Pineda[1,2]* for the Grupo Andaluz para el Estudio de las Enfermedades Infecciosas (GAEI)*

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.

DOI: 10.1111/j.1468-1293.2010.00831.x

*HIV Medicine* (2010), 11, 603–607

SHORT COMMUNICATION

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

MJ Sikora,[1] JM Rae,[1,2] MD Johnson[3] and Z Desta[4]

[1]*Department of Pharmacology,* [2]*Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA,* [3]*Lombardi Cancer Center and Department of Oncology, Georgetown University Medical Center, Washington, DC, USA and* [4]*Division 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