

METABOLIC COMPLICATIONS IN THE HAART ERA

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METABOLIC COMPLICATIONS IN THE HAART ERA

METABOLIC CHANGES

- ◆ Impaired glucose metabolism
 - insulin resistance
 - impaired glucose tolerance
 - increased rate of diabetes
- ◆ Dyslipidemia
 - increased triglycerides
 - increased total and LDL cholesterol; low HDL
 - increased atherogenic lipoproteins

MORPHOLOGIC CHANGES

- ◆ Fat loss
 - appendices
 - buttocks
 - Face
- ◆ Fat accumulation
 - abdominal obesity
 - buffalo hump
 - lipomatosis
 - breast enlargement

PREVALENCE OF DIABETES INCREASED IN PATIENTS WITH HIV (especially on HAART)

	Diabetes*	
	No. Pts (%)	PR (95% CI)
Overall (n=1278)	101 (8)	
HIV- (n=710)	33 (5)	1
HIV+ not using HAART (n=157)	11 (7)	2.21 (1.12,4.38)
HIV+ using HAART (n=411)	57 (14)	4.64 (3.03-7.10)

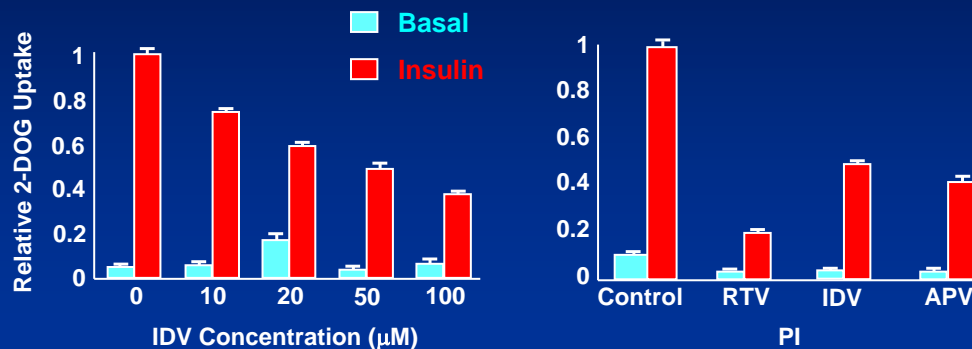
PR = Prevalence Ratio

*Fasting glucose ≥ 126 mg/dL, self-report of DM or use of DM medication

Brown et al. Arch. Int. Med. 165:1179, 2005

PIS INHIBIT GLUCOSE UPTAKE *IN VITRO*

- The effect of PIs on glucose uptake in 3T3-L1 adipocytes; values normalized to control

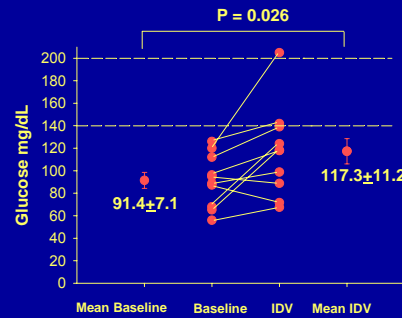
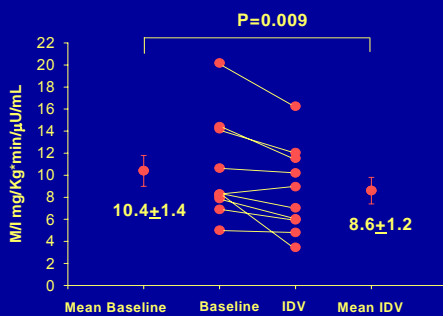


Murata. *J Biol Chem* 2000;275(27):20251.

INDIAVIR INDUCED INSULIN RESISTANCE AND IMPAIRED GLUCOSE TOLERANCE IN HIV- VOLUNTEERS

Indinavir Decreased
Insulin Sensitivity (M/I)
in Clamp

Indinavir Increased
2-hr plasma glucose
during OGTT



EFFECTS OF PIS ON INSULIN SENSITIVITY IN SERONEGATIVE SUBJECTS

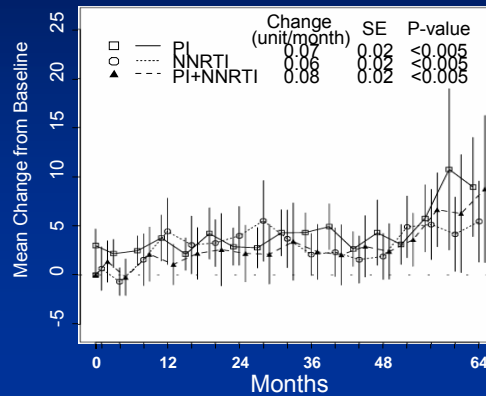
	<u>DOSE</u>	<u>% Δ</u>
<u>Acute studies</u>		
Ritonavir ¹	800 mg	-21%
Indinavir ²	1000 mg	-34%
Indinavir/RTV ³	800/100	-32%
Atazanavir/RTV ³	300/100	-
<u>Longer studies</u>		
Indinavir ⁴	800 mg TID/4 wks	-17%
Indinavir ⁵	800 mg TID/4 wks	-
LPV/RTV ⁶	400/100 BID/4 wks	-
LPV/RTV ⁷	400/100 BID/5 days	-24%
Atazanavir ⁷	400 mg QD/5 days	-

1) Lee Abs #2; 2) Noor AIDS 2002; 3) Doran Abs #6; 4) Noor AIDS 2001; 5) Shankar Abs #95; 6) Lee AIDS 2004; 7) Noor AIDS 2004

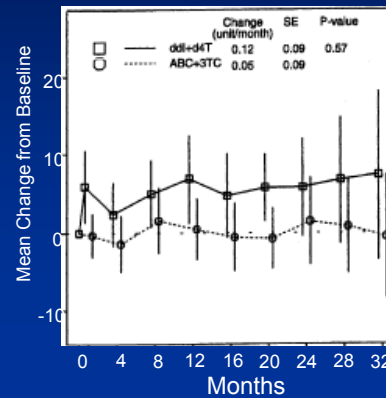
INSULIN LEVELS IN THE FIRST STUDY

($\mu\text{U/mL}$) Shlay et al JAIDS 2005, 2007

PI vs. NNRTI vs. PI+NNRTI
 PI: Slight early increase
 All: Increase later



ddl+D4T vs. ABC+3TC
 ddl+d4T is worse



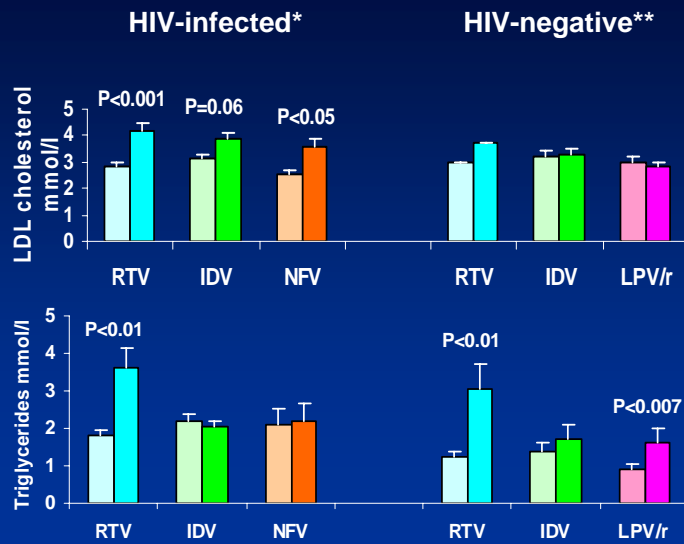
HIV INFECTION BY ITSELF AFFECTS LIPIDS

- ◆ ↓ HDL cholesterol
- ◆ ↓ LDL cholesterol
- ◆ Predominance of small dense LDL (LDL-B phenotype)
- ◆ ↑ Triglycerides
 - Part of the early lipid changes, including an increase in HDLc, observed with any ART combination may represent, in part, a “return to health” rather than a direct “toxic” drug effect

INCREASED LDL WITH THERAPY IS NOT A SPECIFIC DRUG EFFECT WHEREAS INCREASED TRIGLYCERIDES LEVELS ARE

Most PI Increase
LDL in HIV+.
Little increase in
HIV-.

Ritonavir Based
Drugs increase
Triglycerides in Both
HIV+ and HIV-.

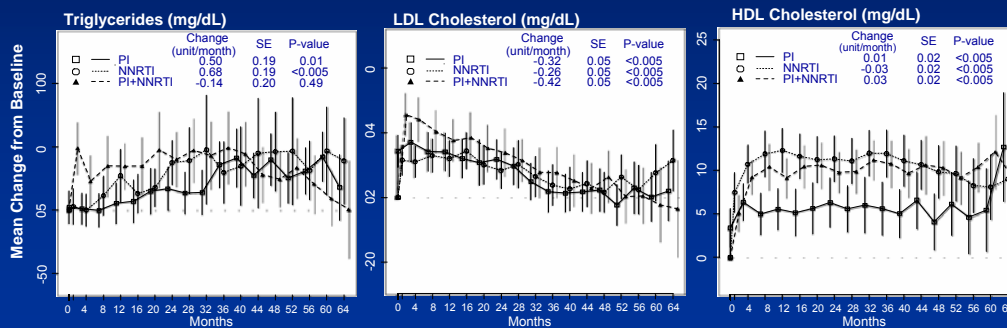


* Periard et al., ** Purnell et al., Noor et al., Lee et al.

The FIRST Study: Randomized treatment strategy of PI vs. NNRTI vs. PI + NNRTI (0-64 months)

Shlay et al JAIDS 44: 506-17, 2007

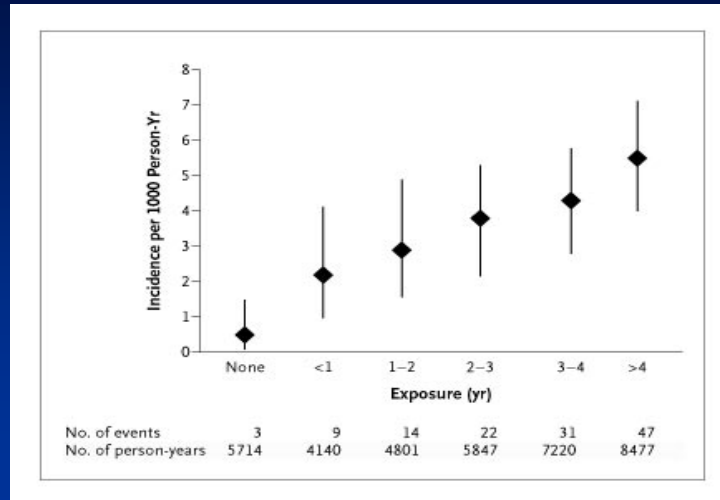
- PI + NNRTI increased TG and LDL more than PI or NNRTI
- Any NNRTI regimen increased HDL more than PI alone
- TG progressively increased
- LDL increased and returned to baseline
- HDL remained increased



PI = NLF, IDV, IDV/r, & Other/r; NNRTI = EFV & NVP

INCIDENCE OF MYOCARDIAL INFARCTION INCREASES WITH THE DURATION OF EXPOSURE TO COMBINATION ANTIRETROVIRAL THERAPY

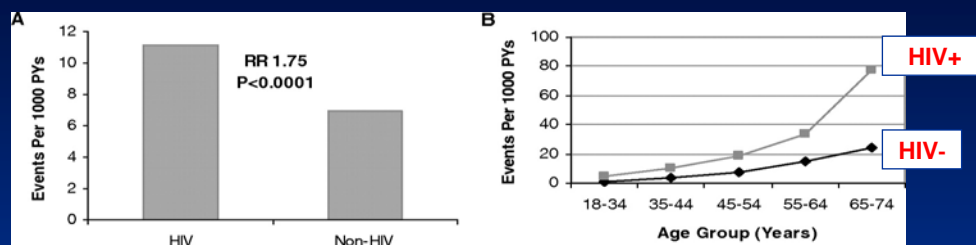
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(DAD) Study Group, *N Engl J Med* 2003;349:1993-2003

ACUTE MI RATES: HIV+ vs. HIV-

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Analysis of patient registry data for two 3^o care hospitals in Boston

- 3,851 HIV+; 1,044,589 HIV- who received care 1996-2004
- MI rates higher in HIV+ in each age stratum
- HIV+ had higher rates of hypertension, diabetes, dyslipidemia

Triant JCEM 2007

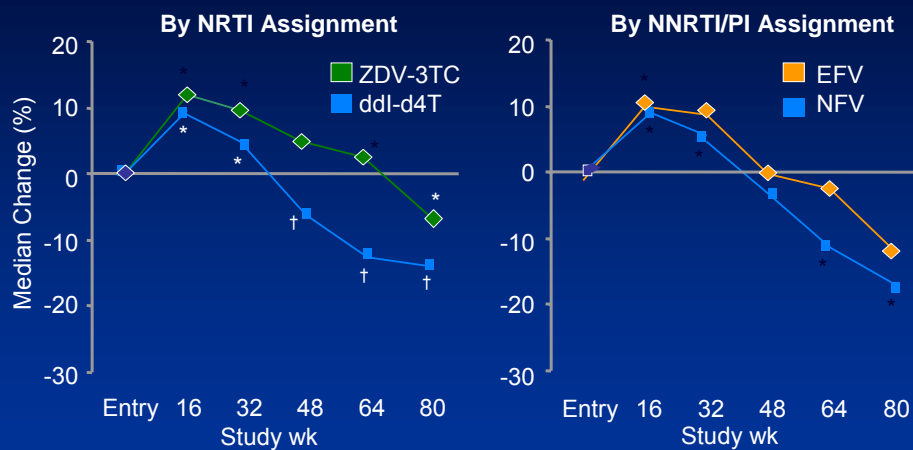
'HIV LIPODYSTROPHY'

- ◆ No consensus on case definition; use is variable
- ◆ General consensus
 - defining feature is subcutaneous fat loss
 - with or without central fat accumulation
 - often accompanied by alterations in lipid and glucose metabolism
- ◆ Central fat accumulation and peripheral lipoatrophy occur by separate mechanisms





ACTG 384/5005s: Median % Change in Limb Fat¹

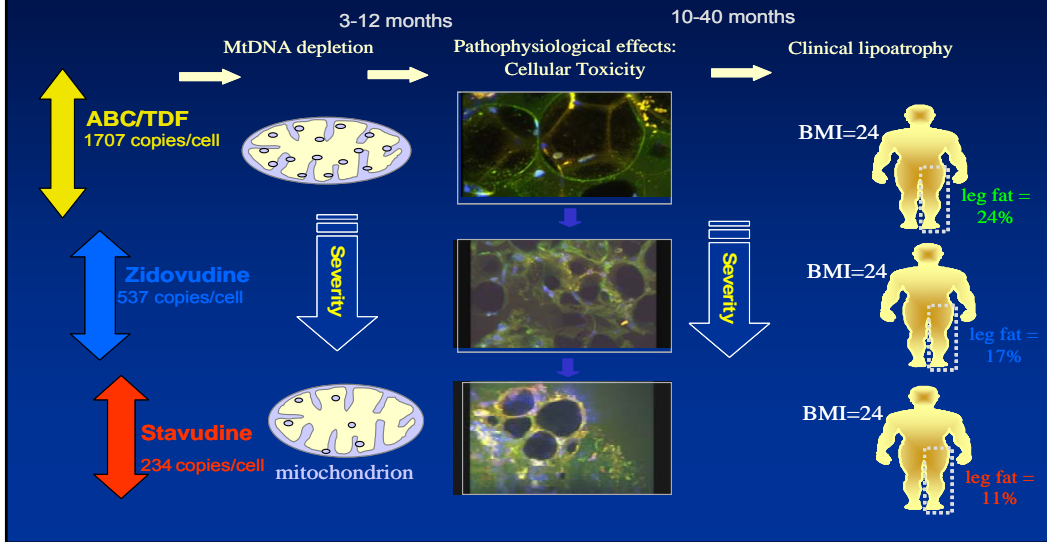


* $P < .05$ within-groups from baseline; †Statistically significant differences between groups.
 NNRTI = nonnucleoside NRTI.
 1. Dubé M. personal communication, 2004.

DIFFERENTIAL EFFECTS OF NRTI REGIMENS ON ADIPOCYTE MITOCHONDRIAL DNA DEPLETION IN HIV-INFECTED PATIENTS

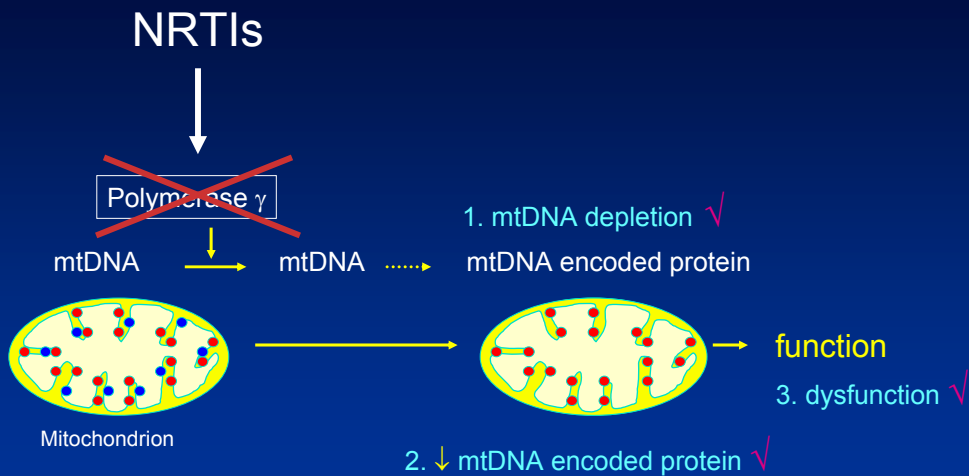
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Nolan et al, Abstract 16



POLYMERASE GAMMA (γ) HYPOTHESIS

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^{1,2} Nolan D et al. *Antiviral Therapy* 2003; 8:617-626.

³ Hammond E et al. *AIDS* 2004; 18:815-817.

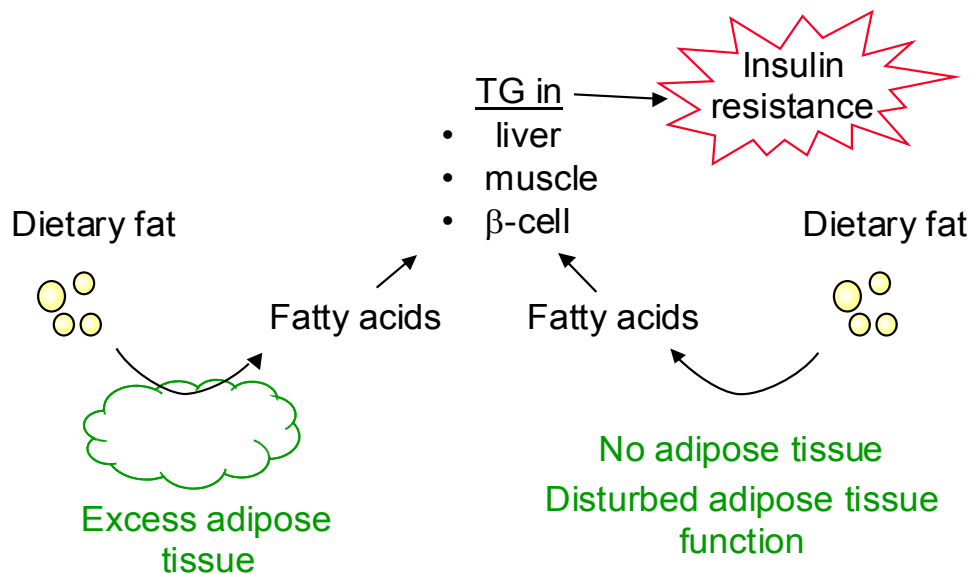
TOO LITTLE FAT CAN PROMOTE METABOLIC DYSREGULATION

Studies in transgenic mice and non-HIV-infected humans with lipodystrophy:

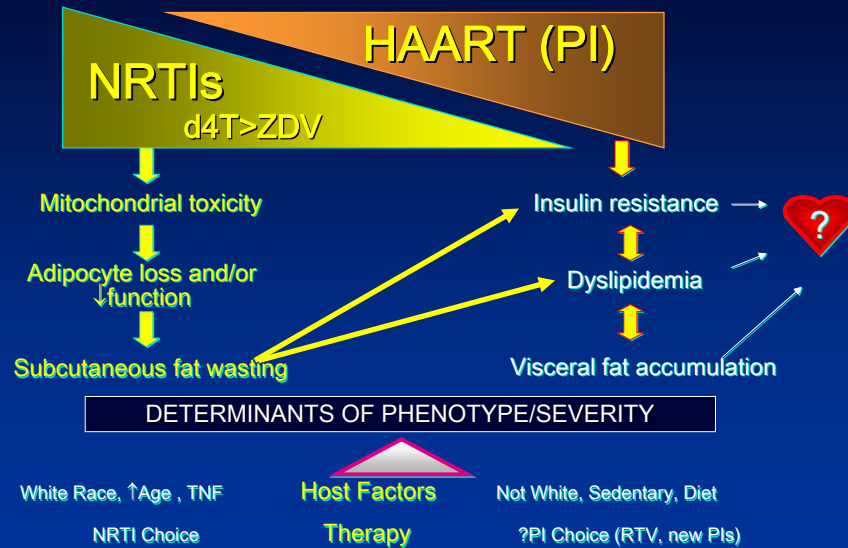
- severe insulin resistance
- hypertriglyceridemia
- hepatic steatosis
- decreased adipocyte-derived proteins involved with glucose, lipid metabolism (leptin, adiponectin)
- transplantation of fat from wild-type mouse of same strain ameliorates metabolic abnormalities

Moitra, 1998; Shimomura, 1998; Gavrilova, 2000; Shimomura, 1999 Reitman 2000; Arioglu 2000; Oral 2002

Insulin resistance in obesity or lipodystrophy



LIPODYSTROPHY MODEL



POTENTIAL INTERVENTIONS FOR MODIFIABLE CHD RISK FACTORS

- ◆ Obesity: weight loss, diet, and exercise
- ◆ Physical inactivity: exercise
- ◆ Atherogenic diet: less atherogenic diet
- ◆ Smoking: smoking cessation
- ◆ Hypertension: control of blood pressure
- ◆ Hyperglycemia: hypoglycemic drugs
- ◆ Insulin resistance: diet, weight loss, exercise, avoid drugs that cause IR
- ◆ Dyslipidemia: diet, weight loss, exercise, treat exacerbating factors, avoid drugs that cause ↑ lipids, use lipid-lowering drugs

Only age and family history are non-modifiable risk factors

POTENTIAL METABOLIC THERAPIES FOR HIV-ASSOCIATED MORPHOLOGIC ALTERATIONS

- ◆ Oral antidiabetic agents:
 - thiazolidinediones
 - metformin
- ◆ Testosterone replacement
- ◆ Growth hormone:
 - physiologic
 - pharmacologic
- ◆ GH secretagogues
- ◆ IGF-I
- ◆ Leptin

CT Scan Measurement of VAT



Patient at baseline



Same patient at 12 weeks

EFFECTS OF TROGLITAZONE ON FAT DISTRIBUTION IN HIV-NEGATIVE SUBJECTS

<u>Author, yr</u>	<u>Patients</u>	<u>N</u>	<u>VAT</u>	<u>SAT</u>
Arioglu, 2000	Lipodystrophy	20	↓	↑
Mori, 1999	T2 DM	18	↓	↑
Kawai, 1999	T2 DM	18	↓	↑
Kelly, 1999	T2 DM	11	↓	no Δ

Arioglu Ann Intern Med 2000; Mori Diabetes Care 1999; Kawai Metabolism 1999; Kelly Diabetes Care 1999

RANDOMIZED TRIALS OF ROSIGLITAZONE IN HIV-INFECTED PATIENTS

<u>Author</u>	<u>N</u>	<u>Subjects</u>	<u>Ins Res</u>	<u>VAT</u>	<u>SC fat</u>	<u>Lipids</u>
Sutinen	30	LA	improved	noΔ	noΔ	worsened
Carr	108	LA	improved	noΔ	noΔ	worsened
Cavalcanti	96	LA on PI	noΔ	-	noΔ	noΔ
Hadigan	28	LA+IR	improved	noΔ	↑	worsened
VanWijk	39	LA/FA+IR	improved	noΔ	↑	worsened
Mulligan	105	FA+IR	improved	noΔ	↑	worsened

Sutinen Antiviral Therapy 2003; Carr Lancet 2004; Hadigan Ann Intern Med 2004; VanWijk Ann Intern Med 2005; Mulligan AIDS 2007; Cavalcanti JID 2007

LA: lipoatrophy; FA: fat accumulation; PI: protease inhibitor; IR: insulin resistance; VAT: visceral adipose tissue; SC: subcutaneous

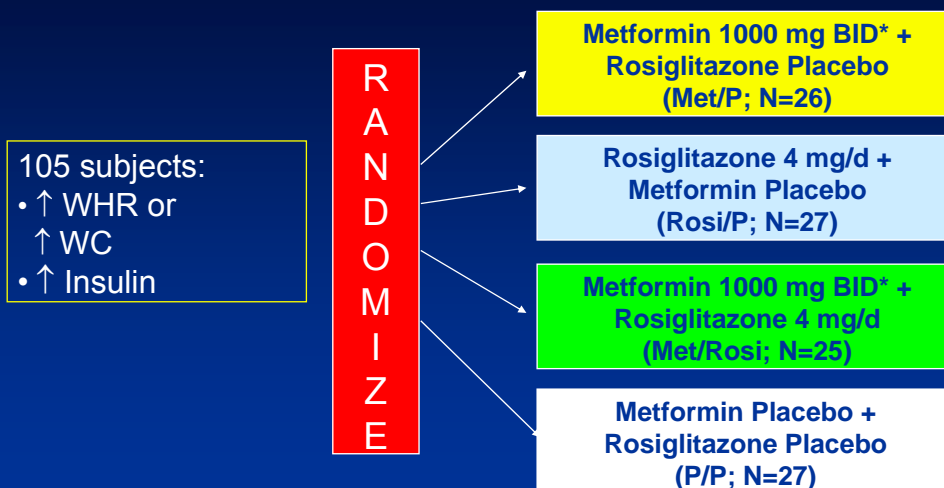
RANDOMIZED TRIALS OF METFORMIN IN HIV-INFECTED PATIENTS

Author	N	Subjects	IR	VAT	SC fat	Lipids
Hadigan	26	FA+IR	improved	some ↓	↓	improved
VanWijk	39	LA or FA	improved	↓	↓	improved
Mulligan	105	FA+IR	improved	no Δ	no Δ	improved
Kohli	48	FA	no Δ	no Δ	↓	no Δ

Hadigan JAMA 2000; VanWijk Ann Intern Med 2005; Mulligan AIDS 2007; Kohli HIV Med 2007

LA: lipoatrophy; FA: fat accumulation; IR: insulin resistance; VAT: visceral adipose tissue; SC: subcutaneous

RANDOMIZED MULTICENTER TRIAL OF ROSIGLITAZONE AND METFORMIN* (ACTG 5082)

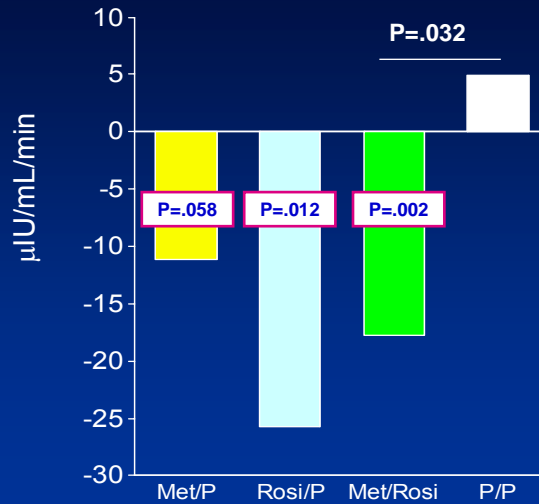


Mulligan AIDS 2007

*Metformin dose for first 2 weeks was 500 mg BID, then escalated to 1000 BID for the remainder of the study period

CHANGES INSULIN AUC over 16 weeks

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P-values in boxes denote significance of within-group changes (Wilcoxon signed rank test). Between-group differences evaluated by Wilcoxon rank sum test

SUMMARY

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- ◆ Both metformin and rosiglitazone, alone and in combination, decreased insulin AUC compared with baseline; the improvement in the combination arm was significant vs. placebo.
- ◆ Neither metformin nor rosiglitazone, alone or in combination, significantly decreased visceral fat.
- ◆ Leg fat increased and subcutaneous fat tended to increase with rosiglitazone, providing additional evidence that rosiglitazone may increase subcutaneous fat in some individuals.

ROSIGLITAZONE: POST-MARKETING SURVEILLANCE

- ◆ Dec 2003 - WHO analysis of AE reports suggested a signal for “cardiac diseases” (CHF and ischemia)
- ◆ October 2005 – based on RCT results, GSK raised question of ischemic cardiac events; proposed formal examination
- ◆ April 2006 - FDA reviewed 52-week echo study in pts with CHF, found increase in CHF and ischemia, issued WARNING in label
- ◆ August 2006 - FDA received GSK’s analysis of 42 RCTs as well as observational studies
- ◆ September 2006 - DREAM published
- ◆ December 2006 - ADOPT published
- ◆ May 2007 – Nissen and Wolski meta-analysis published (NEJM)
- ◆ June 2007 – Interim analysis of RECORD published (NEJM)
- ◆ July 2007 - *FDA Advisory Committee meeting to review data*

RESULTS OF FDA META-ANALYSIS (42 STUDIES)

	RSG (n=8604)	Control (n=5633)	OR (95% CI)	p
IHD	2.0%	1.5%	1.4 (1.1, 1.8)	0.02
SIHD	1.0%	0.8%	1.44 (0.98, 2.1)	0.06
MI/CVD/ST	0.73%	0.67%	1.2 (0.7, 1.8)	0.4

IHD=serious + non-serious ischemia; SIHD=serious ischemia

SUMMARY OF THE FINDINGS

- ◆ Statistically significant overall estimate of risk of a non-serious or serious myocardial ischemic event associated with RSG
 - OR 1.4 95% CI of 1.1 to 1.8 p=0.02
- ◆ No evidence of increased myocardial ischemic risk associated with RSG compared to MET or SU
 - OR 1.0 95% CI of 0.5 to 2.0 p=0.3
- ◆ Increased myocardial ischemic risk associated with RSG compared to placebo
 - Results are heterogeneous
 - Across treatment paradigms/studies
 - Across subgroups

SUMMARY (CONT)

Placebo-controlled trials in meta-analysis database

- ◆ Nominally statistically significant increased risk of a myocardial ischemic event associated with RSG compared to placebo
 - High risk treatment paradigms (e.g. CHF, CHD, elderly)
 - RSG add on to insulin
 - RSG add on to metformin
 - High risk subgroups
 - Nitrates
 - ACE inhibitors?

Active-controlled trials in meta-analysis database

- ◆ No clear evidence of increased risk associated with RSG compared to metformin or sulfonylurea

PROactive RESULTS

Endpoint	Add-On PIO N=2605 n (%)	Add-on PBO N=2605 n (%)	HR (95% CI), p-value
Primary composite	514 (19.7%)	572 (21.7%)	0.90 (0.80, 1.02), p=0.0954
CV mortality (predefined II°)	127 (4.9%)	136 (5.2%)	0.94 (0.74, 1.20), p=0.6163
All-cause mortality + MI + stroke (II°)	301 (11.6%)	358 (13.6%)	0.84 (0.72, 0.98), p=0.0277

TESTOSTERONE SUPPLEMENTATION FOR VISCERAL ADIPOSITY

- ◆ Low testosterone levels common in some studies of HIV-infected men
- ◆ In seronegative men, testosterone inversely associated with VAT
- ◆ Testosterone treatment has decreased VAT, insulin, and glucose in seronegative men with abdominal obesity or type 2 diabetes

Arver J Androl 1999, Grinspoon JCEM 1996, Seidell etabolism 1990; Khaw Ann Epidemiol 1992, Kappor Eur J Endocrinol 2006, Marin Int J Obes 1992

RANDOMIZED TRIAL OF TESTOSTERONE SUPPLEMENTATION IN HIV-INFECTED MEN WITH ABDOMINAL OBESITY (ACTG 5079)

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88 HIV+ men:

- Total T 125-400 mg/dL or Free T <50 pg/mL
- WHR >0.95 or WC >100 cm

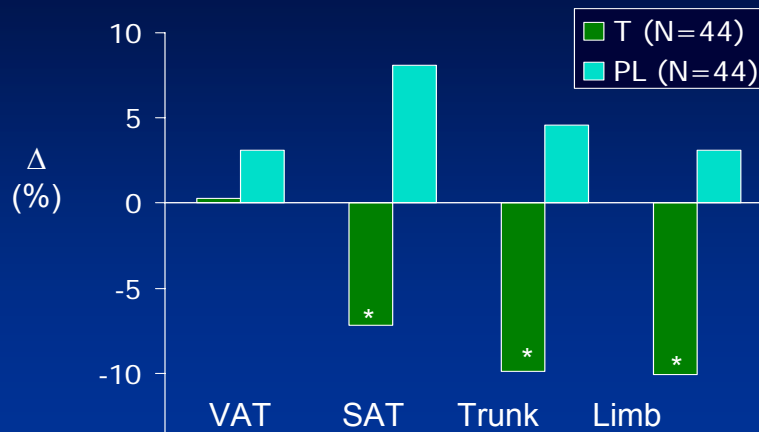
Testosterone gel 10 g/d
24 weeks (N=44)

Placebo gel
24 weeks (N=44)

Bhasin JCEM 2007

EFFECTS OF TESTOSTERONE SUPPLEMENTATION ON FAT DISTRIBUTION IN HIV+ MEN WITH FAT ACCUMULATION AND LOW TESTOSTERONE

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*P<0.001 vs. placebo for trunk and limb fat and SAT

Bhasin JCEM 2007

GROWTH HORMONE FOR CENTRAL FAT ACCUMULATION?

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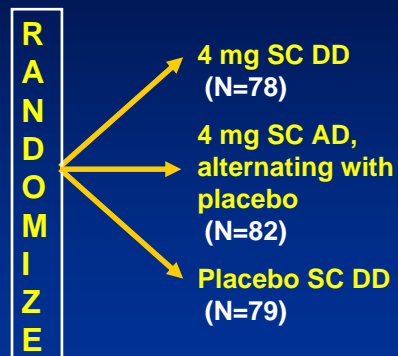
Physiologic (“replacement”) dose (9.5 $\mu\text{g}/\text{kg}/\text{day}$) in HIV-negative men with abdominal obesity:

- ◆ \downarrow abdominal and visceral fat
- ◆ \uparrow insulin sensitivity (after initial worsening)
- ◆ \downarrow triglycerides (after initial worsening)
- ◆ \downarrow cholesterol
- ◆ \downarrow diastolic blood pressure

Johannsson et al, JCEM 52:727, 1997

GH FOR VISCERAL FAT ACCUMULATION AND DYSLIPIDEMIA (SERONO TRIAL)

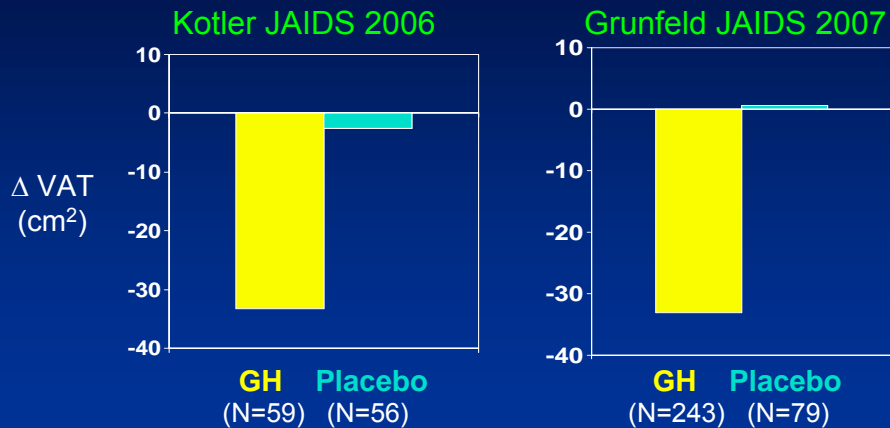
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DD = daily dose

AD = alternate day dose

TWO RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER TRIALS OF GH (4 mg/d) FOR HIV-ASSOCIATED FAT ACCUMULATION: effects on VISCERAL FAT



VAT and SAT measured by CT (L4-L5); GH vs. placebo $P < 0.001$

GH FOR HIV-ASSOCIATED FAT ACCUMULATION: RESULTS OF TWO CLINICAL TRIALS (TOTAL N: 437)

- ◆ 21-24% reduction in VAT with 4 mg/d dose
- ◆ Decreases in SAT and limb fat
- ◆ Modest decrease in TG (-11 to -35 mg/dL, NS)
- ◆ Improvements in non HDL-C (-13 to -15 mg/dL; $P < .05$)
- ◆ Improvement in body image scores
- ◆ Increases in fasting insulin (+7.2 μ U/mL; $P < .001$)
- ◆ Contraindicated for persons with impaired glucose tolerance

Kotler JAIDS 2004, 2006; Grunfeld JAIDS 2007

Tesamorelin, a GRF Analogue

- ◆ Synthetic human GRF (1-44) analogue
 - Hydrophobic chain at N-terminus
- ◆ Increased in vitro half-life as compared to natural hGRF
- ◆ Raises GH secretion in a physiological manner, resulting in increased IGF-1 levels generally within the physiological range
- ◆ Well tolerated at single doses up to 2 mg/day, including with regard to glycemic control in type 2 diabetic patients (1)

(1) Clemmons Endoc Soc 2004

TH9507 (SYNTHETIC GHRH ANALOG) IN HIV+ PATIENTS WITH FAT ACCUMULATION

Preliminary results of Phase III study (2 mg/d sc for 6 months; N=412):

- ◆ 15% decrease in VAT (vs. 5% increase with placebo; $P < 0.001$)
- ◆ No change in SAT
- ◆ TG decreased (~50 mg/dL; $P < 0.001$)
- ◆ Slight decrease in cholesterol (~10 mg/dL; $P = 0.01$)
- ◆ Minimal effect on glucose or insulin
- ◆ "Generally well tolerated," even among patients with IGT
- ◆ Confirmatory trial underway

Falutz, 13th CROI, 2007

RATIONALE FOR IGF-I/IGFBP-3 IN HIV-ASSOCIATED FAT ACCUMULATION AND INSULIN RESISTANCE

- Central fat accumulation is strongly associated with insulin resistance
- Growth hormone removes fat but worsens glucose homeostasis
- In contrast to GH, IGF-I improves insulin sensitivity
- IGF-I promotes lipid oxidation, similar to GH
- Thus, IGF-I would be predicted to decrease fat

IGF-I/IGFBP-3 STUDY AT SFGH

Study Design: Open-label, proof-of-principle study in 12 subjects

Eligibility Criteria:

- HIV+ men and women ages 21-65 on stable ART
- Objective evidence of visceral obesity:
 - Waist circumference >100 cm
 - Waist hip ratio >0.95 in men and >0.90 in women
- Insulin resistance (HOMA-IR)
- Nonobese (BMI < 30 kg/m²)
- Stable hypolipidemic Rx and testosterone replacement OK

Treatment: Recombinant human IGF-I/IGFBP-3 for 3 months (0.5–1.0 mg/kg/day by sc injection)

RATIONALE FOR LEPTIN THERAPY

- ◆ **Fatless mice (A-ZIP/F-1, nSREBP-1c) exhibit:**
 - severe insulin resistance
 - hypertriglyceridemia
 - hepatic steatosis
 - decreased adipocyte-derived proteins involved in glucose and lipid metabolism (e.g. leptin, adiponectin)
- ◆ **Transplantation of fat from wild-type mice of the same strain ameliorates these metabolic abnormalities.**
- ◆ **HIV-infected and uninfected humans with lipoatrophy manifest a similar metabolic profile, including hypoleptinemia, hypertriglyceridemia and hyperinsulinemia.**
- ◆ **Treatment with leptin ameliorates these metabolic abnormalities in mice as well as patients with lipoatrophy.**

Shimomura Genes Dev 1998; Moitra Genes Dev 1998; Gavrilova JCI 2000; Reitman Trends Endocrinol Metab 2000; Carr AIDS 1998; Nagy CID 2003; Oral NEJM 2002; Shimomura Nature 1999; Lee JCEM 2006

SUMMARY AND CONCLUSIONS

In this small open-label proof-of-principle study:

- ◆ Leptin treatment was well tolerated; no clinical or laboratory adverse events were observed.
- ◆ Leptin improved dyslipidemia: total, LDL, and non-HDL cholesterol decreased, while HDL tended to increase.
- ◆ Leptin treatment was associated with improvements in insulin sensitivity in the liver but the increase in whole-body glucose uptake did not achieve significance.
- ◆ Visceral fat decreased in all subjects.
- ◆ There was no exacerbation of peripheral lipoatrophy.
- ◆ These latter results suggest that leptin may have a depot-specific effect in adipose tissue.

ACKNOWLEDGMENTS

UCSF-SFGH Endocrinology

Kathleen Mulligan, PhD

Joan Lo, MD

Giorgos Sakkas, PhD

Hootan Khatami, MD

Viva Tai, RD, MPH

Melissa Weinberg, MD

Jean-Marc Schwarz, PhD

Mike Wen, MS

Seongsoo Park, PhD

Seungki Kim, PhD

Jeongae Lee, PhD

SFGH-General Clinical Research Center (NIH - RR00083)

NIH (DK45833; DK54615; DK63640; DK69185; **UARP** (90SF211))

UCSF-VA Med Center

Carl Grunfeld, MD, PhD

Mustafa Noor, MD

Grace Lee, MD