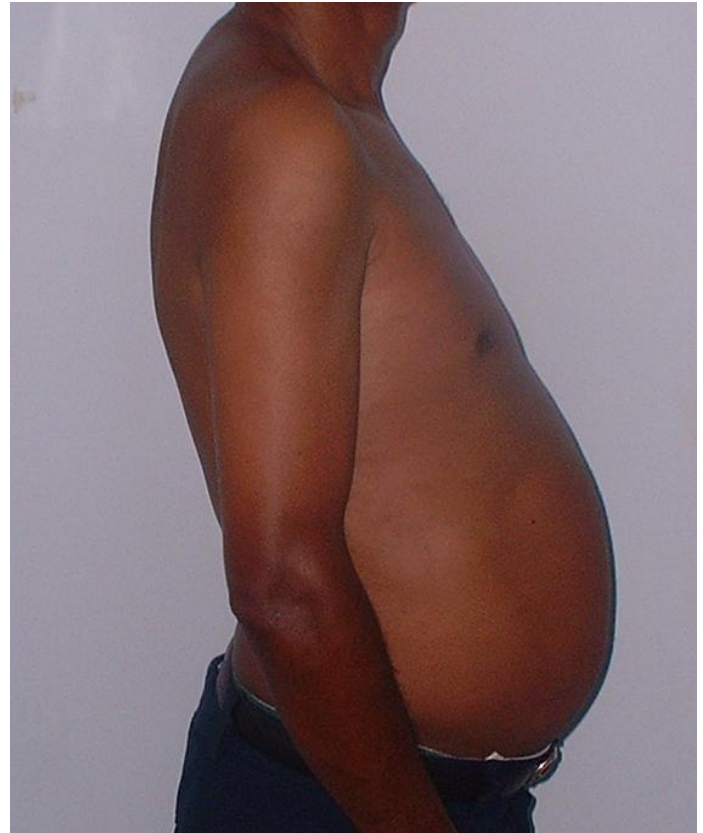


# Fat redistribution on ARVs: dogma versus data

Gary Maartens



# Lipohypertrophy – fat accumulation



# Lipoatrophy – fat loss



# Fat redistribution

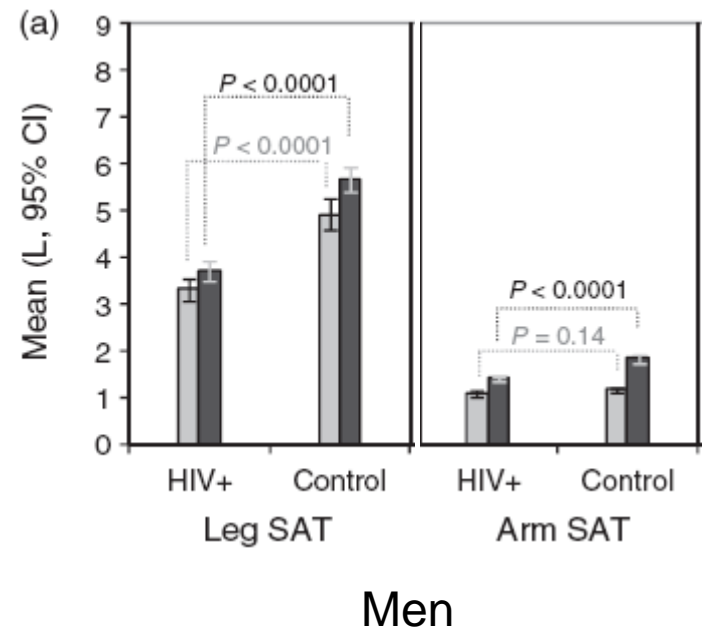
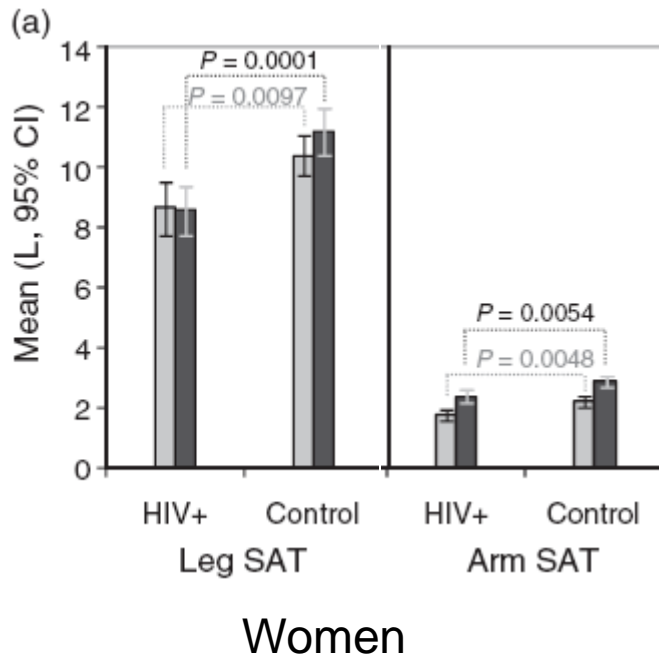
- Fat loss & fat accumulation may occur together or separately
  - Term “lipodystrophy” not clinically useful
- Fat loss:
  - Subcutaneous fat everywhere
  - Most noticed face, buttocks, limbs
- Fat accumulation
  - Visceral fat
  - Buffalo hump
  - Subcutaneous & breasts

# Lipodystrophy questions

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

# Fat loss HIV+ vs controls

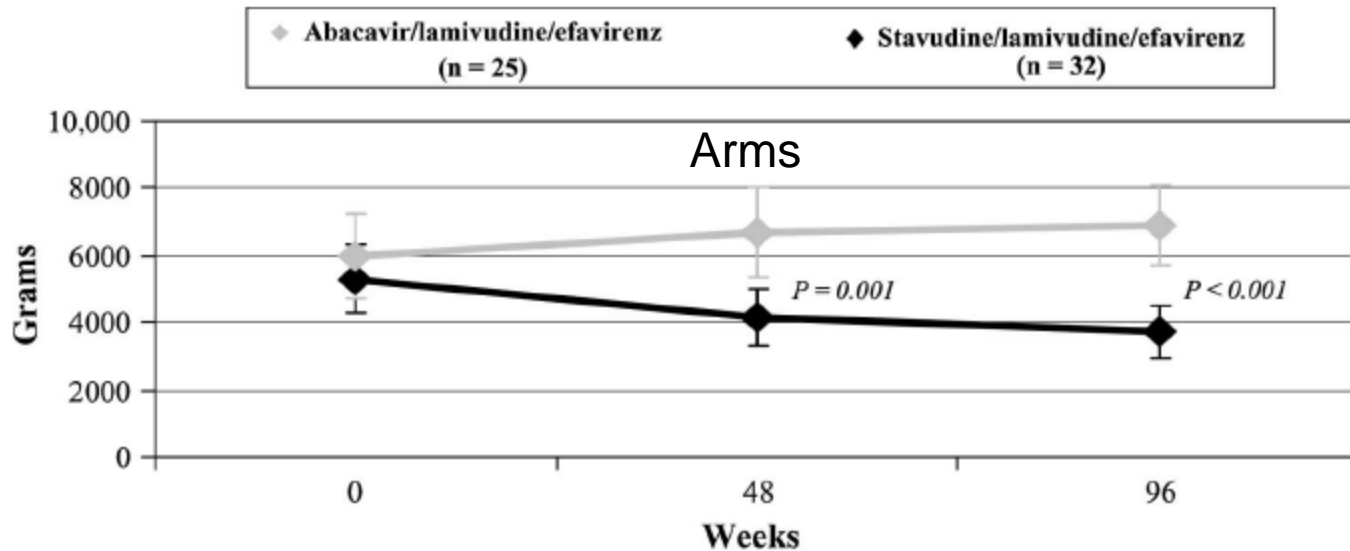
FRAM study: HIV+ (on ART about 5 years at baseline) vs controls  
Age & ethnicity reasonable match, HIV+ men mostly MSM (unknown in controls)  
Fat measured by MRI baseline  & 5 years



# 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, ddl, AZT)
- Genetic predisposition

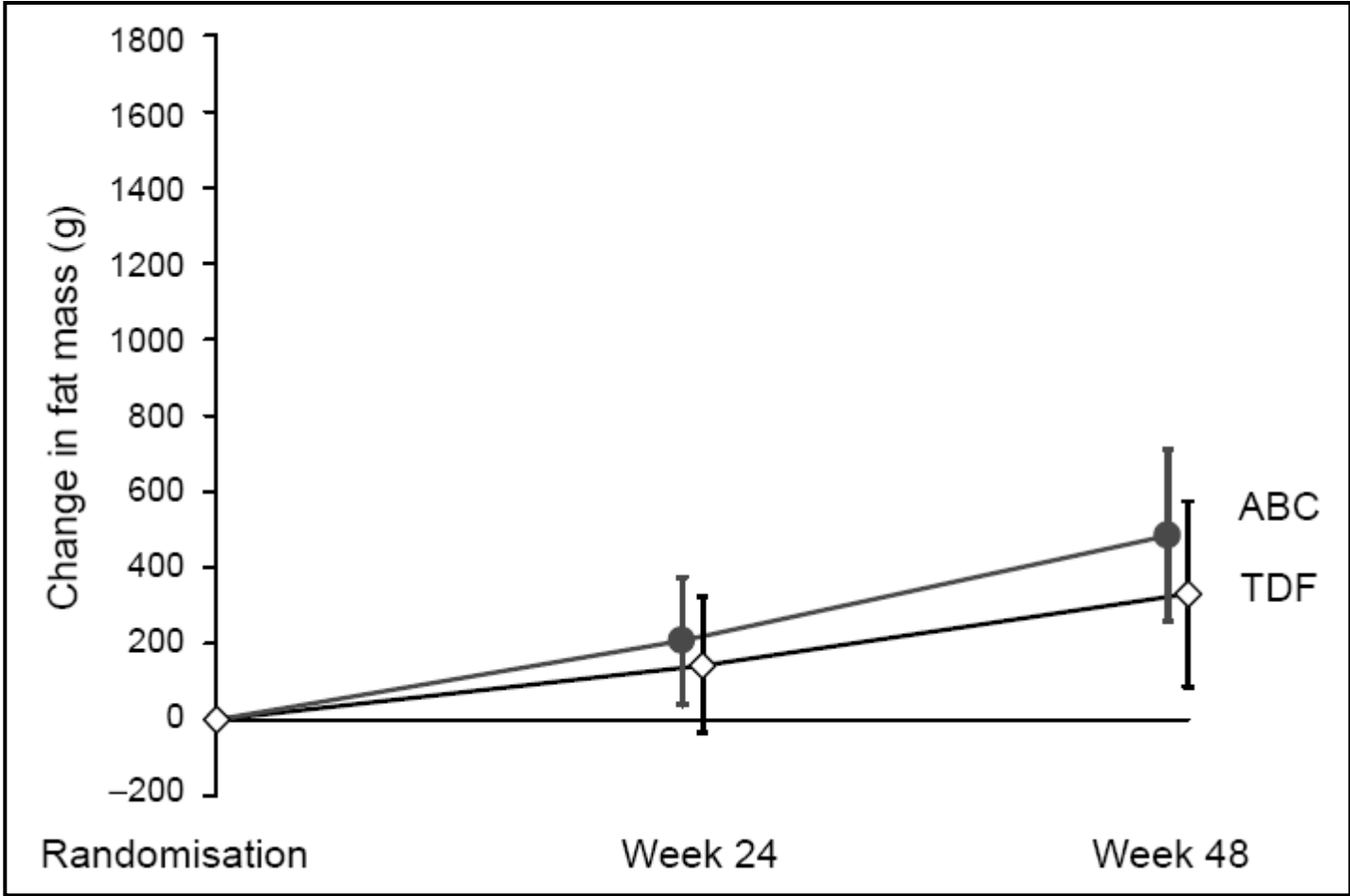
# Fat loss: RCTs of NRTIs



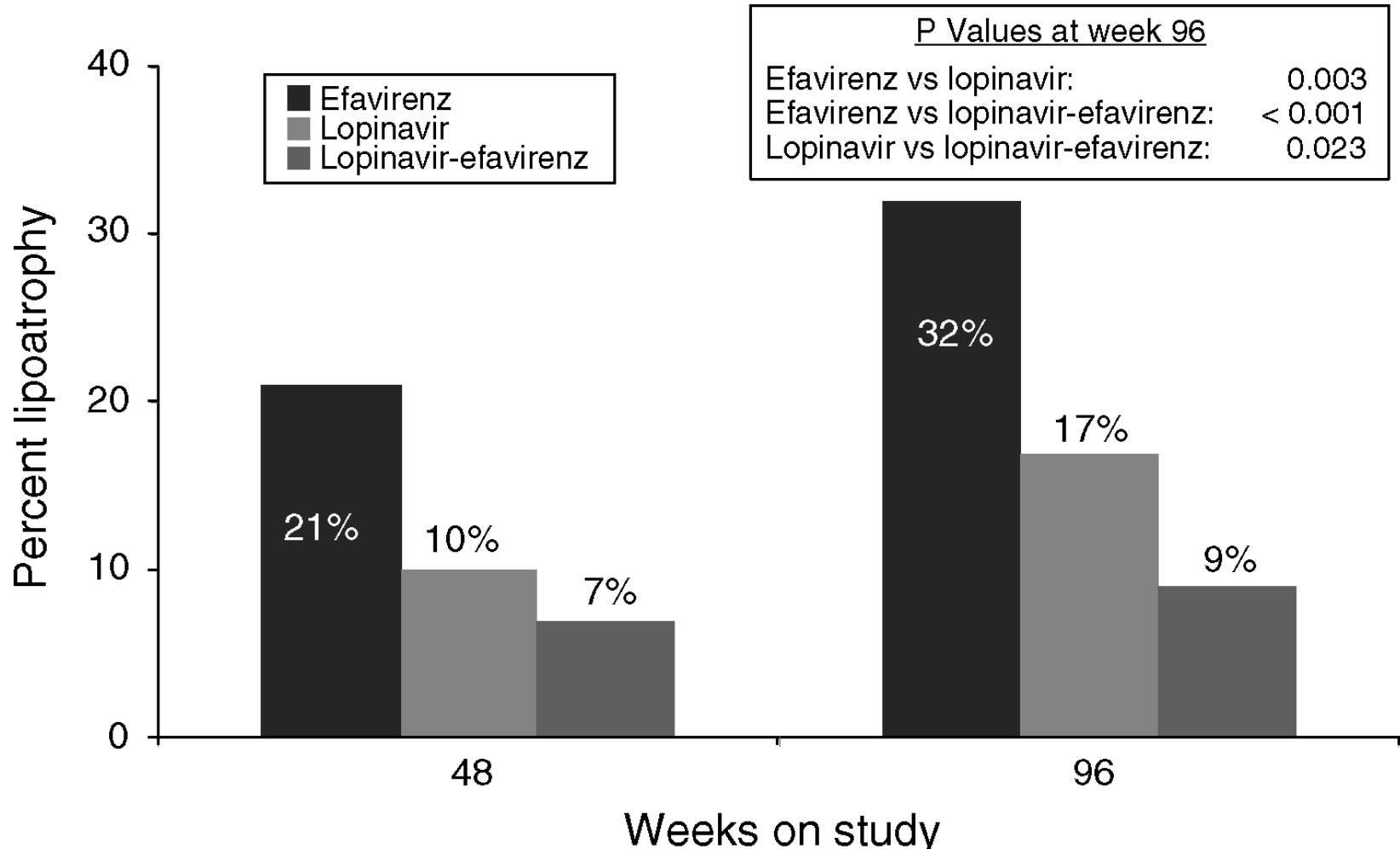
TDF vs d4T @ 96 weeks: total limb fat 7.9 kg vs 5.0 kg (P.001)

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

# Increase in limb fat after switching d4T/AZT



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

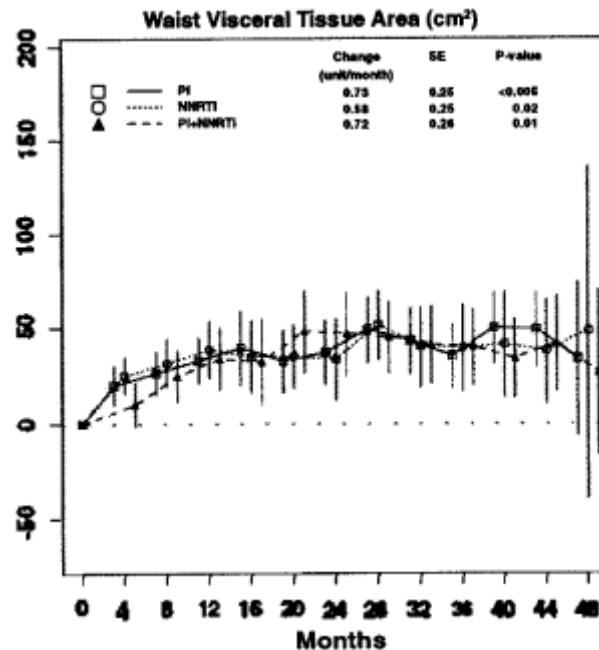


Which ARVs cause fat  
accumulation?

Protease inhibitors implicated in  
initial observations

# FIRST study – visceral fat

RCT: PI or NNRTI + 2NRTIs; or PI+NNRTI  
70% unboosted PI  
n=422 metabolic sub-study



No significant difference by strategy

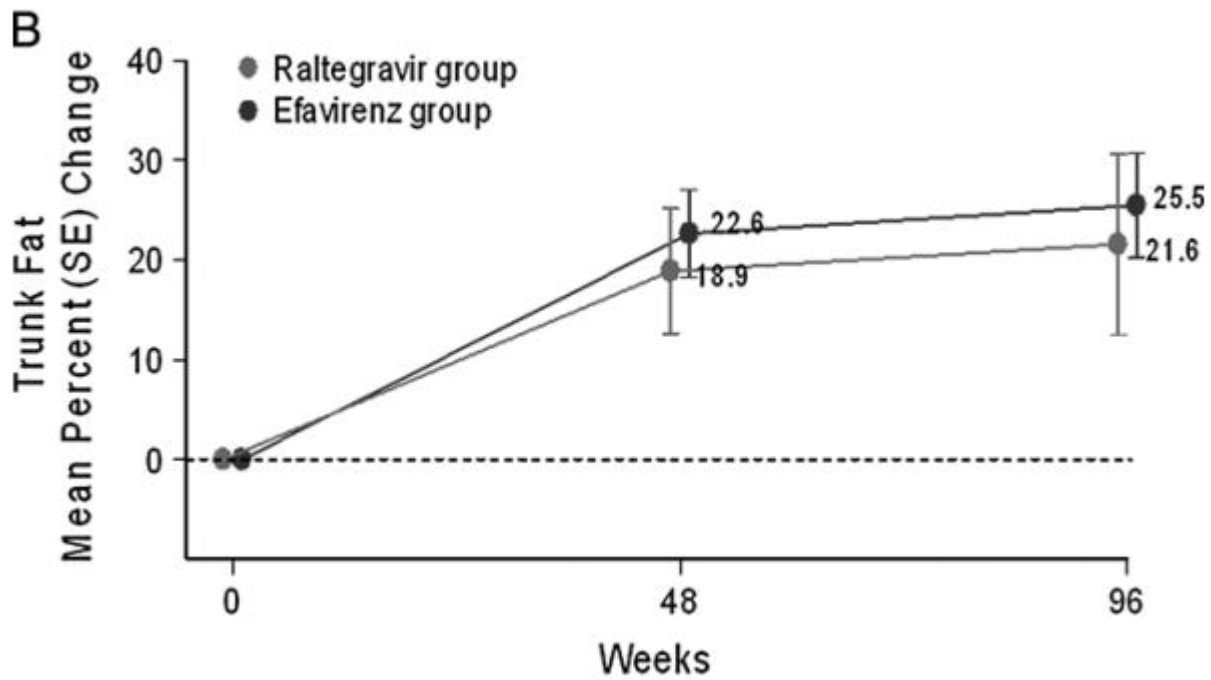
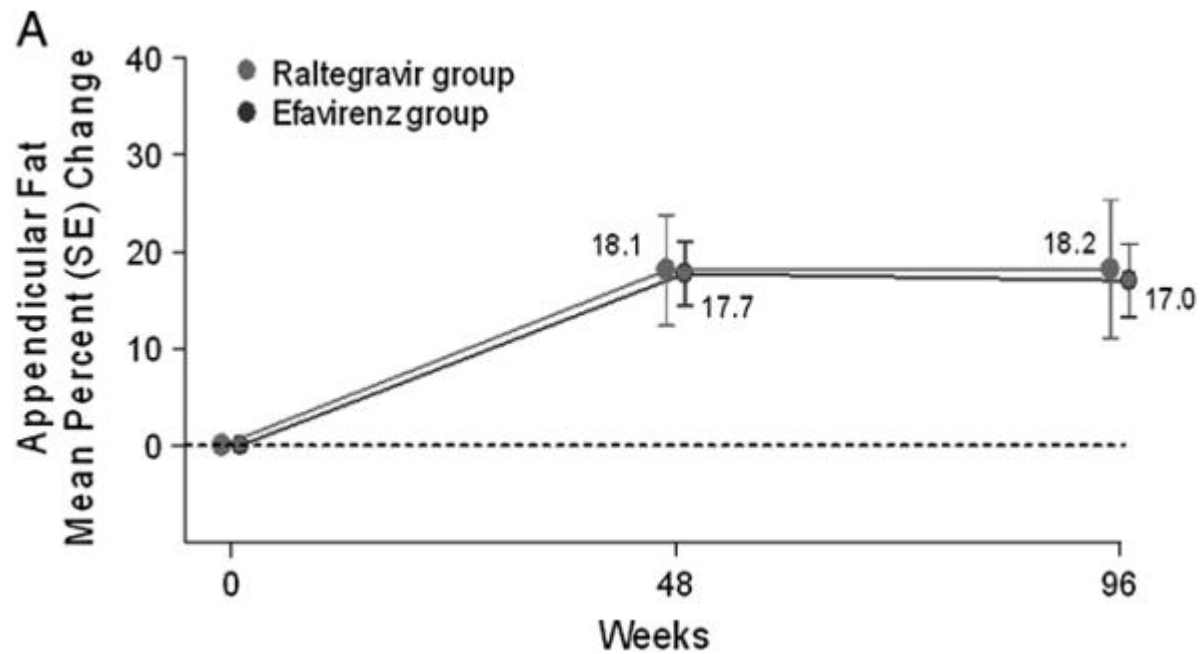
# Fat accumulation:

LPV/r vs EFV (+2 NRTIs) vs LPV/r + EFV

n=753

No significant differences in trunk fat gain at  
weeks 48 or 96

What about raltegravir &  
atazanavir?



# ATV/r vs EFV ACTG5224S

Metabolic sub-study of RCT (n=269):

– TDF+FTC vs ABC+3TC (no  $\Delta$  in fat changes)

– ATV/r vs EFV:

Visceral fat P=0.2

Limb fat P=0.025

Does switching ARVs  
reduce fat gain?

# 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

# Switch to raltegravir

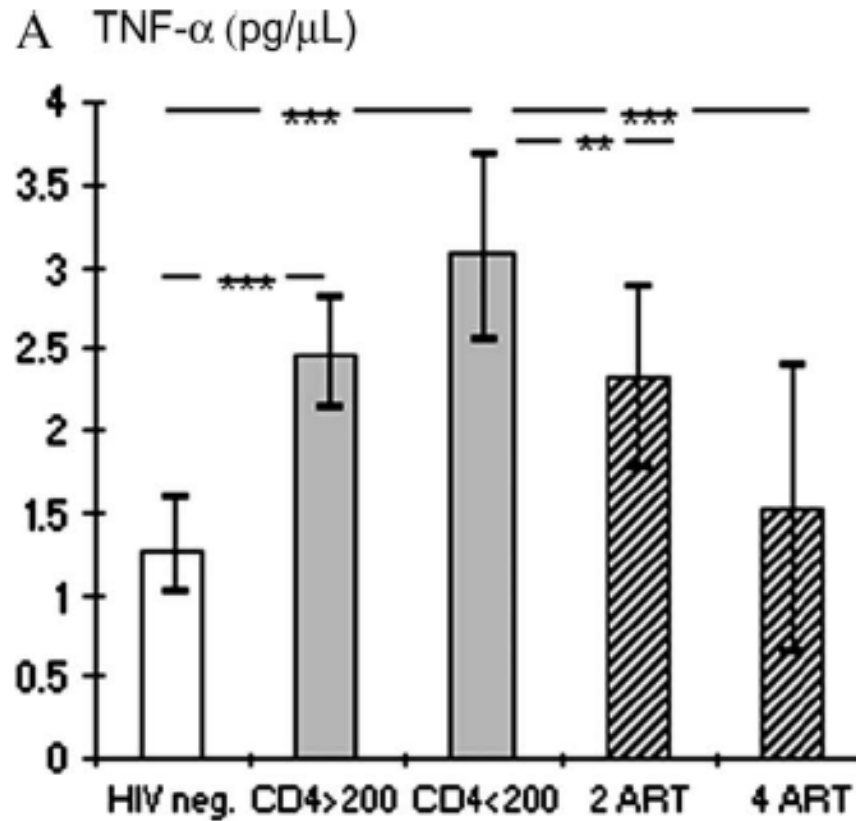
- Women lipohypertrophy on NNRTI or PI/r
- N=39
- No difference at 24 weeks

# Switching ARVs for fat accumulation

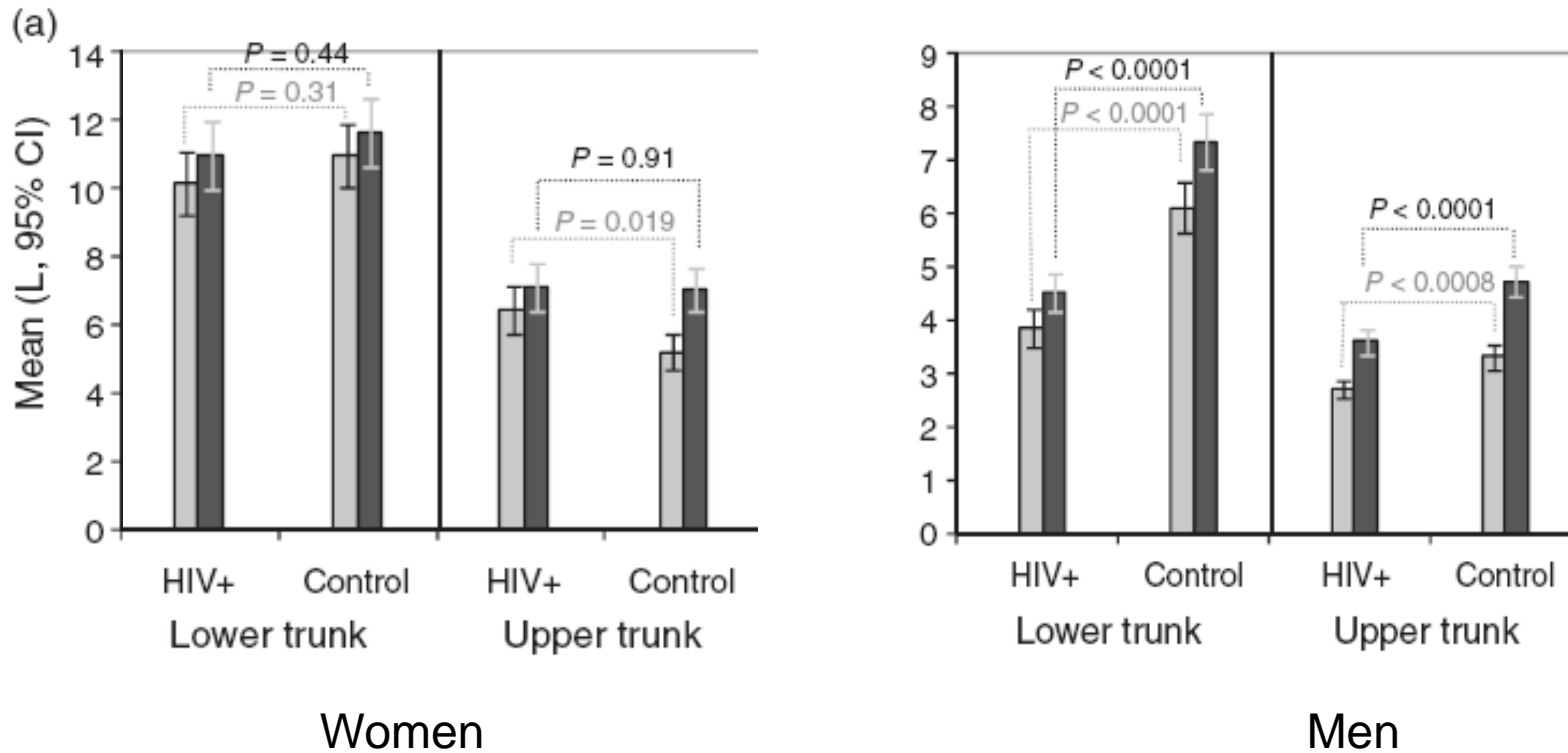
“we do not recommend switching antiretrovirals to combat lipohypertrophy”

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

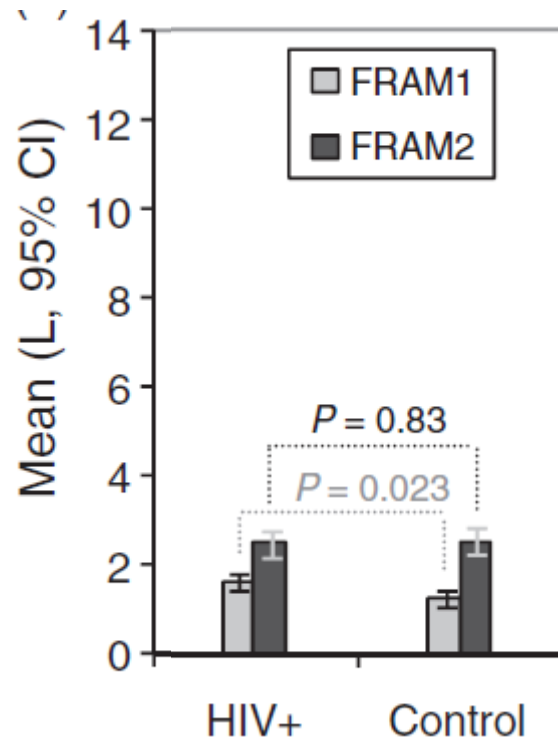
# Effect of ART on pro-inflammatory cytokines causing wasting



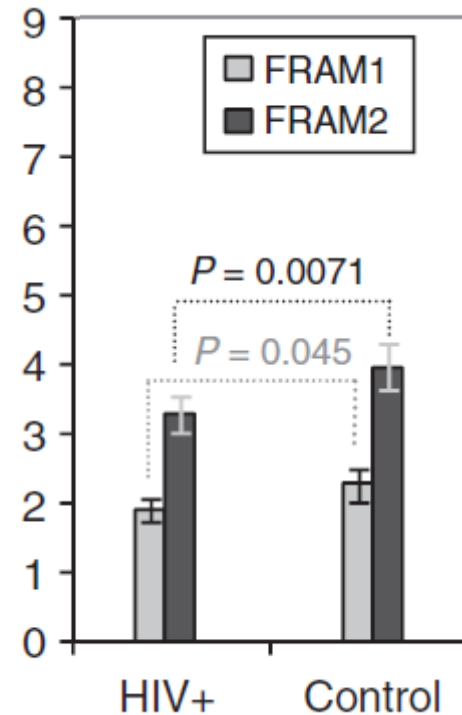
# Trunk fat HIV+ vs controls



# Visceral fat HIV+ vs controls



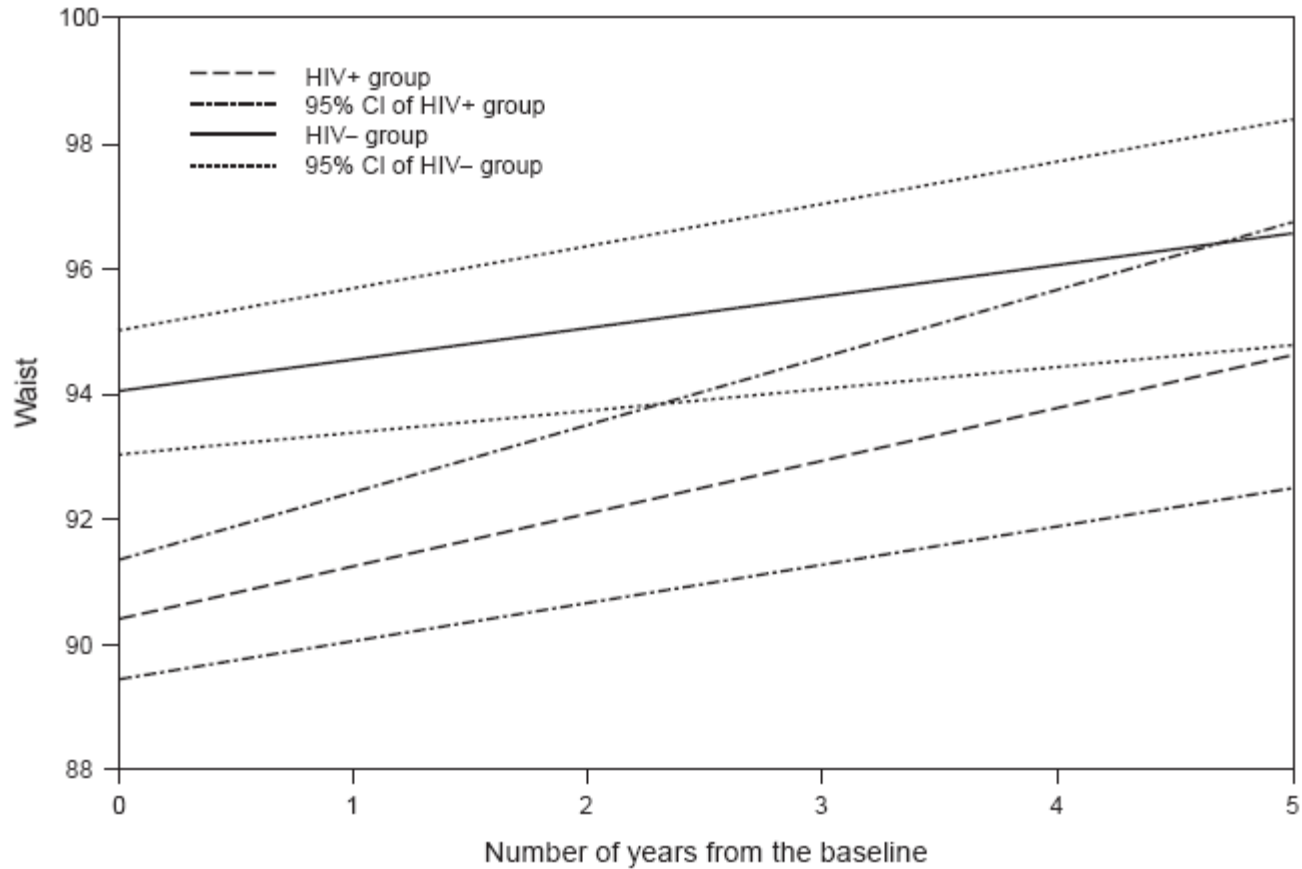
Women



Men

Fat increase in 5 years not significantly different

# MACS – change in waist circumference MSM



# Conclusions – fat loss

- Due to NRTIs that are toxic to mitochondria
- Switching to less toxic NRTIs slowly reverses fat loss
- PIs less associated than NNRTIs (?due to PI's anti-apoptotic properties)

# Conclusions – fat accumulation

- Likely a consequence of treating HIV & not ARV adverse drug reaction
- Loss of subcutaneous fat (from some NRTIs) together with fat gain (due to ageing & lifestyle) results in unusual appearance
- Switching ARVs for fat gain doesn't work & can cause harm