

# LIPODYSTROPHY MEETING UPDATE I

## BODY HABITUS ALTERATIONS THERAPEUTICS

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# Regulatory Considerations for the Treatment of Lipodystrophy – Roundtable Discussion - Forum for Collaborative HIV Research

Moderator

Bill Powderly

University College Dublin

Ireland

Forum for Collaborative HIV Research:

Veronica Miller, Ben Cheng

[www.hivforum.org](http://www.hivforum.org)

# FDA PERSPECTIVE

## Safety endpoints for antiretroviral trials

- ◆ Commonly monitored labs (e.g. lipids, glucose)
- ◆ Other labs (e.g. insulin, insulin resistance): look for clinical consequences (e.g. diabetes)
- ◆ Specific morphologic changes (facial wasting, fat loss in limbs, central fat accumulation); “lipodystrophy” too ambiguous for labeling

## Interventions for morphologic abnormalities

- ◆ Objective measurements (CT, DEXA, anthropometry, ultrasound)
- ◆ Indices of clinical relevance (QOL, photographs, biochemical data)

*Overall evaluation of risk/benefit*

# POTENTIAL TREATMENTS FOR MORPHOLOGIC ALTERATIONS

## Lipoatrophy

- ◆ NRTI substitution
- ◆ Thiazolidinediones
- ◆ Surgical implants
- ◆ Uridine????

## Central fat accumulation

- ◆ Diet, exercise
- ◆ Metformin
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# Differential effects of nucleoside reverse transcriptase inhibitor (NRTI) regimens on adipocyte mitochondrial DNA depletion in HIV-infected patients.

Study Groups (n=103 individuals, 147 biopsies)

- (1) HIV(-) controls (n=7)
- (2) ART naive HIV-infected individuals (n=34)
- (3) current zidovudine therapy (n=41)
- (4) current stavudine therapy (n=35)
- (5) non-thymidine analogue therapy (n=25)
- (6) no current therapy (n=7)

Ongoing non-randomised cohort study

Biopsy Procedure

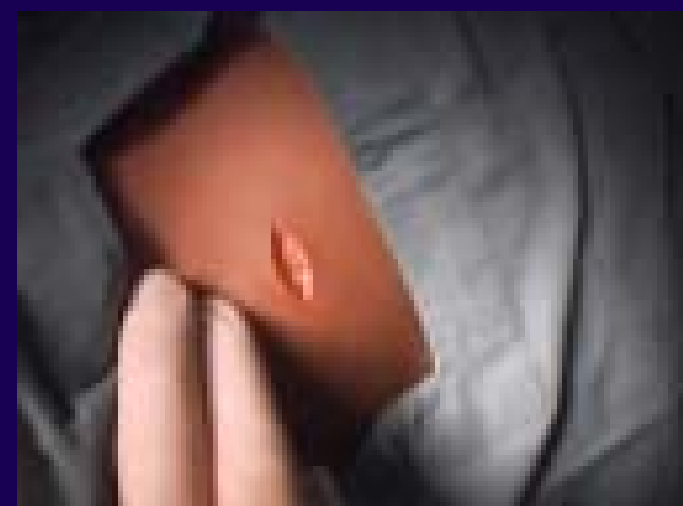
- Excisional biopsy subcutaneous fat (3-5cm incision), suprailiac site
- Fresh frozen tissue -90°C
- Collagenase treatment to remove non-adipocytes

Measurement

- Adipocyte Mitochondrial DNA and adipose tissue (copies/cell) and RNA content (relative to GAPDH) determined using quantitative real-time PCR (ABI Prism 7700)<sup>1,2</sup>

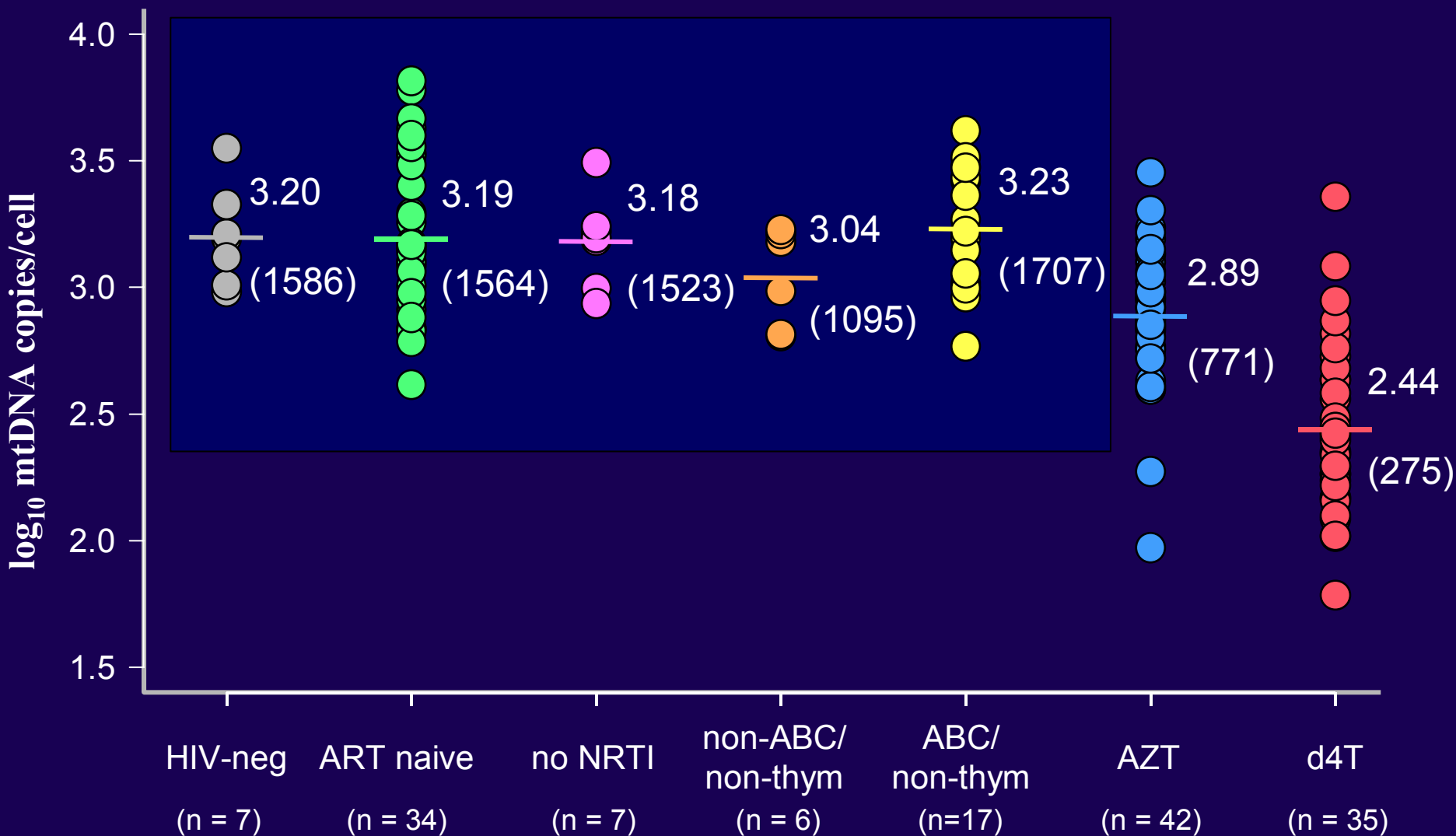
Statistical analysis

- Log transformed data analysed using linear mixed effects models



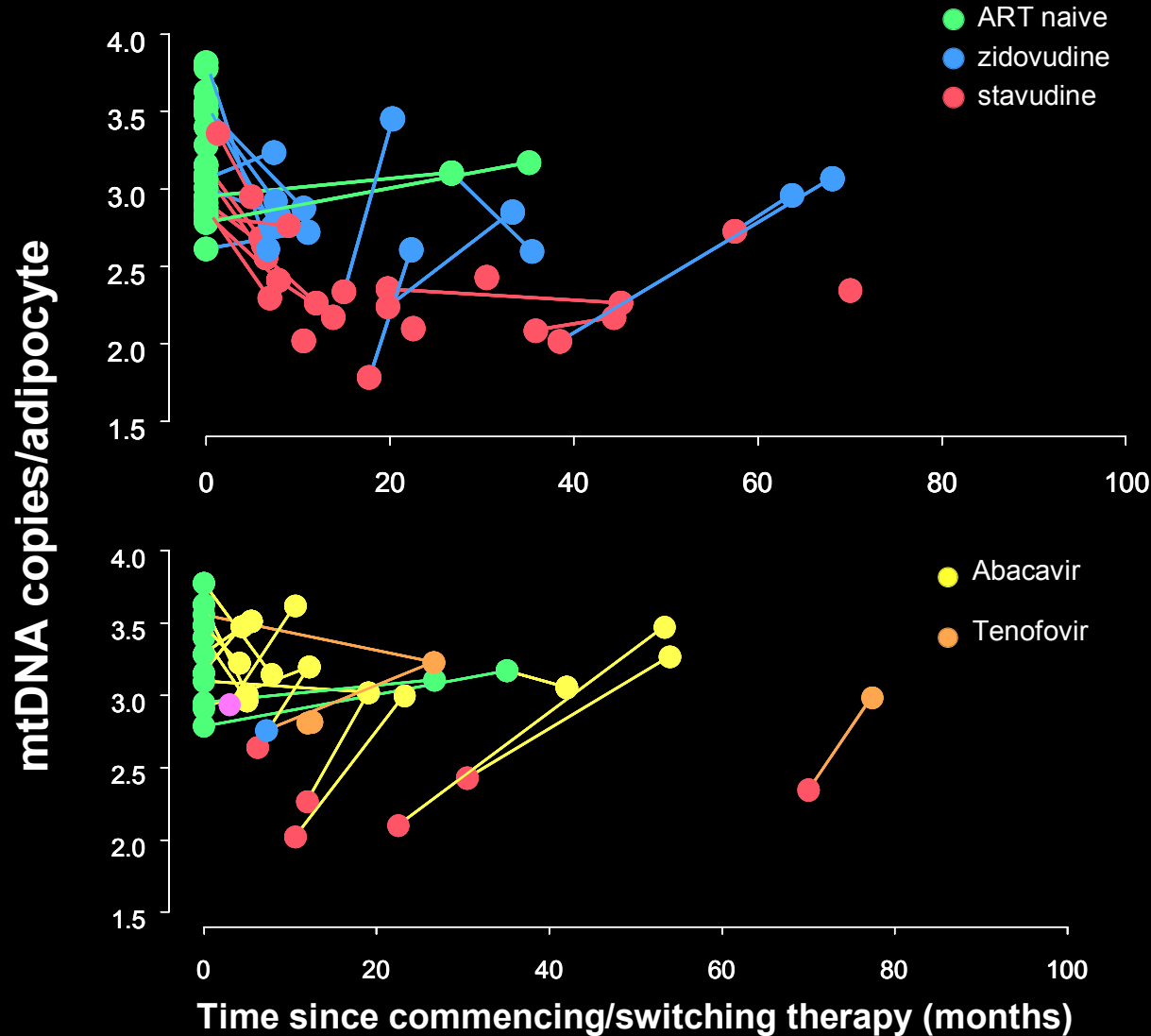
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*Nolan et al, Abstract 16*



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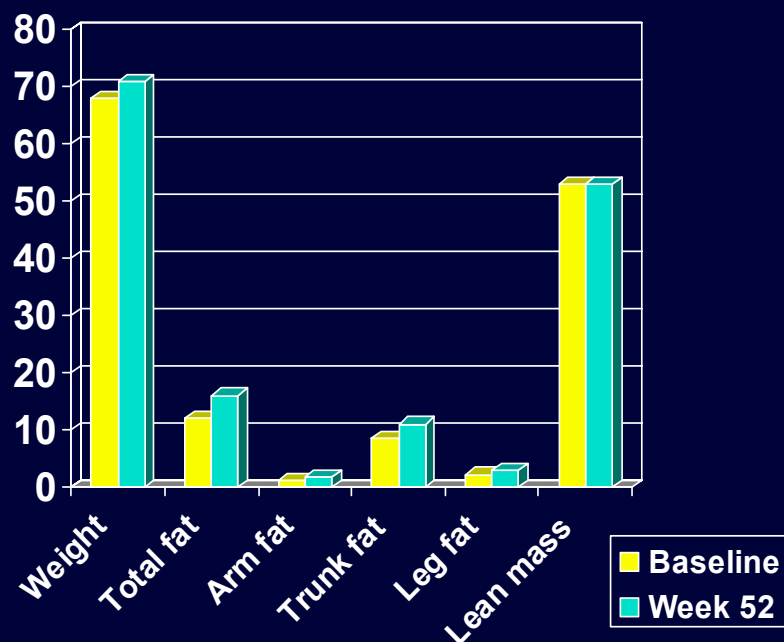


**Switching NRTI therapy associated with normalization of adipocyte MtDNA content over 3-12 months**

# SWITCH STUDIES

Stavudine switching (to abacavir or ZDV) beneficial for lipoatrophy: *statistically significant but not perceptible*

(MITOX and TARHEEL studies; *Martin AIDS. 2004;18:1029-36; McComsey Clin Infect Dis. 2004;38:263-70*)



n=10 (7M, 3F; age  $42 \pm 7.3$  yrs)

d4T → TDF switch (7 PI+)

52 weeks follow-up

Results: significant increase in:  
weight (+3.5kg, P=0.01)  
total fat (+3.7kg, P=0.004)  
arm fat (+0.5kg, P=0.03)  
trunk S/C fat (2.5kg, P=0.002)

*but not* leg fat (+0.7kg, P=0.08)  
Lean mass (+0.1kg, P=0.7)

# Uridine improves adipocyte morphology and mitochondrial membrane potential

# “Uridine abrogates the adverse effects of stavudine and zalcitabine on adipose cell functions”

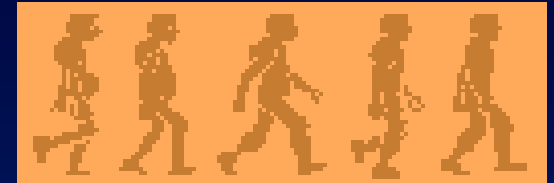
*Walker Abstract #14*

Uridine had no intrinsic effects on adipocyte functions.

Concurrent administration of “..uridine almost totally prevented the effects of d4T and ddC on...”

- increased apoptotic cell death
- decreased lipid content
- altered cell morphology
- loss of mitochondrial membrane potential
- mtDNA depletion and
- loss of mtDNA-encoded respiratory chain units

**Clinica Metabolica**  
**dell'Università degli Studi di Modena**



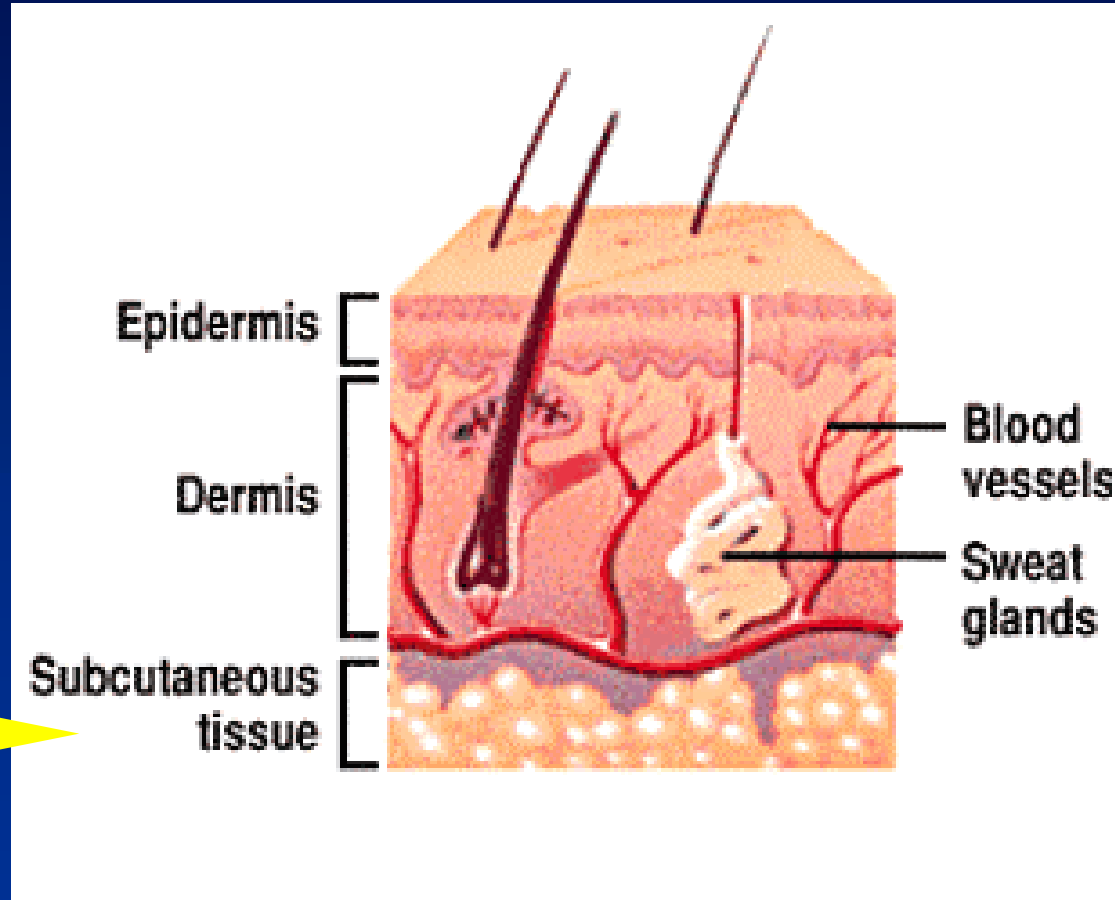
Guaraldi G, Orlando G, De Fazio D, Callegari M, De Santis G, Pedone A, Spaggiari A, Baccarani A, Pinelli M, Borghi V, Nardini G, Beghetto B, Esposito R.

**PROSPECTIVE, PARTIALLY RANDOMIZED, 24 WEEK  
STUDY TO COMPARE THE EFFICACY AND  
DURABILITY OF DIFFERENT SURGICAL TECHNIQUES  
AND INTERVENTIONS FOR THE TREATMENT OF  
HIV-RELATED FACIAL LIPOATROPHY**

# PROSPECTIVE, PARTIALLY RANDOMIZED, 24 WEEK STUDY TO COMPARE INTERVENTIONS FOR HIV- RELATED FACIAL LIPOATROPHY

Autologous fat transfer  
(Coleman's technique)

N=24

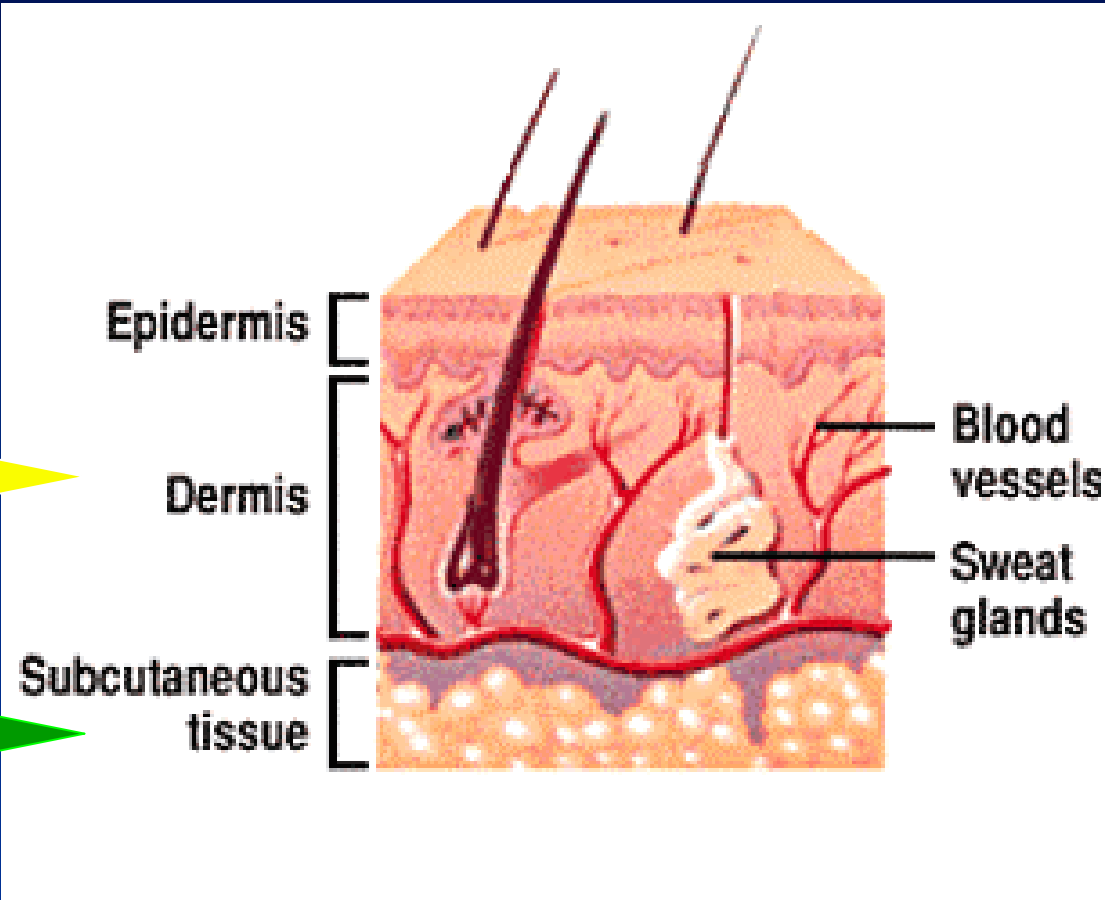


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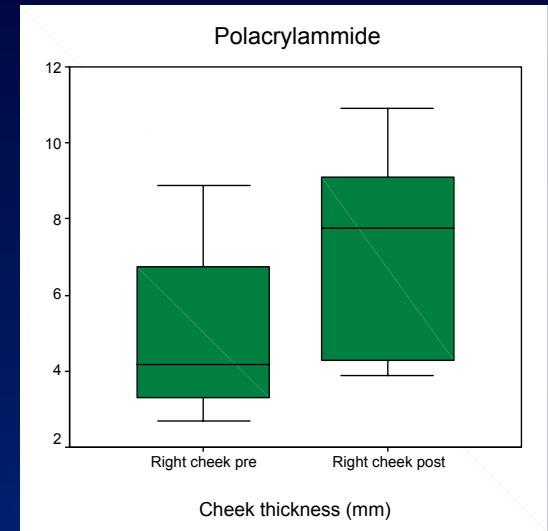
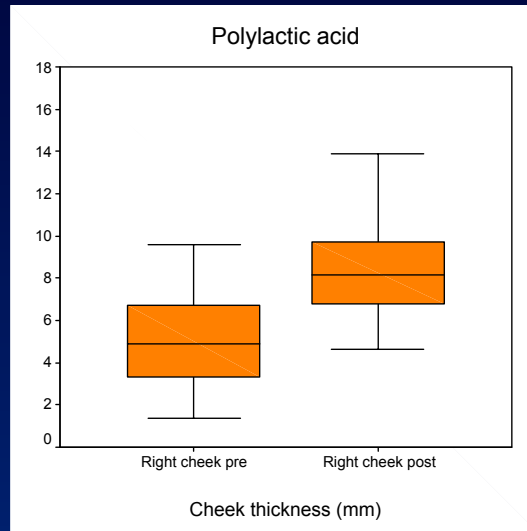
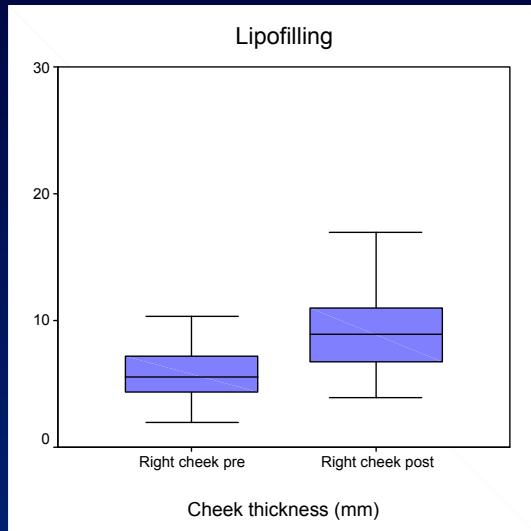
Poly lactic acid  
(N=20)



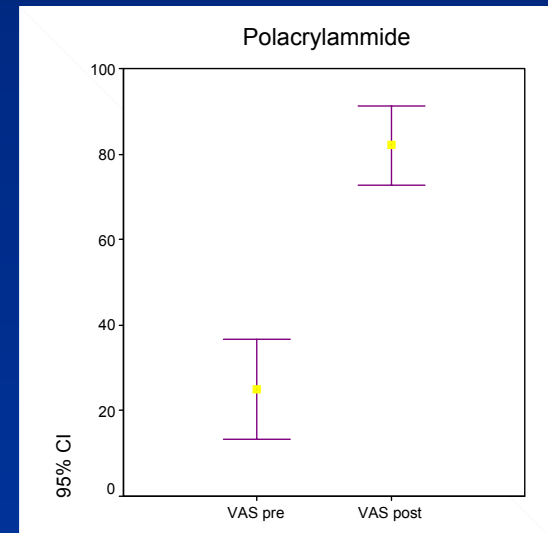
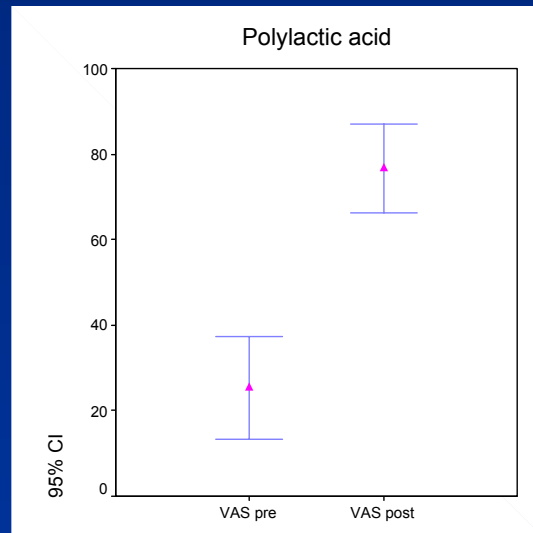
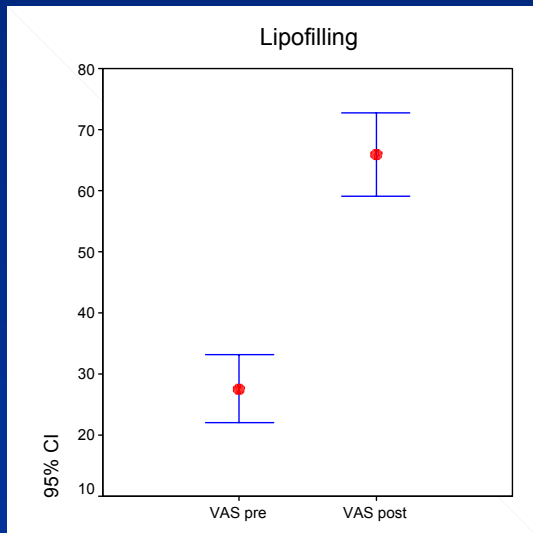
Polyacrylamide  
(N=15)



# Ultrasound



# Aesthetic Satisfaction (VAS)



# Adverse Events

- ✓ No serious adverse events
- ✓ No skin infections

Autologous fat transfer

- 4/24 Hamster syndrome (16%)
- 9/24 Aesthetic re-touch (37%)
- 12/24 Mild face oedema (50%)

Polylactic Acid

- 8/20 Incomplete PLA absorption (40%)  
*(mean 5 injections)*

Polyacrylamide

- Excellent tolerability  
*(mean 6 injections)*

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# **Effects of TH9507, a Growth Hormone Releasing Factor (GRF) Analog, on body composition in patients with abdominal fat accumulation associated with HIV lipodystrophy syndrome**

**Steve Grinspoon<sup>1</sup>, Donald Kotler<sup>2</sup>, Soraya Allas<sup>3</sup>, Bruno Lussier<sup>3</sup>, Alcide Chapdelaine<sup>3</sup>, Jean-Marc Tellier<sup>3</sup>, Marie-Christine Domec<sup>3</sup>, Luc Vachon<sup>3</sup>, Thierry Aribat<sup>3</sup>, Julian Falutz<sup>4</sup>**

**<sup>1</sup> Mass. General Hospital and Harvard Medical School**

**<sup>2</sup> St Luke's Roosevelt Hospital Center and Columbia University**

**<sup>3</sup> Theratechnologies**

**<sup>4</sup> Montreal General Hospital and McGill University**

# Study features

12-week study in patients with abdominal fat accumulation

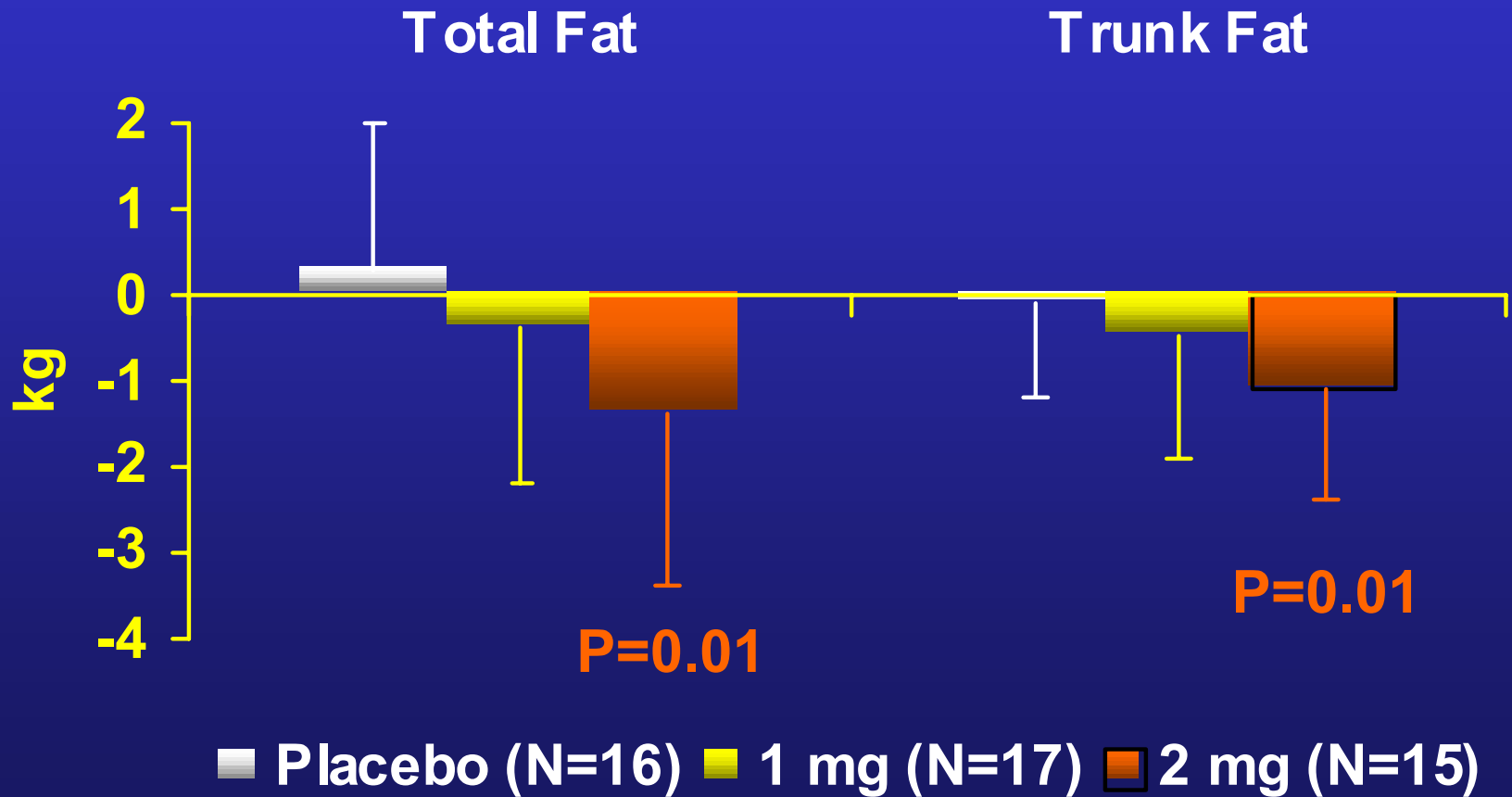
- WC >95 cm and WHR  $\geq 0.94$  for males
- WC >94 cm and WHR  $\geq 0.88$  for females

61 randomized:

- GRF 1 mg/day (N=19)
- GRF 2 mg/day (N=21)
- Placebo (N=21)

48 completed

# Change in Fat Mass



# Change in Fat by CT scan

	Placebo N=14	1 mg N=16	2 mg N=11
VAT (cm <sup>2</sup> )	-12 (32) -5.4%	-12 (29) -3.6%	<b>-21.5 (28)*</b> <b>-15.7%</b>
SAT (cm <sup>2</sup> )	-10.5 (31.6)	6.8 (21.2)	4.4 (19.8)
VAT:SAT	-0.0 (0.1)	<b>-0.2 (0.5)**</b>	<b>-0.1 (0.2)**</b>

Data are mean (SD), \*P<0.05 vs baseline, +P<0.05 vs placebo

# Sum: GRF analog

Metabolic effects of 2 mg/day dose

- ◆ Slight ↑ HDL-C
- ◆ ↓ total/HDL cholesterol
- ◆ ↓ TG
- ◆ ↑ fasting insulin

Safety: no significant difference in adverse events, but 11/21 in 2 mg/day dose reported headache, paresthesia

Phase III study in development

# TREATMENT STUDIES AT SFGH

*open-label proof-of-principle studies*

***IGF-I/IGFBP-3*** FOR CENTRAL FAT  
ACCUMULATION AND INSULIN  
RESISTANCE

***LEPTIN*** FOR METABOLIC COMPLICATIONS  
OF LIPOATROPHY

*Information, telephone screening: Viva Tai 206-4090*