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A randomised, doble-blind, placebo-controlled, comparative study on the effects of metformin o gemfibrozil in lipodystrophic HIV-1-infected patients receiving protease inhibitors (PI).

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Metformin or gemfibrozil in HIV-associated lipodystrophy: a randomised, doble-blind, placebo-controlled study

BACKGROUND

- Though not invariably together, metabolic abnormalities such as dyslipemia and insulin resistance are common in lipodystrophic HIV-1-infected patients receiving PI-containing HAART.

- Lipid-lowering agents such as gemfibrozil and insulin sensitizers such as metformin have been used for treating dyslipemia and insulin resistance in HIV-1-infected patients though studies are few, uncontrolled, or with short follow-up.

- The long-term effects of a therapeutic approach addressed to treat either dyslipemia or insulin resistance in lypodystrophic HIV-1-infected patients with those metabolic abnormalities are unknown.

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METHODS

- **Inclusion criteria:**

  Adult, clinically stable HIV-1-infected patients on PI-containing HAART, HIV-RNA <200 copies/mL for at least 3 months, subjective perception of body fat changes including abdominal obesity confirmed by WHR >0.8 (women) or 0.9 (men), BMI <30kg/m^2, and fasting plasma triglycerides >200 mg/dL.

- **Exclusion criteria:**

  Creatitine >1.3 mg/dL, AST/ALT >5x, pO_2 <80 mmHg, vascular or heart insufficiency, alcohol abuse (>80 g/day), pregnancy, prior history of lactic acidosis or biliary lithiasis, use of drugs with metabolic effects or with known interactions with study drugs, fasting glycemia >140 mg/dL, need to change HAART regimen.

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METHODS

Drugs (masked) po:

metformin 850 mg/12h, gemfibrozil 600 mg/12h, or placebo /12h.

Measurements:

Baseline and every 3 months: fasting glucose, triglycerides, cholesterol (total, HDL, and LDL),weight, height, waist/hip

Baseline and every 6 months: OGTT, bioimpedance analysis, sonography at predefined points to measure subcutaneous and intrabdominal fat thickness. Insulin sensitivity index (ISI) calculated from: Matsuda M, DeFronzo RA. Diabetes Care 1999; 22: 1462-70.

Primary end-point:

Proportion of patients with WHR ≤0.8 (women) or ≤0.9 (men) at 12 months

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METHODS

- **Statistics:**

  Sample size:

  At least 20 patients per arm should be included to detect an improvement in at least 25% of the patients in the best arm with a 80% power and an alfa error <0.05, assuming that lipodystrophy on placebo would not spontaneously improve.

  Analysis:

  Comparisons among groups were done with the Kruskal-Wallis test. A random effect regression model with a panel data structure was used to evaluate the effect of time and therapy. Metabolic laboratory parameters and fat measurements were used as dependent variables. Logaritmic transformation was done in cases of no normality.

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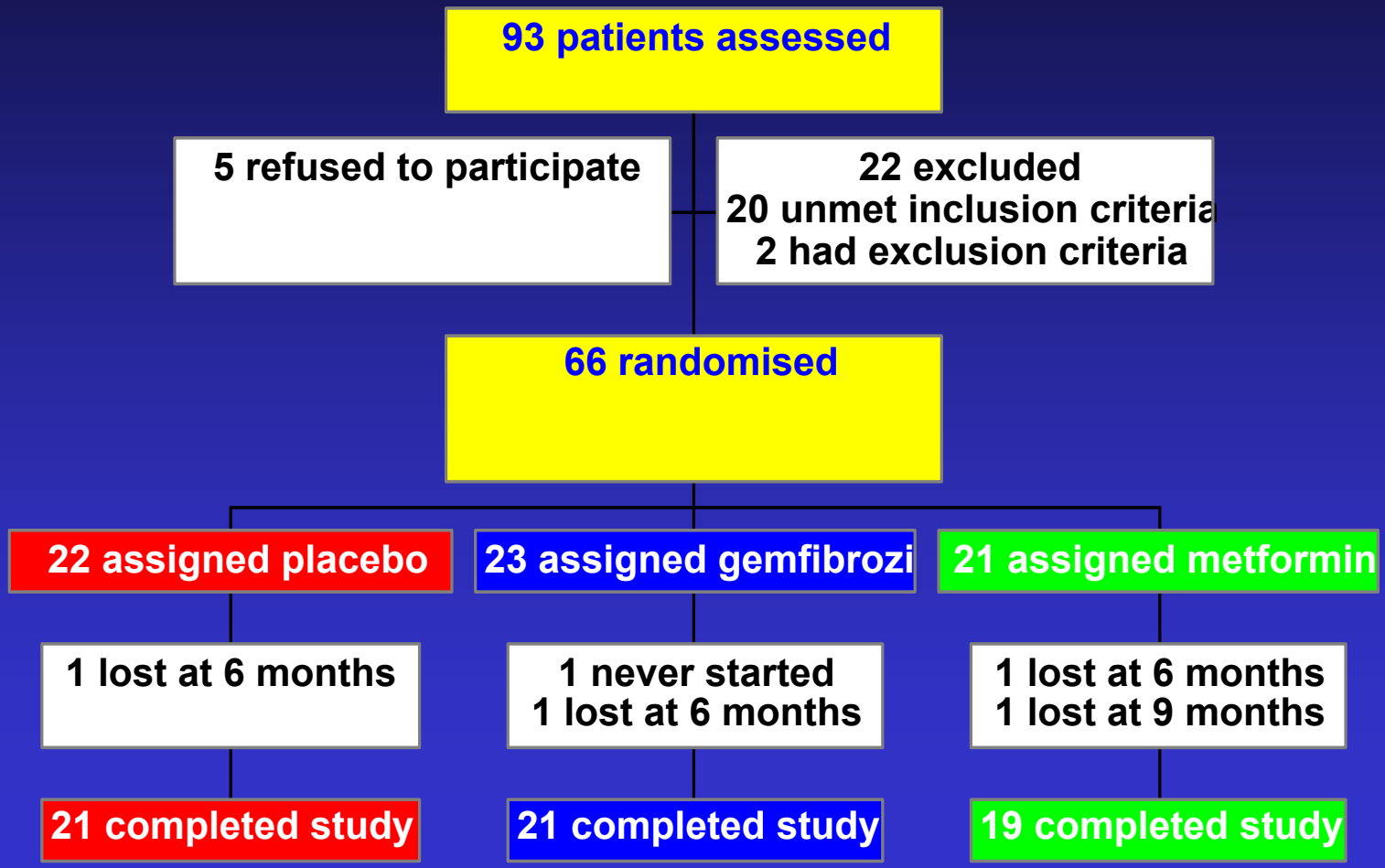
TRIAL PROFILE



BASELINE CHARACTERISTICS

	Placebo (n=22)	Gemfibrozil (n=23)	Metformin (n=21)	P value
Men (%)	15 (68)	16 (70)	17 (81)	0.59
Age, years	38 (7)	42 (7)	43 (9)	0.05
Weight, kg	66.4 (13.8)	69.7 (9.0)	68.1 (9.2)	0.60
WHR	0.93 (0.05)	0.95 (0.06)	0.96 (0.05)	0.22
CD4, cells/mm ^{3}	577 (337)	547 (271)	657 (437)	0.57
Total cholesterol, mg/dL	228 (68)	237 (48)	263 (69)	0.18
HDL-cholesterol, mg/dL	37 (11)	38 (15)	36 (14)	0.87
LDL-cholesterol, mg/dL	127 (43)	140 (37)	172 (57)	0.006
Triglycerides, mg/dL	403 (225)	312 (74)	399 (169)	0.14
Glucose, mg/dL	91 (13)	95 (16)	92 (14)	0.50
Insulin, mU/L	24.1 (15.4)	25.4 (22.2)	24.7 (16.9)	0.97
IA fat thickness, mm	19.4 (4.2)	23.5 (3.6)	21.5 (6.2)	0.02
SC abdomen fat thickness, mm	12.9 (5.9)	17.5 (7.2)	11.5 (5.5)	0.006
SC arm fat thickness, mm	3.8 (1.3)	4.5 (1.6)	3.7 (0.8)	0.10
SC face fat thickness, mm	3.8 (1.2)	4.7 (1.7)	4.0 (1.5)	0.12
Fat, kg	11.6 (4.4)	14.2 (4.8)	12.5 (3.4)	0.14
Fat-free mass, kg	54.1 (12.2)	55.6 (8.4)	55.6 (8.0)	0.95

Data are mean±SD, unless otherwise expressed

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RESULTS

- **Porportion of patients with WHR ≤0.8 (women) or ≤0.9 (men):**

Men

	Baseline	3m	6m	9m	12m
P	0 (0/15)	13 (2/15)	0 (0/15	7 (1/14)	0 (0/14)
G	0 (0/16)	20 (3/15)	0 (0/15)	0 (0/14)	0 (0/14)
M	0 (0/17)	12 (2/17)	6 (1/17)	13 (2/16)	0 (0/15)

P >0.05 for each time point

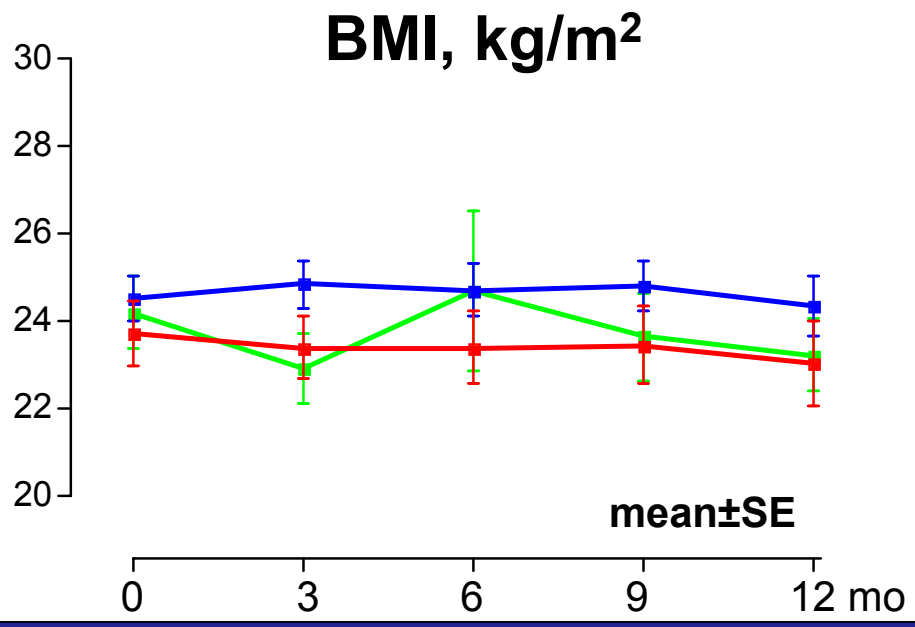
Women: No women acquired WHR ≤0.8 during follow-up

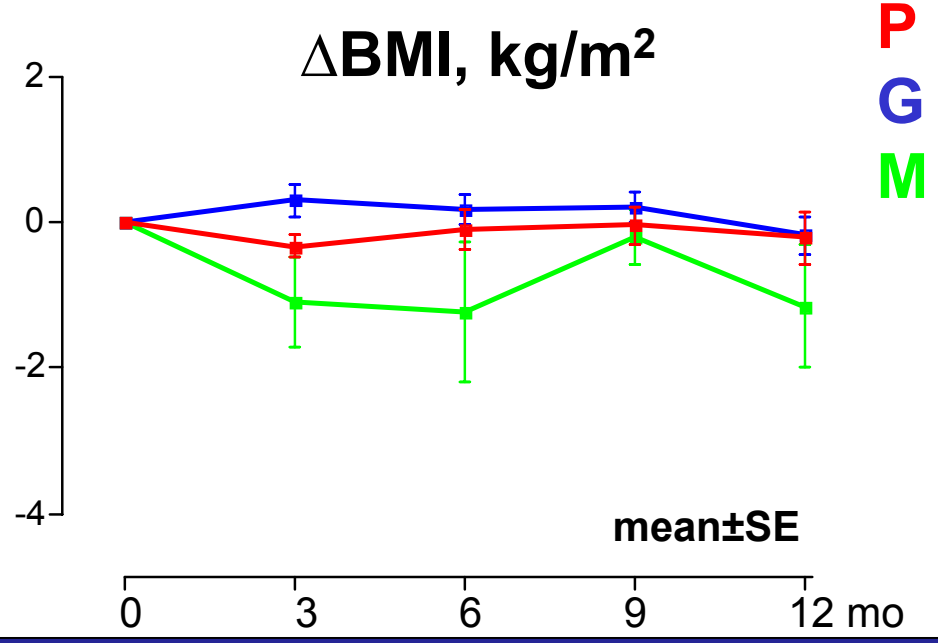
- **Adverse effects:**

No patient discontinued study drugs due to adverse effects

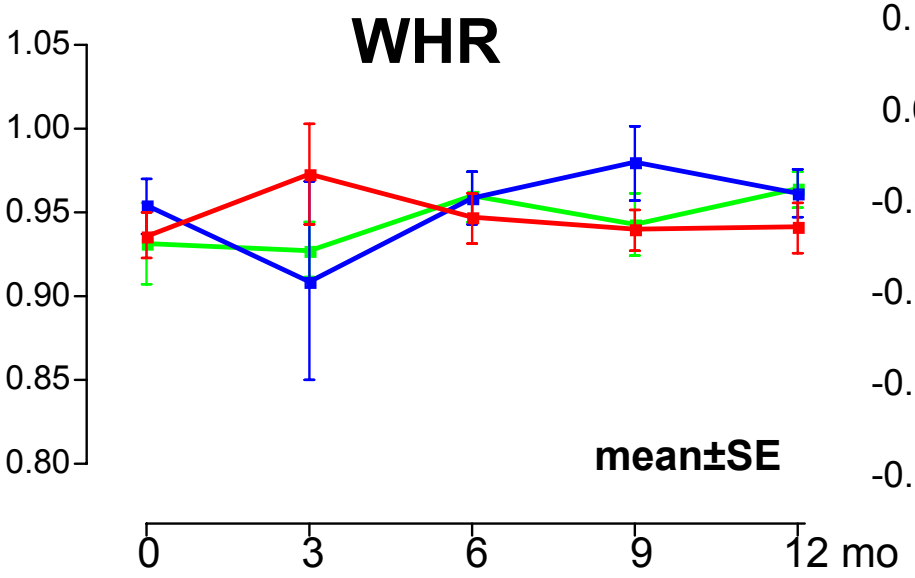
6 patients assigned to metformin reported mild diarrhea.

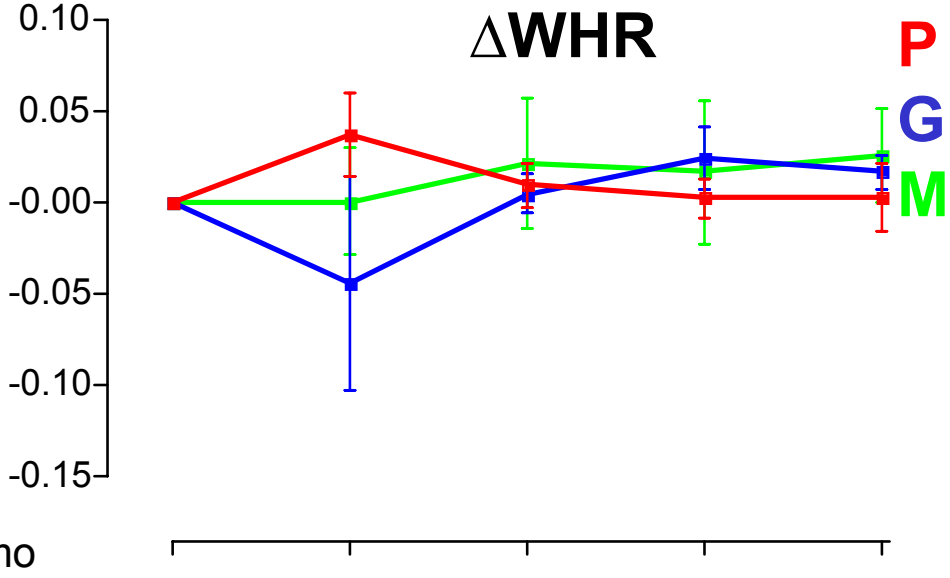
1 patient assigned to gemfibrozil reported abdominal discomfort.


BMI, kg/m²
30
28
26
24
22
20
mean±SE
0
3
6
9
12 mo

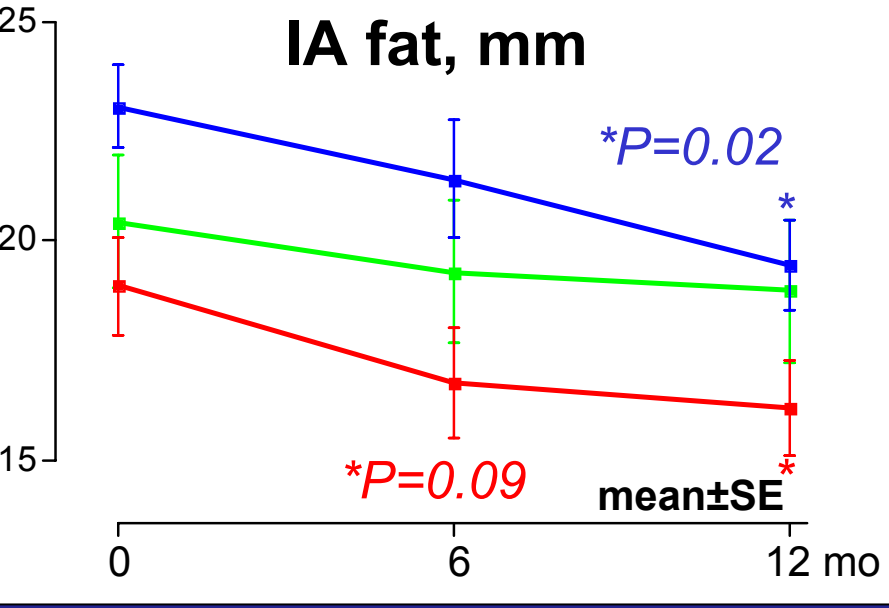

ΔBMI, kg/m²
2
0
-2
-4
mean±SE
0
3
6
9
12 mo

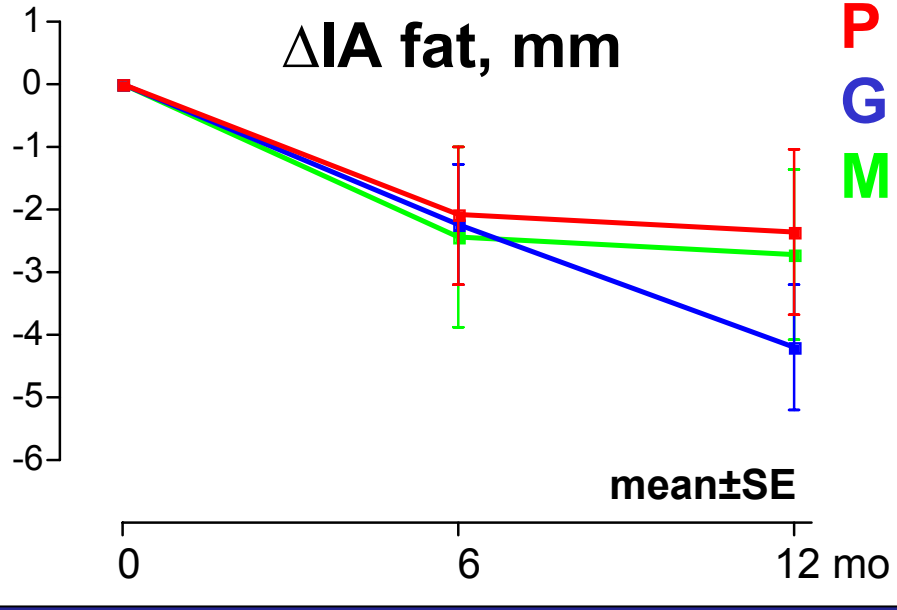
P
G
M

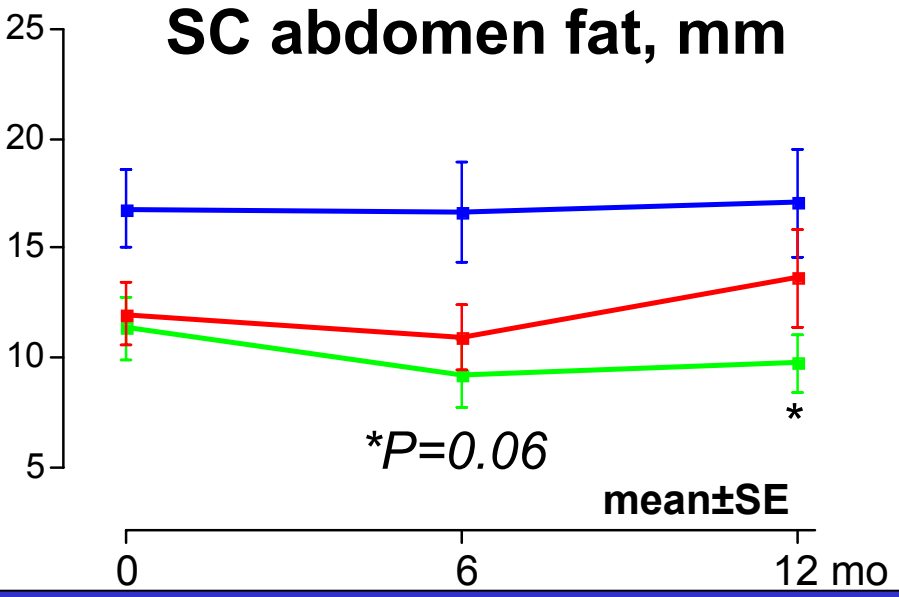

WHR
1.05
1.00
0.95
0.90
0.85
0.80
mean±SE
0
3
6
9
12 mo

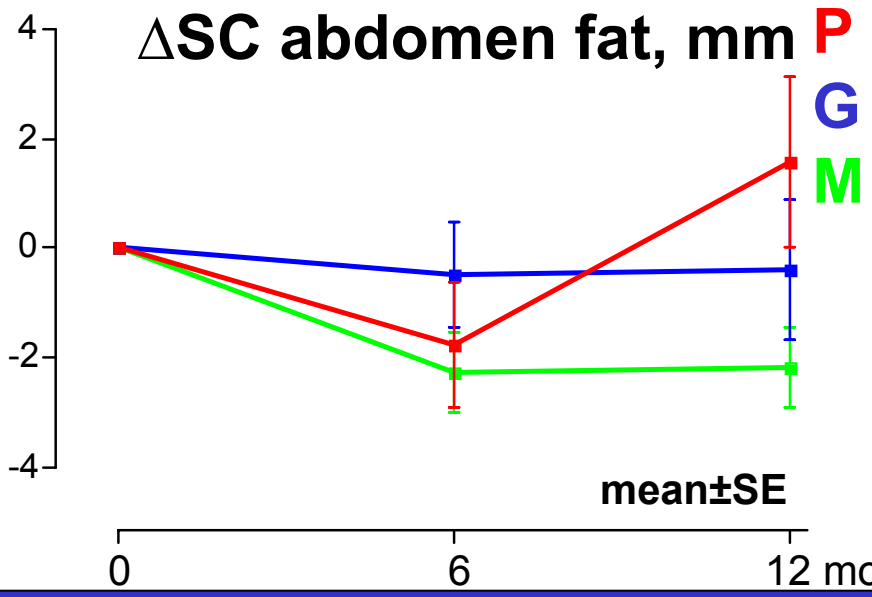

ΔWHR
0.10
0.05
-0.00
-0.05
-0.10
-0.15

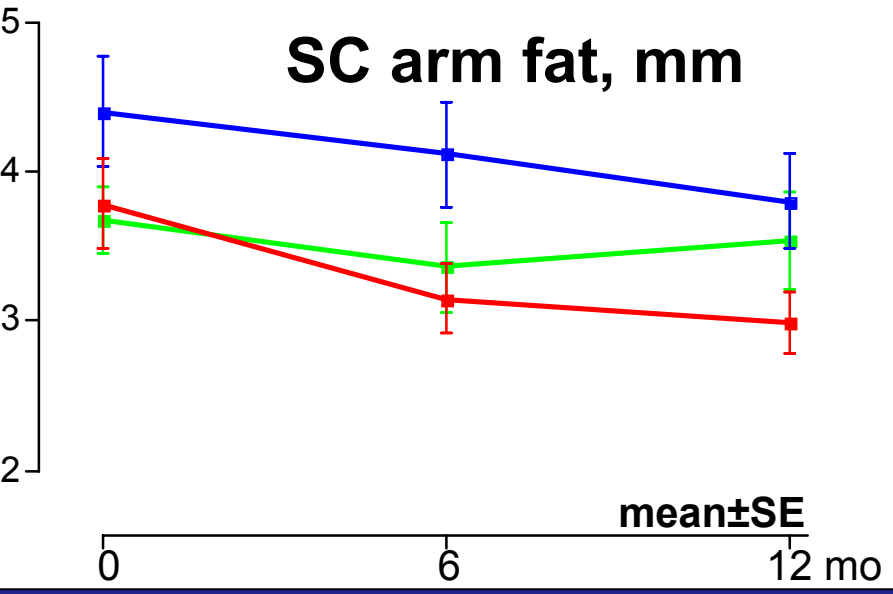
P
G
M

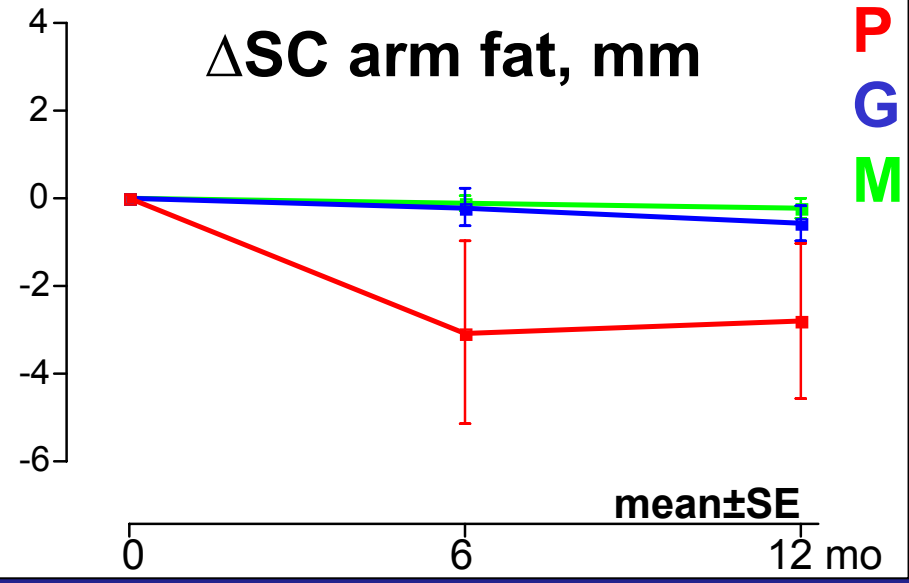

IA fat, mm
*P=0.02
*P=0.09
mean±SE
25
20
15
0
6
12 mo

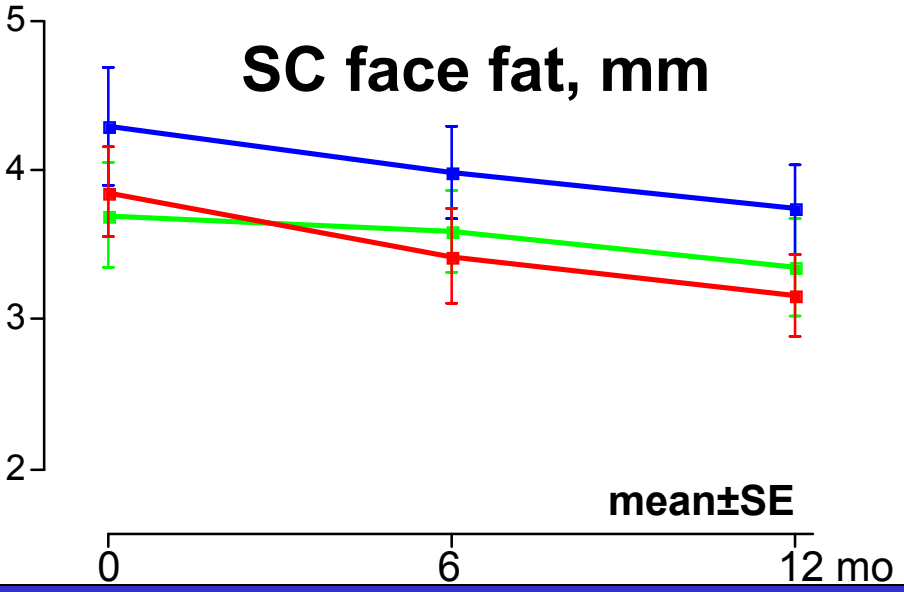

ΔIA fat, mm
P
G
M
mean±SE
1
0
-1
-2
-3
-4
-5
-6
0
6
12 mo

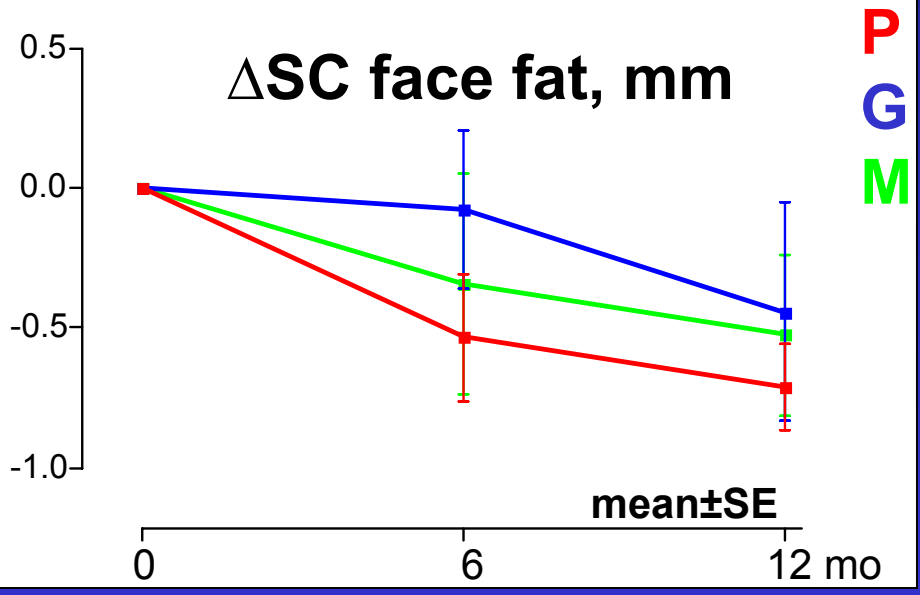

SC abdomen fat, mm
*P=0.06
mean±SE
25
20
15
10
5
0
6
12 mo

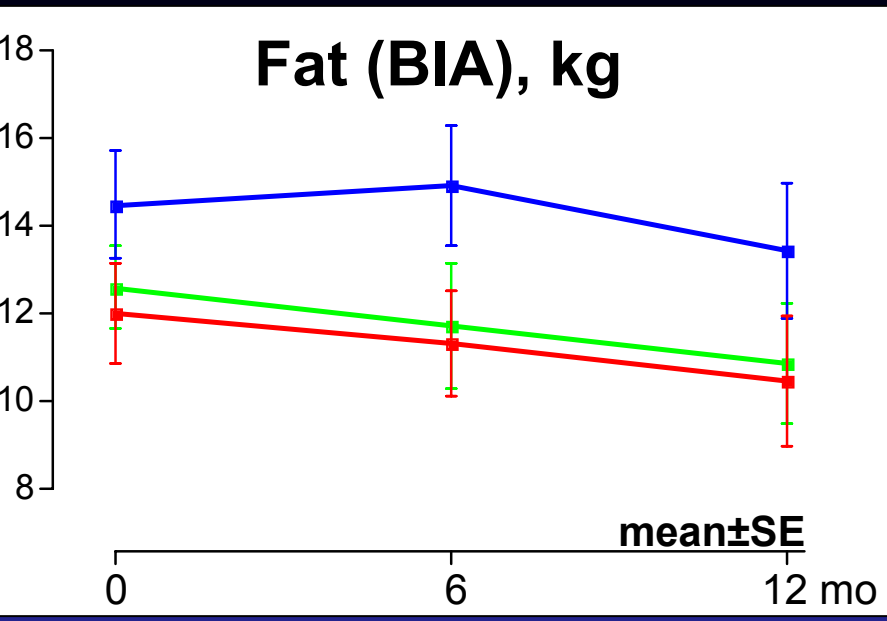

ΔSC abdomen fat, mm
P
G
M
mean±SE
4
2
0
-2
-4
0
6
12 mo

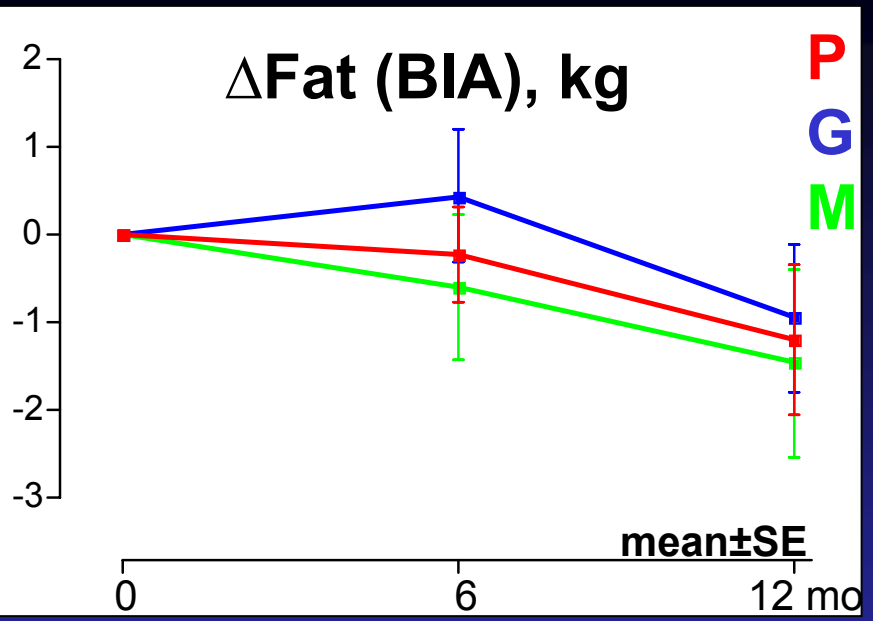

SC arm fat, mm
5
4
3
2
mean±SE
0
6
12 mo

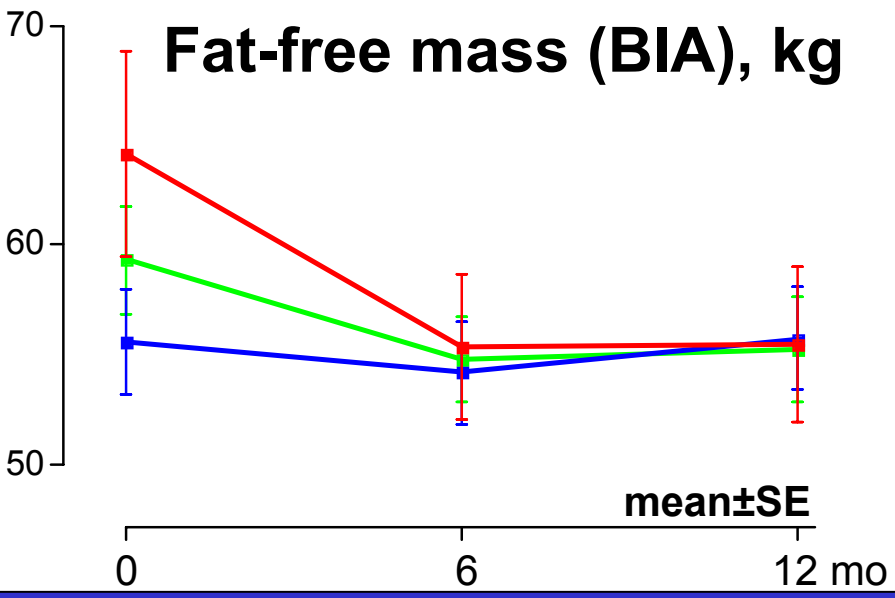

ΔSC arm fat, mm
4
2
0
-2
-4
-6
mean±SE
0
6
12 mo
P
G
M

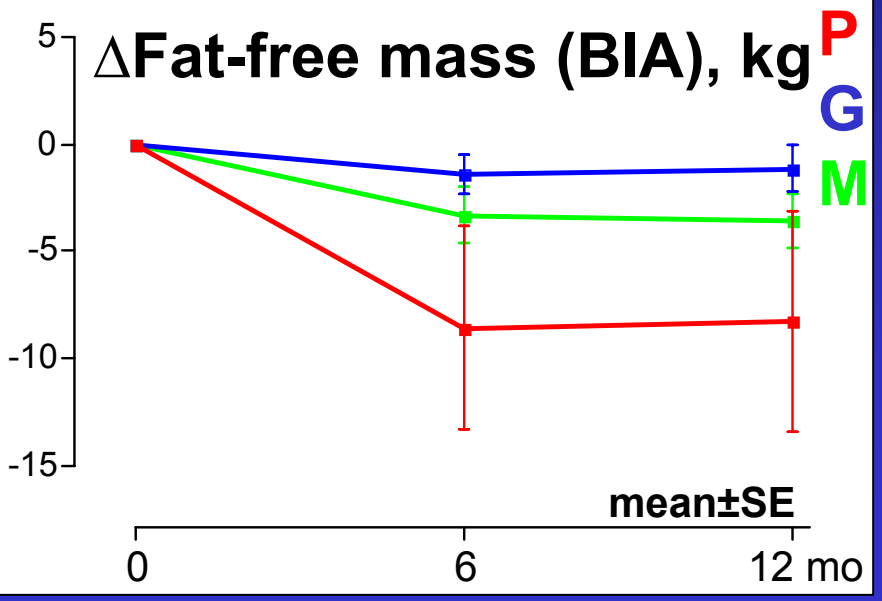

SC face fat, mm
5
4
3
2
mean±SE
0
6
12 mo


ΔSC face fat, mm
0.5
0.0
-0.5
-1.0
mean±SE
0
6
12 mo
P
G
M


Fat (BIA), kg
18
16
14
12
10
8
mean±SE
0
6
12 mo


ΔFat (BIA), kg
2
1
0
-1
-2
-3
P
G
M
mean±SE
0
6
12 mo


Fat-free mass (BIA), kg
70
60
50
mean±SE
0
6
12 mo


ΔFat-free mass (BIA), kg
5
0
-5
-10
-15
P
G
M
mean±SE
0
6
12 mo

Metformin or gemfibrozil in HIV-associated lipodystrophy:
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METABOLIC PARAMETERS

Gemfibrozil vs placebo

RANDOM EFFECT REGRESSION MODEL

- **Triglycerides**

  Decrease constantly over time.

  The decrease is deeper for gemfibrozil group than for placebo.

- **Total cholesterol**

  Decreases significantly in the first 3 months but the decrease every 3 months after the 3r month is not significant.

  No differences could be seen between groups.

- **AUC insulin**

  Values increase at the 6th month, but there are no differences between 12th month and baseline.

- **No model found for: total cholesterol and fractions, glucose, AUC glucose (OGTT), and ISI.**

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METABOLIC PARAMETERS

Metformin vs placebo

RANDOM EFFECT REGRESSION MODEL

- **Triglycerides**
  Decrease at the 6th month, but no differences at other time points.
- **Total cholesterol**
  Increases significantly every 3 months. Higher significant increase with metformin as compared with placebo
- **HDL-cholesterol**
  Increases significantly every 3 months.
- **LDL-cholesterol.**
  Higher significant values in metformin group
- **Glucose and insulin**
  Both decrease significantly every 3 months.
- **AUC insulin**
  Decrease significantly in metformin as compared with placebo depending on time.
- **ISI**
  Increases significantly every 6 months.

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BODY COMPOSITION

Gemfibrozil vs placebo

RANDOM EFFECT REGRESSION MODEL

- **Intraabdominal fat (sonography)**

  Decrease every 6 months. The decrease is lower for gemfibrozil than for placebo.

- **Subcutaneous abdominal fat (sonography)**

  Higher increase for gemfobrozil than for placebo.

- **Subcutaneous arm fat (sonography)**

  Significant increase every 6 month. The increase is higher for gemfibrozil than for placeb

- **Subcutaneous facial fat (sonography)**

  Significant increase every 6 month. The increase is higher for gemfibrozil than for placeb

- **Total body fat (bioimpedance analysis)**

  Increase every 6 months. The increase is higher for gemfibrozil than for placebo.

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BODY COMPOSITION

Metformin vs placebo

RANDOM EFFECT REGRESSION MODEL

- **Intraabdominal fat (sonography)**

  Decrease at the 6th and 12th months. No differences between groups

- **Subcutaneous abdominal fat (sonography)**

  Decrease significantly in metformin as compared with placebo depending on time.

- **Subcutaneous arm fat (sonography)**

  Decreases constantly every 6 months.

- **Subcutaneous facial fat (sonography)**

  Decrease at the 6th and 12th months.

- **Total body fat (bioimpedance analysis)**

  Decreases constantly every 6 months.

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CONCLUSIONS

- Both gemfibrozil and metformin showed expected effects on metabolic parameters as compared with placebo, but their effect on body fat was different: an increase with gemfibrozil and a decrease with metformin.
- The impact of study drugs on both metabolic parameters and body fat had low clinical relevance.
- The results of this study do not support the recommendation of either metformin or gemfibrozil to treat body fat redistribution in HIV-1-infected patients.