

CROI 2006 UPDATE: INTERVENTIONS FOR FAT DISTRIBUTION ALTERATIONS

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RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES

- ◆ Testosterone in men with visceral obesity and low testosterone levels (ACTG 5079; Shikuma/Bhasin, abs 139)
- ◆ Metformin, rosiglitazone in patients with elevated waist/hip and insulin (ACTG 5082; Mulligan/Grinspoon, abs 147)
- ◆ Metformin in patients with visceral obesity and normal insulin (Tufts; Kohli/Shevitz, abs 148)
- ◆ Pioglitazone in patients with lipoatrophy (ANRS 113; Slama/Rozenbaum, abs 151LB)

Effects of Physiologic Testosterone Supplementation on Fat Mass and Distribution in HIV-Infected Men with Abdominal Obesity

CM Shikuma¹, RA Parker², F Sattler³, B Alston⁴, R Haubrich⁵, T Umbleja², S Bhasin⁶, for the AIDS Clinical Trials Group Protocol A5079 Study Team

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ACTG 5079: TESTOSTERONE FOR VISCERAL OBESITY

Rationale:

- ◆ HIV-negative men with visceral obesity tend to have low testosterone levels
- ◆ Testosterone replacement in hypogonadal HIV-negative middle-aged men decreases visceral fat, increases insulin sensitivity and lowers triglyceride and cholesterol levels

Subjects: 88 HIV+ men

- waist-to-hip ratio >0.95 or mid-waist circumference > 100 cm
- serum total T 125-400 ng/dL, or free T < 50 pg/mL

Treatment: testosterone gel (10 g/d) or placebo for 24 weeks

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SUM: TESTOSTERONE FOR EXCESS VISCERAL FAT

- ◆ Testosterone supplementation in men with mild-moderate hypogonadism did not reduce visceral fat
- ◆ However, total, trunk, and limb fat decreased significantly with testosterone
- ◆ Lean body mass increased slightly
- ◆ Biochemical results, including serum testosterone levels, pending
- ◆ Testosterone gel well tolerated

ORAL INSULIN SENSITIZING AGENTS

Thiazolidinediones: ↑ peripheral insulin sensitivity

- ◆ Troglitazone in HIV-negative:¹ ↓ visceral fat (VAT) and ↑ subcutaneous fat (SAT) in 4 studies in subjects with lipodystrophy and/or diabetes
- ◆ Rosiglitazone, pioglitazone in HIV+ subjects with lipoatrophy:
 - 2 studies: No effect of rosi on VAT or SAT²
 - ↑ SAT in 3 studies of rosi³ and 1 of pio⁴

Metformin: ↓ hepatic glucose output

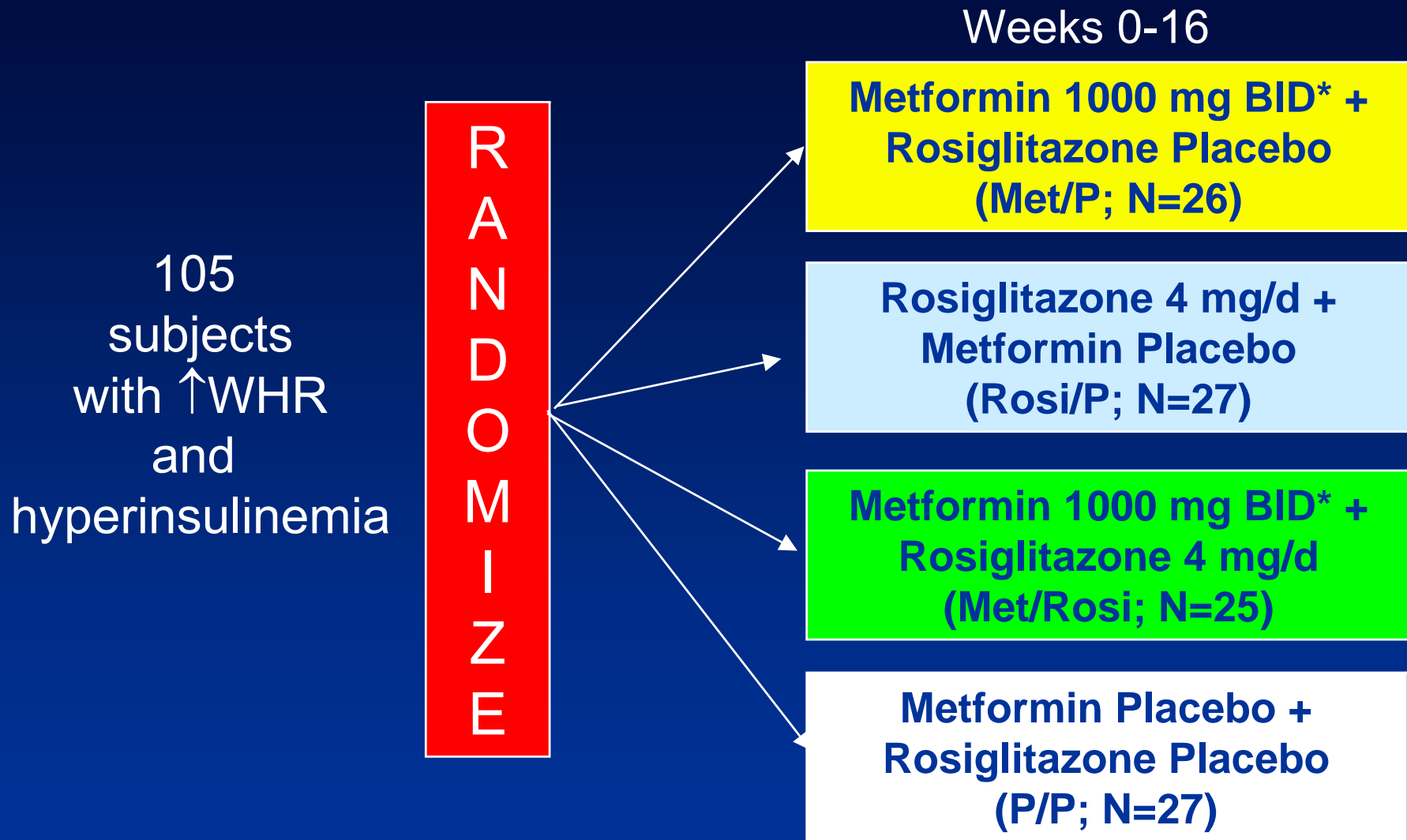
- ◆ in HIV, ↓ VAT, SAT, total fat, waist circumference, weight⁵

1) Kelly 1999, Mori 1999, Kawai 1999, Arioglu 2000; 2) Sutinen 2003, Carr 2004; 3) Gelato 2002, Hadigan 2003, VanWijk 2005; 4) Calmy 2003 ; St Marc 1999, Hadigan 2000, Martinez 2003, VanWijk 2005

EFFECTS OF METFORMIN AND ROSIGLITAZONE
ON BODY COMPOSITION IN HIV-INFECTED
PATIENTS WITH HYPERINSULINEMIA AND
ELEVATED WAIST/HIP RATIO: A RANDOMIZED,
PLACEBO-CONTROLLED TRIAL (ACTG 5082)

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R Parker, B Alston-Smith, M Basar, S Grinspoon
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ACTG 5082



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

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Sum: Metformin, rosiglitazone in hyperinsulinemic subjects with ↑ waist/hip

- ◆ Both treatments improved insulin sensitivity
- ◆ Neither treatment significantly reduced visceral fat
- ◆ Leg fat increased and subcutaneous fat tended to increase with rosiglitazone, but not with metformin.
- ◆ Significant weight loss in both metformin groups
- ◆ Rosiglitazone alone increased LDL-C and decreased HDL-C, but no such effect was seen with metformin alone or when metformin was given in combination with rosiglitazone.
- ◆ Stringent toxicity monitoring; high dropout rate in metformin alone group (diarrhea, mild lactate elevations)

A Randomized Placebo-Controlled Trial of Metformin for the Treatment of HIV Lipodystrophy

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METFORMIN FOR VISCERAL OBESITY

- ◆ 48 HIV+ men and women with self-reported increase in abdominal girth and abnormal waist-hip ratio (≥ 0.95 in men and ≥ 0.85 in women)
- ◆ Insulin in *normal* range
- ◆ Randomized to receive metformin 1500 mg or placebo daily for 24 weeks

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Metformin in normoinsulinemic subjects with elevated WHR

- ◆ No significant decrease in visceral fat
- ◆ Significant decrease in limb fat (DEXA)
- ◆ Significant decrease in BMI
- ◆ No improvement in lipids
- ◆ No improvement in fasting insulin or glucose or insulin AUC

NO EVIDENCE TO SUPPORT USE OF METFORMIN FOR ALTERED FAT DISTRIBUTION IN PATIENTS WITH NORMAL INSULIN LEVELS

Effect of pioglitazone on HIV-1 lipoatrophy : a randomised, double-blind, placebo-controlled trial (ANRS 113)

Laurence Slama, Emilie Lanoy, Marc-Antoine Valentin,
Jean Philippe Bastard, Aziza Chermak, Amal Boutekadjirt,
Demiana William-Faltaos, Jacqueline Capeau,
Dominique Costagliola, Willy Rozenbaum

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décompresseur TIFF (non compressé)
sont requis pour visionner cette image.

PIOGLITAZONE FOR LIPOATROPHY

Aim: To assess the efficacy, safety of pioglitazone 30 mg qd in 130 lipoatrophic HIV-1+ adults receiving antiretroviral therapy, and to measure the effects of this treatment on glucose and lipid metabolism, over 48 weeks

Primary outcome: change in limb fat between week 0 and 48 (DEXA)

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Pioglitazone in normoinsulinemic subjects with lipoatrophy

- ◆ Significant increase in limb fat
- ◆ No effect on VAT or SAT
- ◆ No improvement in subject-rated lipodystrophy
- ◆ Slight increase in HDL-C
- ◆ No significant effects on glucose, insulin LDL-C, triglycerides
- ◆ Generally well tolerated

WHITHER THIAZOLIDINEDIONES IN HIV 'LIPODYSTROPHY?'

- ◆ Virtually no evidence of decrease in visceral fat
- ◆ Inconsistent effects on subcutaneous fat
 - Increases, when observed, have been modest (<0.5 kg) and rarely detectable by patients
 - Greatest “benefit” seen in patients not using thymidine analog NRTI
 - Role of insulin resistance unclear
- ◆ Rosiglitazone, but not pioglitazone, adversely affects lipids
- ◆ Pioglitazone partly metabolized through CYP3A4; possible pK interactions not studied

OPEN-LABEL STUDIES OF NOVEL METABOLIC AGENTS AT SFGH

- ◆ IGF-I/IGFBP-3 in patients with excess visceral fat and insulin resistance
- ◆ Leptin in patients with elevated triglycerides and low leptin levels

TELEPHONE SCREENING

VIVA TAI 206-4090; FLYERS AVAILABLE