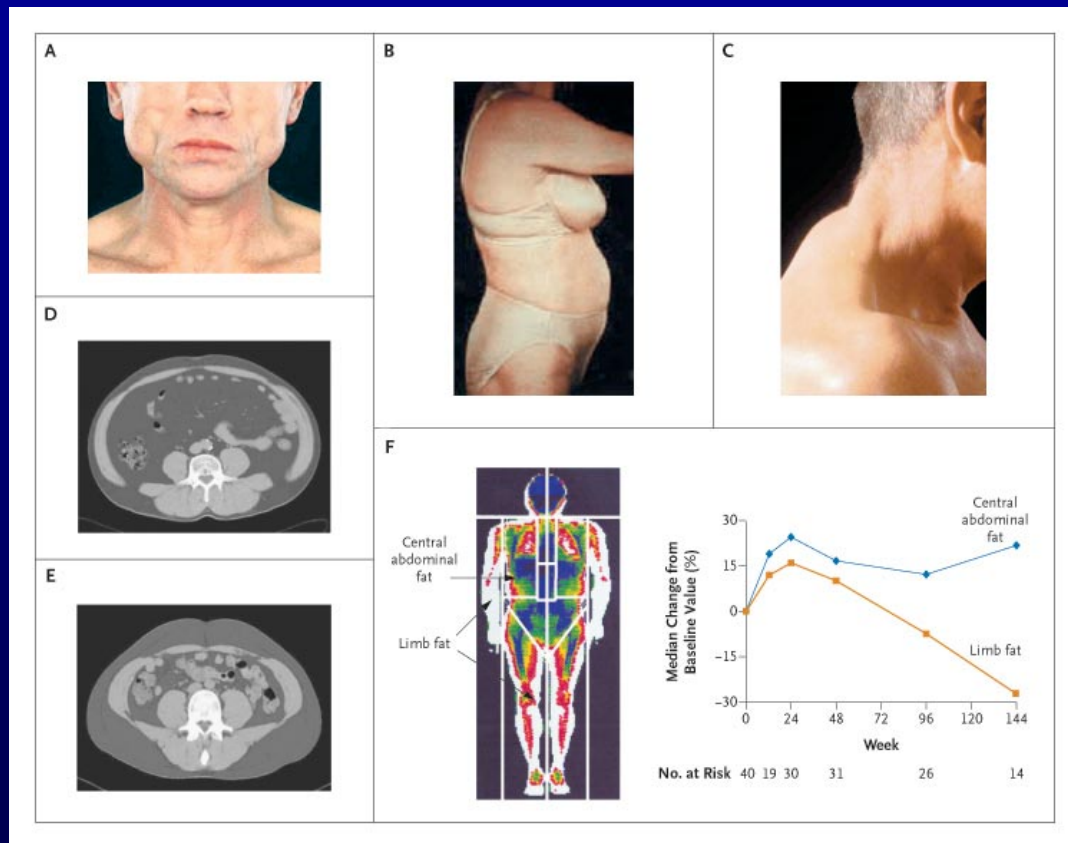


Switch to a PI-Containing/NRTI-Sparing regimen (LPVr/EFV) increases appendicular fat content and serum lipid levels without affecting glucose metabolism or bone mineral density. The results of a prospective randomized trial.
ACTG 5125

P Tebas*, J Zhang, K Yarasheski, S Evans, MA Fischl, A Shevitz, J Feinberg, A Collier, C Shikuma, B Brizz, F Sattler, and the Adult AIDS Clinical Trials Group (AACTG)

Lipoatrophy and Fat Accumulation in HIV-Infected Adults

- Lipoatrophy and fat accumulation are frequent complications of HIV or its treatment



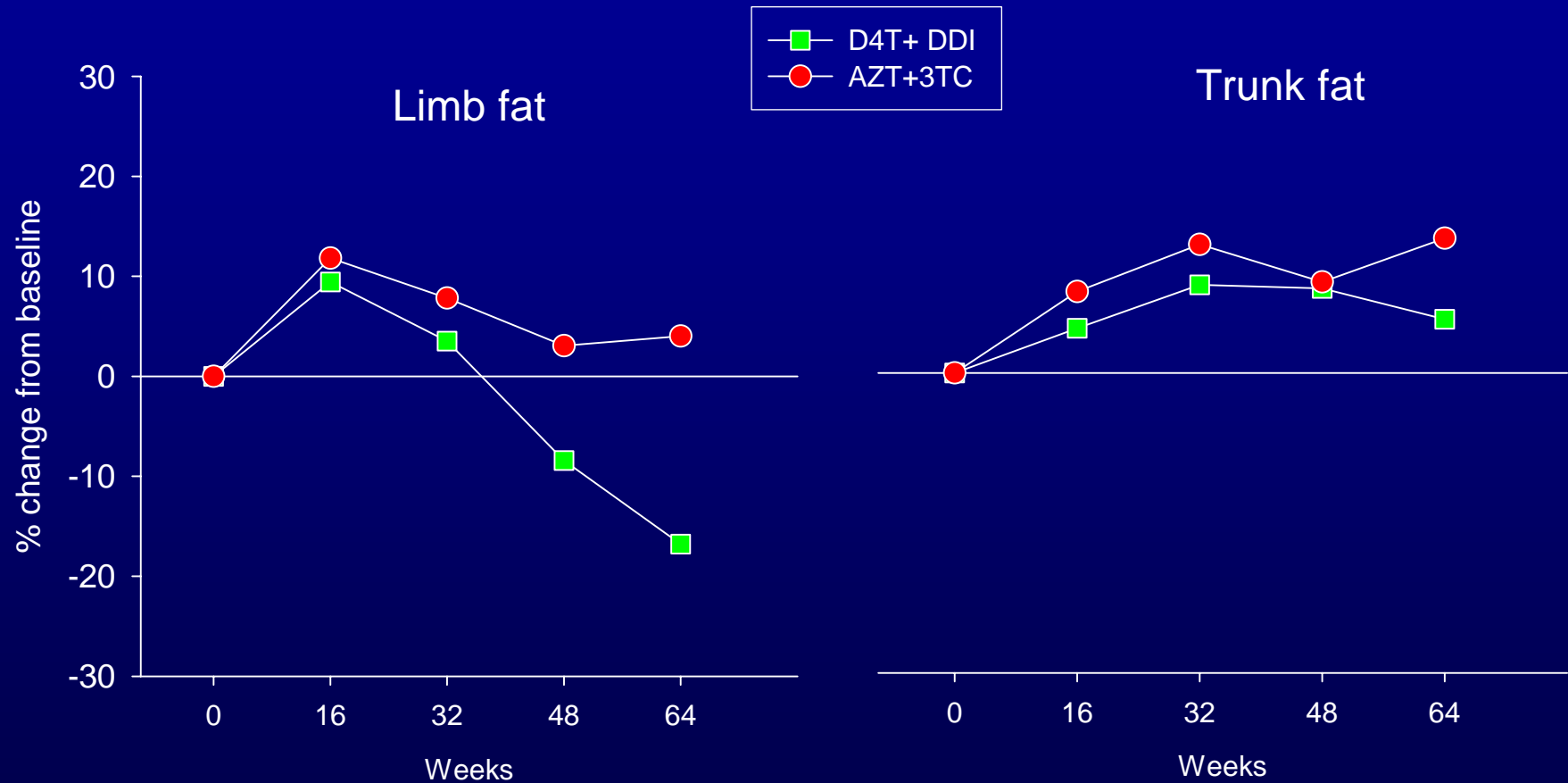
Grinspoon, S. et al. N Engl J Med 2005;352:48-62



The NEW ENGLAND
JOURNAL of MEDICINE

The initiation of ART

ACTG 5005. Changes in body composition according to NRTI assignment in ACTG 384



Lipoatrophy effects

- Negative impact on physical and psychosocial well-being
- Social stigmatization and easy identification as HIV+
- Increased risk of depression
- Decreased self-esteem, daily performance, and sexual and social functioning
- Increases the risk of non adherence
- Increases the cost of treatment
- Probable metabolic consequences

Treatment options for lipoatrophy

Things that work:

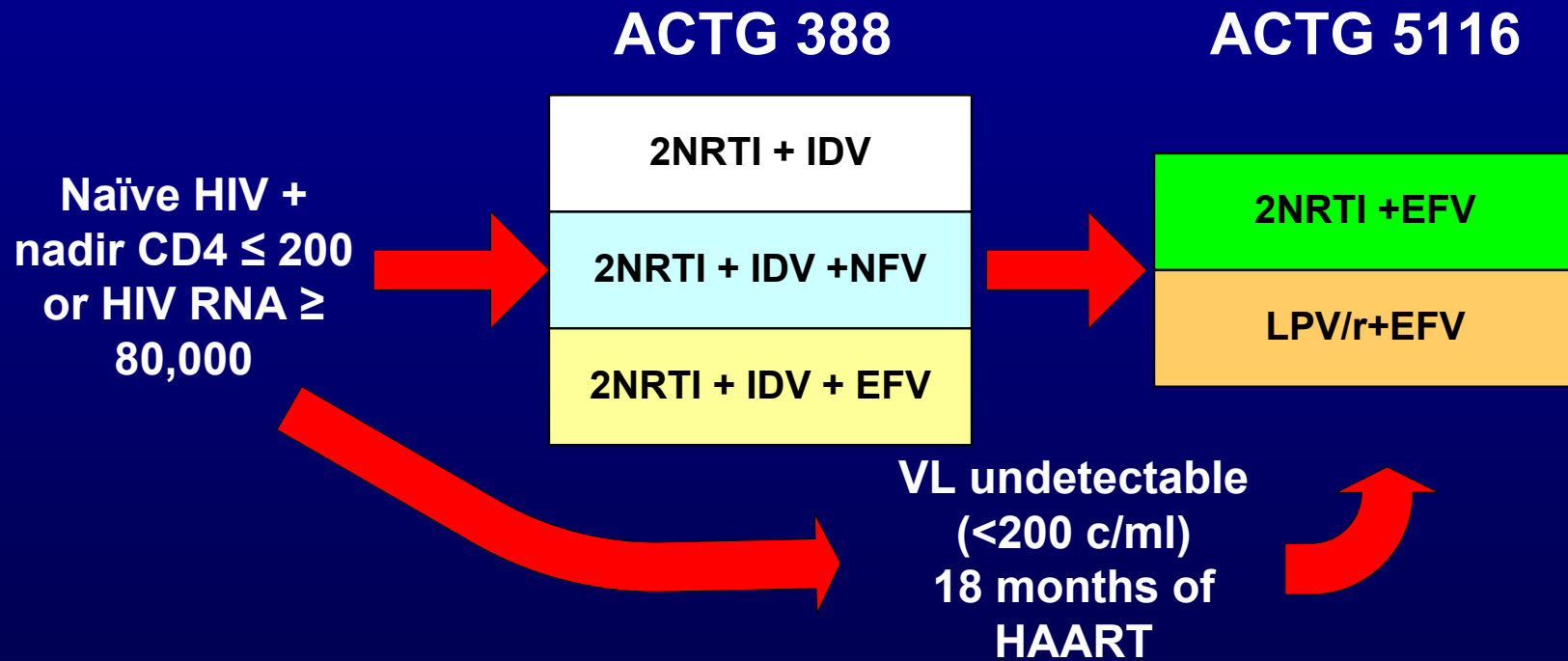
- **Switching NRTIs**
 - **D4T to abacavir or ZDV** (TARHEEL, McComsey, G. CID 2004;38:263-270)
 - **D4T or ZDV to abacavir** (MITOX. A. Martin et al. AIDS 2004;18:1029-1036)
- **Poly-L-lactic acid.**(Sculptra™)
AIDS. 2003;17:2471-2477

Things that do not work:

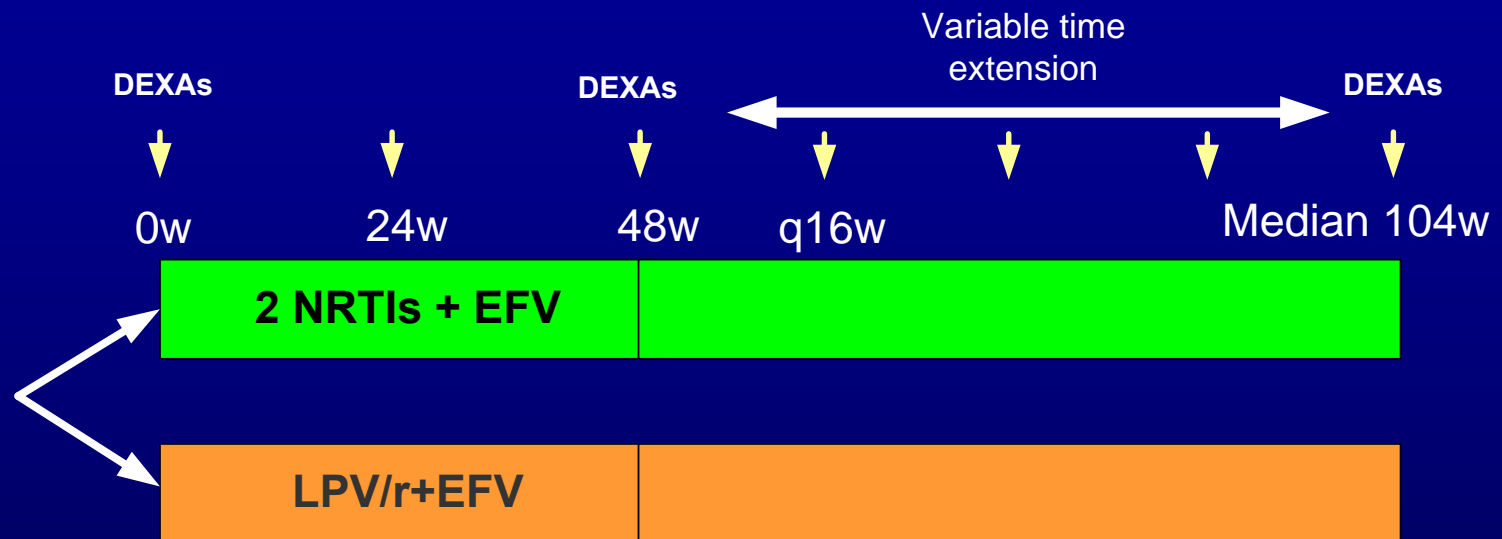
- **Switching PIs** (Tebas P. AIDS Res Hum Retroviruses. 2004;6:589-94).
- **Rosiglitazone** (Carr A. Lancet, 2004; 363(9407):429-38)

Do regimens without NRTIs
increase appendicular fat?

ACTG 5125s



ACTG 5125s. Schema



- Power

- Within arm 86% 0.4 kg ($n=32$, $\alpha=0.05$, $SD=0.65$)
- Between arms >90% 0.6 kg ($n_1=n_2=32$, $\alpha=0.05$, $SD_1=SD_2=0.65$)

Objectives

- **Primary Objective**
 - Examine changes in **appendicular fat** at 48 weeks
- **Secondary Objectives**
 - Examine changes in
 - Lipids (**HDL, LDL cholesterol, total cholesterol, triglycerides, and free fatty acids**)
 - Fasting **glucose, insulin, and HOMA**
 - Regional **bone mineral density** (BMD)
 - **Bone metabolic markers** in serum
 - Examine the **relationship between changes in regional fat** and measures of **fasting lipids and insulin sensitivity**.
 - Explore the association between prior antiretroviral therapy and changes in BMD and regional fat distribution as measured by DEXA

Inclusion/Exclusion criteria

- Inclusion

- Enrollment in A5116
- Signed informed consent document specific to this substudy
- No need for clinical lipoatrophy

- Exclusion

- Uncontrolled hypogonadism.
- Receipt during the last 6 months:
 - Growth hormone (Serostim®)
 - Megestrol acetate (Megace®)
 - Anticytokine agents
 - Ketoconazole (Nizoral®)
 - Systemic glucocorticoids
 - Treatment for osteoporosis
- Cushing's syndrome and American Diabetes Association (ADA)-defined diabetes mellitus.

Status

- 62 patients enrolled, 31 in each arm
- 9 confirmed patients did not complete the study:
 - 7 in the LPV/r + EFV arm (1 death, 5 withdrew consent, 1 other)
 - 2 in the NRTI+EFV arm (1 lost to follow up, 1 other)

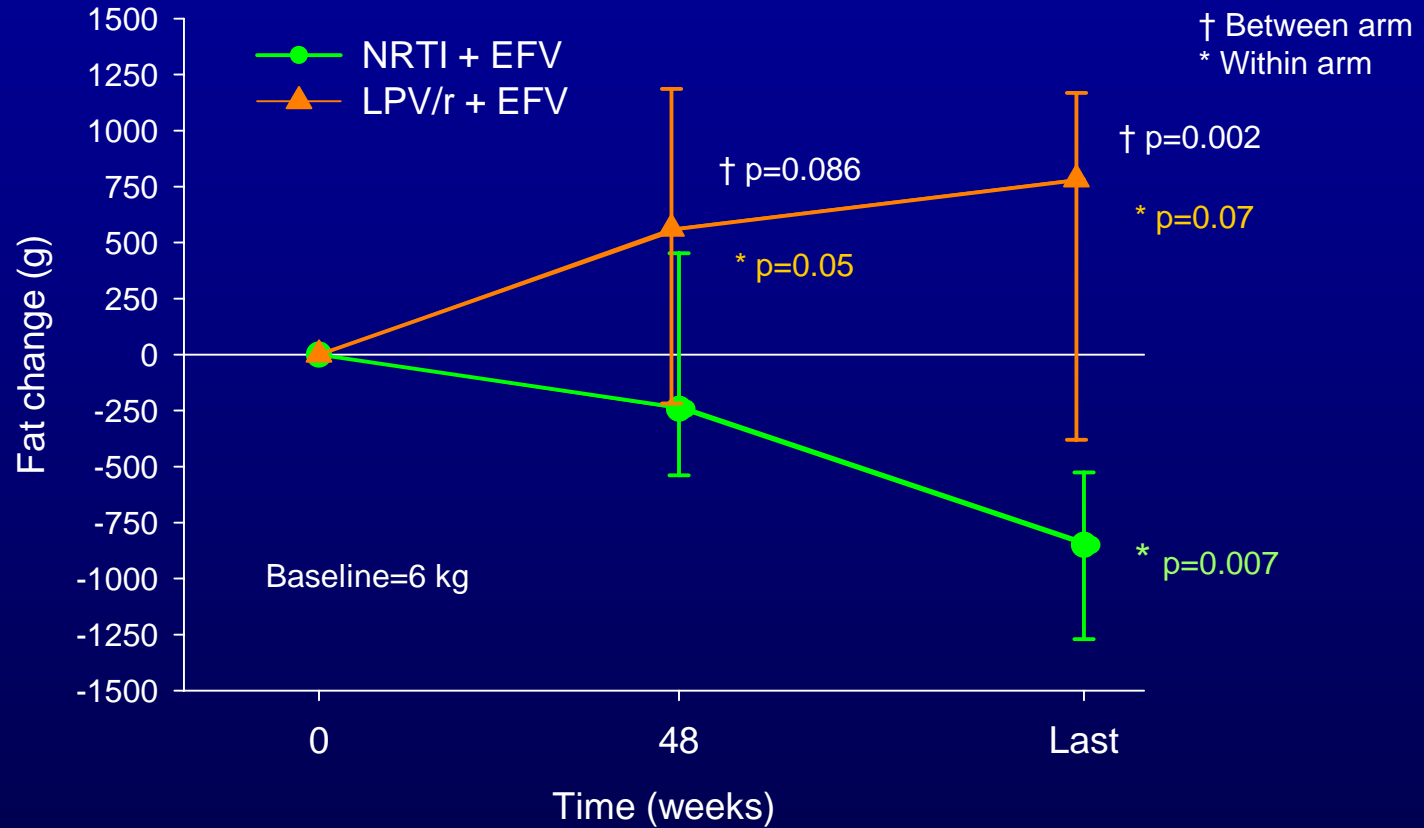
Baseline characteristics

	LPV/r + EFV (n=31)	NRTI + EFV (n=31)	p value
Male %	84	87	NS
Caucasian %	61	58	NS
Hx IVDU %	3	10	NS
Age y (median)	41	42	NS
CD4/ml (median)	431	444	NS
% HIV RNA < 200 c/ml	97	100	NS
% on D4T (n)	19 (6)	25 (8)	NS

- No significant differences at baseline between arms:
 - Glucose metabolism
 - Lipids
 - Fat distribution
 - BMD

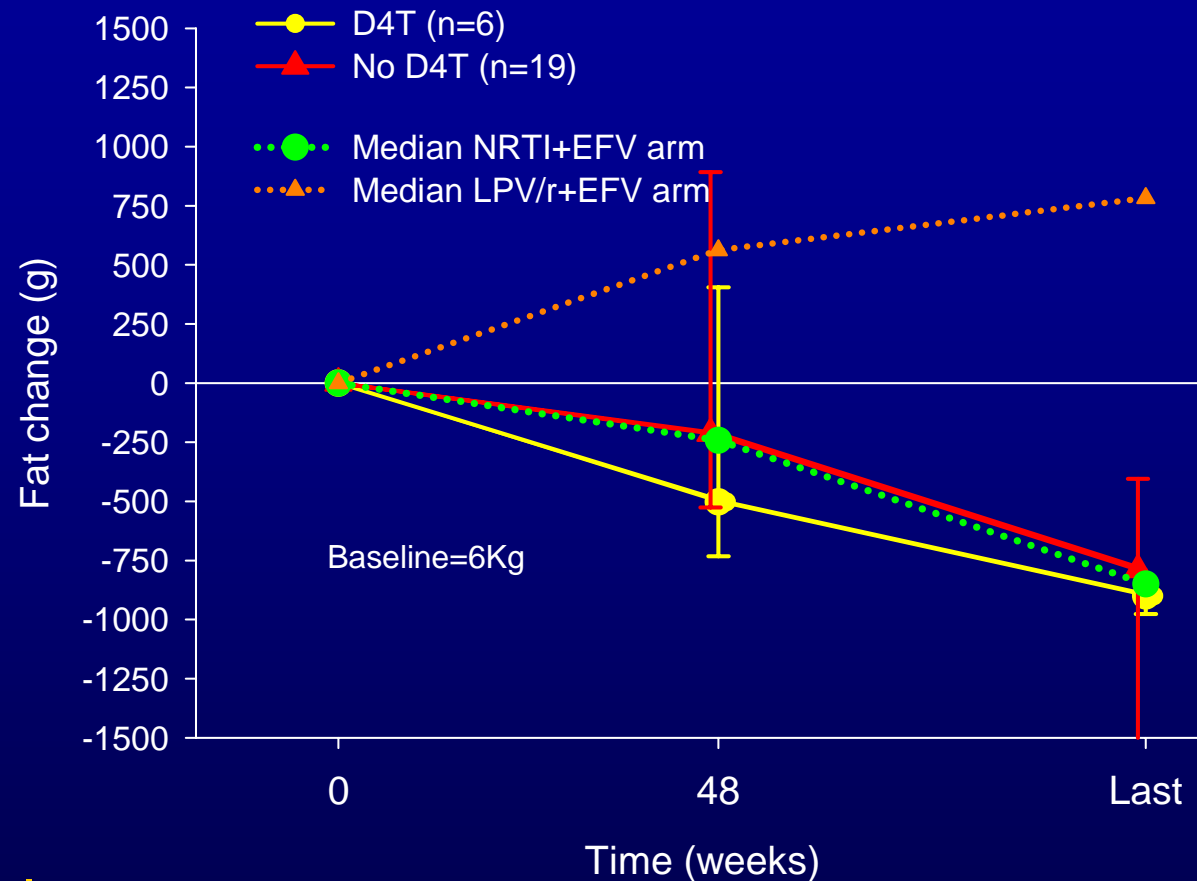
Appendicular fat change

median (IQR) ITT analysis



●	NRTI + EFV	30	25	25
▲	LPV/r + EFV	27	22	22

Is D4T driving the fat loss in the NRTI arm?

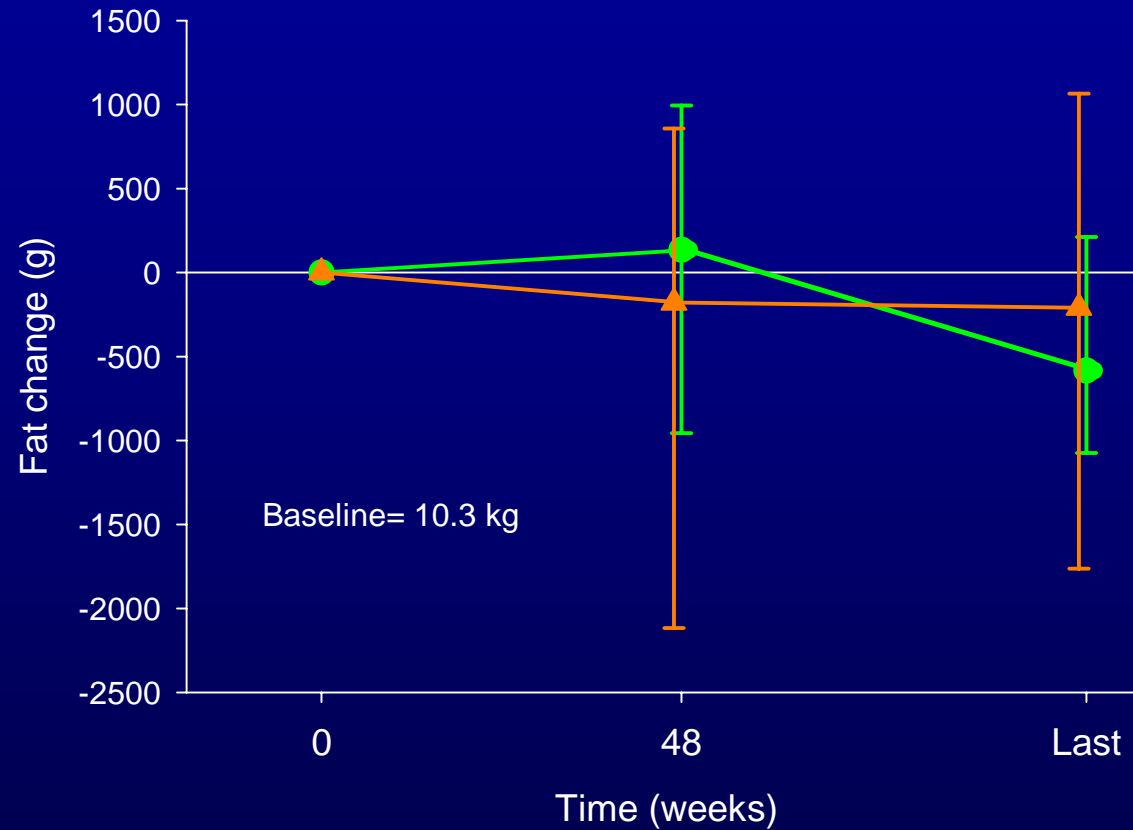


Probably not

Caveat: we were not powered to detect differences within the NRTI groups

Trunk fat change

median (IQR)



- No significant differences between or within arms

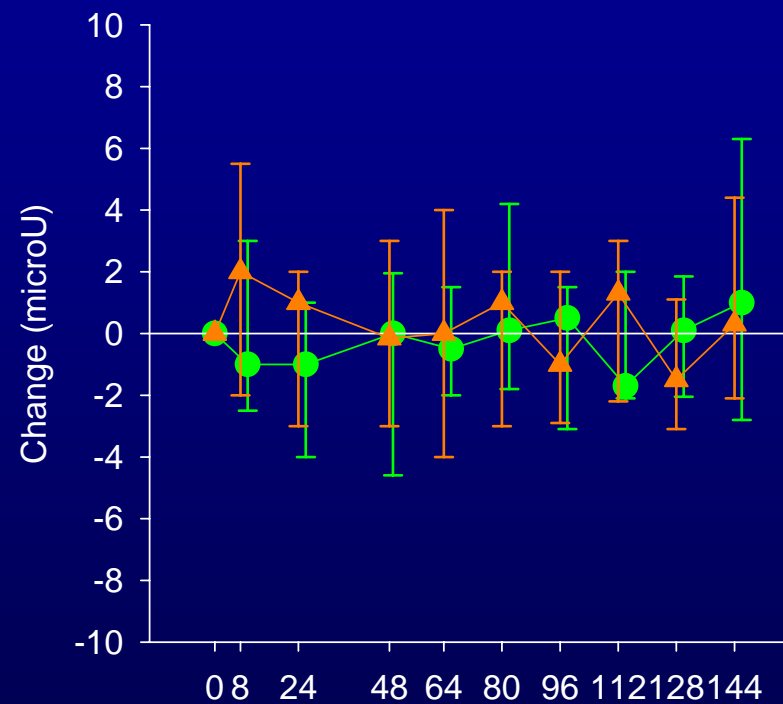
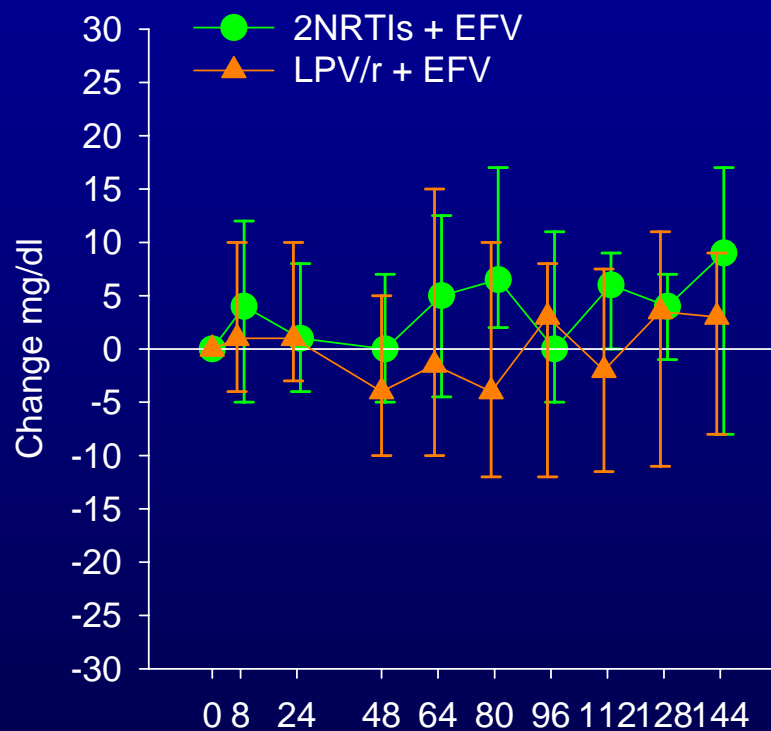
● NRTI + EFV	30	25	25
▲ LPV/r + EFV	27	22	22

Glucose/Insulin

median (IQR)

Glucose

Insulin

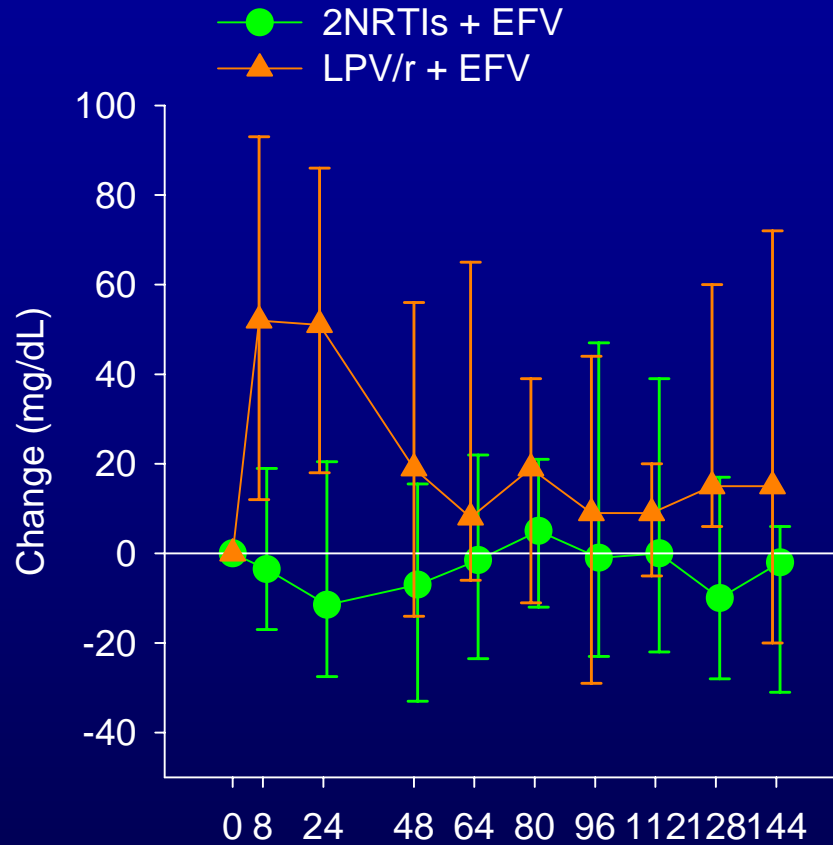


Weeks 30 24 22 2NRTI+EFV
 31 26 17 LPV/r +EFV

- No significant changes from baseline within or between arms

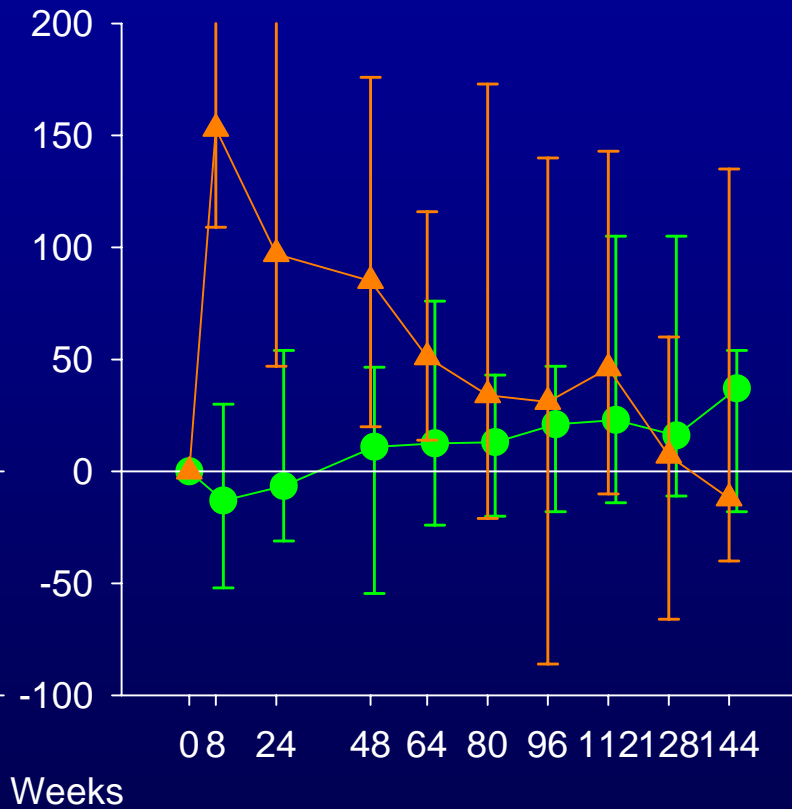
Cholesterol

median (IQR)



Triglycerides

median (IQR)



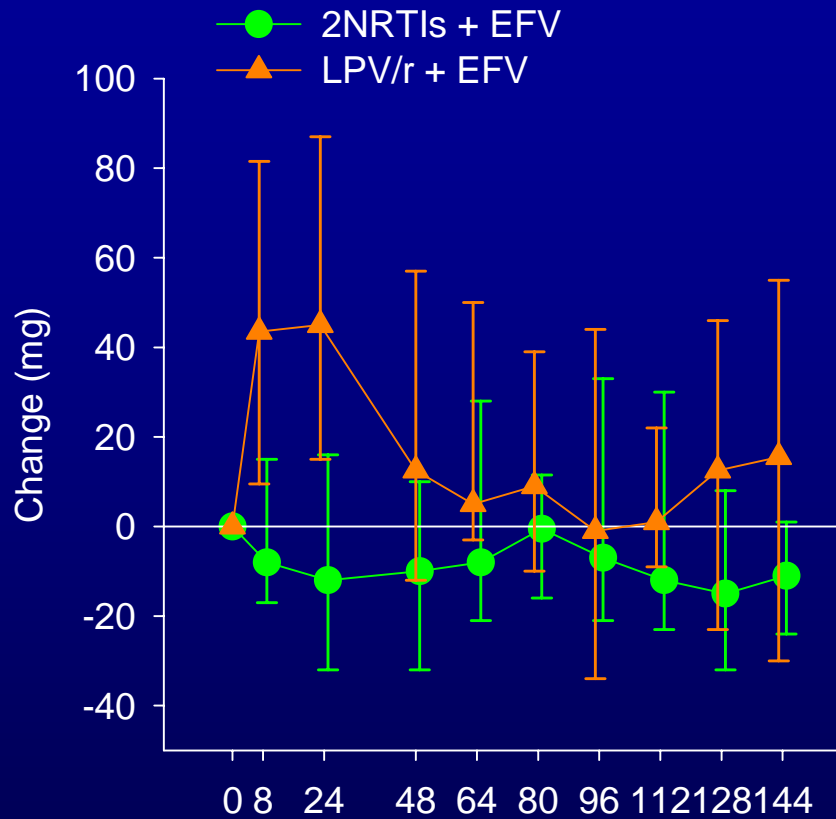
$p < 0.0001$ mixed model
repeated measures ANOVA

31	28	25	2NRTI+EFV
31	25	19	LPV/r +EFV

- LPV/r + EFV had higher cholesterol and TG levels over time

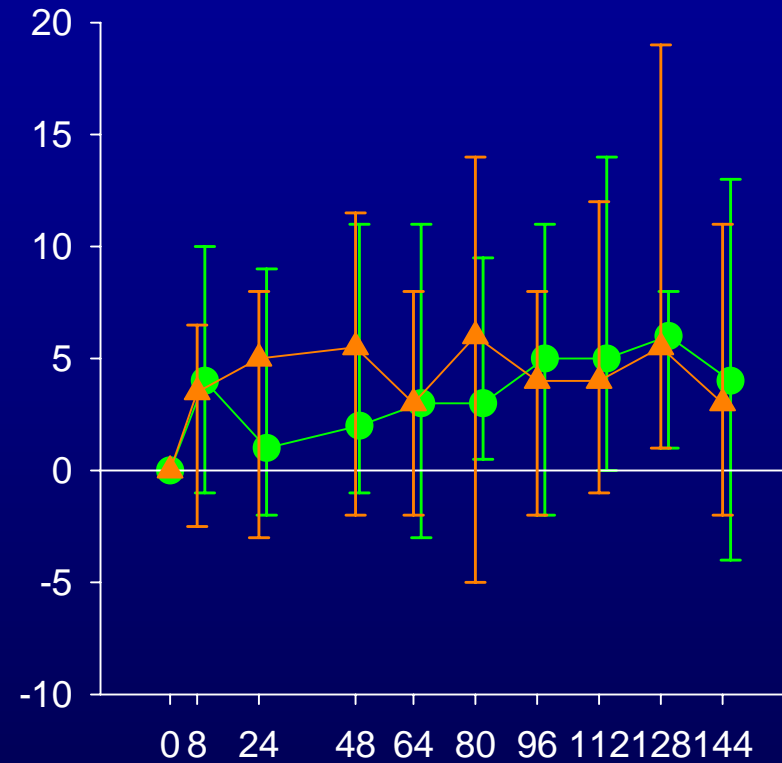
Non HDL-Cholesterol

median (IQR)



HDL cholesterol

median (IQR)



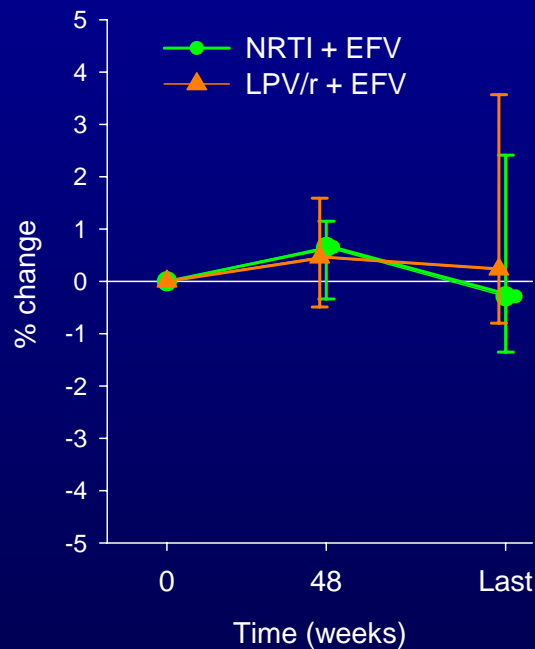
$p < 0.0001$ mixed model
repeated measures ANOVA

Weeks	31	28	25	2NRTI+EFV
	31	24	19	LPV/r +EFV

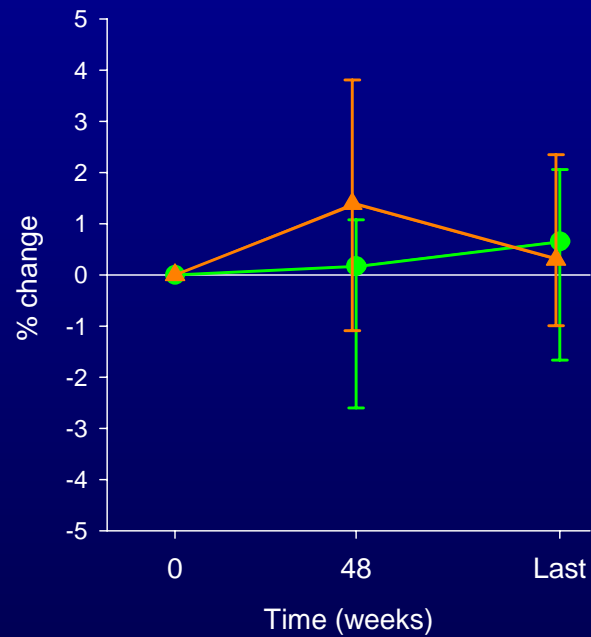
- LPV/r + EFV had higher non HDL cholesterol and both arms moderately increased HDL levels over time

Changes in BMD median (IQR)

Total body BMD



Lumbar spine BMD



● NRTI + EFV
▲ LPV/r + EFV

30	25	25
27	22	22

27	24	24
23	19	19

- 35% of the patients had osteopenia or osteoporosis (lumbar) at baseline
- No significant changes overtime in whole body or regional BMD
- No significant changes on osteocalcin and NTx

Baseline predictors of appendicular fat change

- We evaluated the correlation between baseline predictors and changes in appendicular fat overtime:
 - Baseline appendicular fat
 - Gender
 - Age
 - Race
 - CD4
 - D4T use
- No evidence that baseline variables were associated with changes in peripheral fat

Conclusions

- The switch to a non-NRTI containing combination of LPV/r+EFV was associated with
 - significant improvement in appendicular fat (p=0.08 at 48 weeks and p=0.002 at last observation, median 104 weeks)
 - significant increases in serum lipids
 - stable glucose metabolism
 - stable whole body and regional BMD

Conclusions

- These results provide additional evidence that NRTIs are important in progressive appendicular fat loss that characterizes HIV-lipoatrophy
- The switch to a NRTI-sparing regimen LPV/r + EFV may represent a therapeutic option for patients with lipoatrophy.
- This option has to be balanced with the increased lipids and the trend to increase virologic failure of the LPV/r + EFV regimen
- Please see the presentation of A5116 on Friday (Margaret Fischl Session 37 #162 at 11:30 am)

Acknowledgments

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* $p < 0.001$