

# No effect of rosiglitazone for treatment of HIV-1 lipodystrophy: randomised, double-blind, placebo-controlled trial

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## Summary

**Background** Lipodystrophy commonly complicates antiretroviral therapy of HIV-1 infection. Thiazolidinediones such as rosiglitazone promote subcutaneous fat growth in type 2 diabetics and adults with congenital lipodystrophy, and can prevent HIV-1 protease inhibitor toxicity to adipocytes in vitro. We postulated that rosiglitazone would improve HIV lipodystrophy.

**Methods** 108 HIV-1-infected lipodystrophic adults on antiretroviral therapy were randomised to rosiglitazone 4 mg twice daily (n=53) or matching placebo (n=55) for 48 weeks. The study had 80% power to detect a 0.5 kg difference in changes in limb fat (using dual-energy X-ray absorptiometry) between groups at week 48 by intention-to-treat analysis, and a 0.7 kg difference within each protease inhibitor stratum.

**Findings** Limb fat increased by 0.14 kg in the rosiglitazone group and 0.18 kg in the placebo group (mean difference -0.04 kg [95%CI -0.29 to 0.21];  $p=0.74$  by  $t$  test), with three participants (one on rosiglitazone and two controls), lost to follow-up. Rosiglitazone had no significant benefit on any other measure of lipodystrophy, despite large relative increases in plasma adiponectin (4.2 mmol/L [102%];  $p<0.0001$ ) and in three markers of insulin sensitivity ( $p=0.01$  to  $0.02$ ). Six participants ceased study drug in each group, four participants (three on rosiglitazone and one control) for related adverse events. The main adverse effects, which seem to be almost unique to this population, were asymptomatic hypertriglyceridaemia (mean relative increase 0.9 mmol/L at week 48;  $p=0.04$ ) and hypercholesterolaemia (1.5 mmol/L;  $p=0.001$ ).

**Interpretation** Rosiglitazone for 48 weeks did not improve lipodystrophy in HIV-1-infected adults receiving antiretroviral therapy. Use of less toxic antiretroviral treatment is necessary to prevent lipodystrophy.

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## Background

Lipodystrophy (peripheral lipodystrophy, central fat accumulation, and lipomatosis) affects at least 50% of HIV-1-infected adults receiving antiretroviral therapy, can be stigmatising and painful, and leads to suboptimal adherence to antiretroviral treatment.<sup>1</sup> The associated dyslipidaemia and type 2 diabetes increase cardiovascular disease risk proportional to the duration of antiretroviral therapy, although these metabolic factors may not fully account for this increased risk.<sup>2</sup>

Lipodystrophy is caused by some drugs within two of the four antiretroviral classes, namely, nucleoside analogue reverse transcriptase inhibitors and protease inhibitors, especially when both classes are combined.<sup>3,4</sup> Lipodystrophic fat has reduced expression of the adipocyte differentiation factor peroxisome proliferator activator receptor- $\gamma$  (PPAR $\gamma$ ).<sup>5</sup> Protease inhibitors may contribute to lipodystrophy by inhibition of sterol regulatory enhancer binding protein 1 (SREBP1)-mediated activation of the adipocyte retinoid-X-receptor:PPAR $\gamma$  heterodimer.<sup>6,7</sup> Nucleoside analogues may inhibit adipocyte mitochondrial DNA polymerase- $\gamma$  and so reduce the generation of mitochondrial proteins needed for oxidative phosphorylation.<sup>8,9</sup>

The only proven intervention for HIV lipodystrophy is switching from a thymidine-based nucleoside analogue (particularly stavudine) to the nucleoside analogue abacavir. This strategy, however, led to only a moderate improvement in limb fat mass after 2 years.<sup>10–13</sup> For reasons unknown, protease inhibitor cessation does not seem to improve lipodystrophy.<sup>14,15</sup>

Thiazolidinediones are PPAR $\gamma$  agonists that are effective for the treatment of type 2 diabetes, in part by partitioning fatty acids and glucose within adipocytes.<sup>16,17</sup> In vitro, thiazolidinediones promote adipogenesis, even in the presence of an HIV-1 protease inhibitor.<sup>6</sup> Thiazolidinedione treatment in diabetics and adults with congenital lipodystrophy increased peripheral fat, decreased visceral fat, and improved glycaemic abnormalities over 24 weeks, and might have had similar effects in autoimmune lipodystrophy.<sup>18,19</sup> Five studies, two of which were randomised, assessed rosiglitazone or the related pioglitazone for HIV lipodystrophy, with variable outcomes.<sup>20–24</sup> These studies were not powered adequately, however, to detect changes in lipodystrophy.

We undertook a randomised, placebo-controlled, 48-week trial to test the hypothesis that rosiglitazone would improve lipodystrophy in adults receiving antiretroviral therapy. The primary objective was to determine the effect of rosiglitazone 4 mg twice daily over 48 weeks on limb (arm plus leg) fat with dual energy X-ray absorptiometry (DEXA) (which cannot quantitate facial fat). Secondary endpoints comprised other body composition measures, metabolic measures and safety.

## Methods

### Participants

Participants were recruited at 17 HIV primary care (n=13) or hospital outpatient (n=4) sites in Australia.

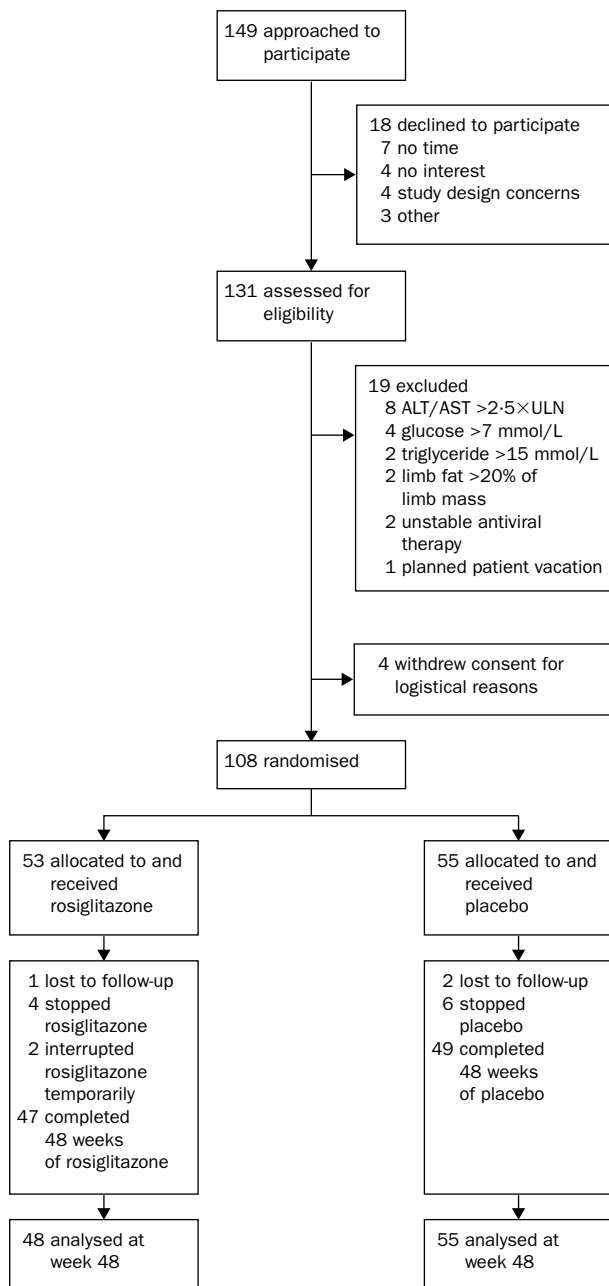


Figure 1: Trial profile

Eligibility criteria included documented HIV-1 infection, age greater than 17 years, and limb fat less than 20% of limb tissue or limb fat percentage at least 10% less than truncal fat percentage by DEXA. These DEXA criteria were chosen so that participants would be similar to those recruited in two earlier randomised HIV lipodystrophy studies.<sup>10,13</sup> Participants had to have been receiving combination antiretroviral therapy unchanged for 12 weeks, and have no screening lipid and glycaemic indices needing treatment, apart from diet or exercise, and a negative pregnancy test. Women of childbearing potential had to be using contraception. Contraceptive, sex hormone replacement, and lipid-lowering treatments used in the preceding 6 months could be continued.

Patients were ineligible if they had HIV wasting syndrome, heart failure of New York Heart Association

class 2 or greater, uncontrolled hypertension, any serious medical condition such as active AIDS, pancreatitis, or hepatitis within the previous 6 months, or if they were breast-feeding. Insulin, oral anti-diabetic agents, anabolic steroids (except testosterone replacement for proven hypogonadism), oral glucocorticosteroids at greater than replacement dose (prednisolone 7.5 mg per day or equivalent), growth hormone, other agents intended to stimulate appetite or weight gain, immune modulators, hydroxyurea, and cimetidine were not permitted. Laboratory exclusion criteria were serum transaminases, bilirubin and lactate greater than 2.5 times the upper normal limit, serum creatinine above the upper normal limit, haemoglobin less than 95 g/L, fasting glucose greater than 7.0 mmol/L, and fasting triglycerides greater than 15.0 mmol/L.

All participants provided written, informed consent after approval by the local human research ethics committee.

### Definitions

In the absence of an objective case definition when the study commenced, lipodystrophy was defined subjectively by presence of lipoatrophy or fat accumulation, or both, in the face, dorso-cervical spine, arms, breasts, abdomen, buttocks, or legs by use of standardised physical examination criteria.<sup>10,13</sup> The objective lipodystrophy case definition and severity scoring system developed subsequently were incorporated before study completion as secondary endpoints.<sup>25,26</sup> Virological failure was previously defined.<sup>10</sup>

### Intervention

The study was designed to randomise equally 100 eligible participants to rosiglitazone 4 mg twice daily or matching placebo for 48 weeks. Rosiglitazone was chosen for its safety profile and lack of interaction with antiretroviral-metabolising cytochrome P450 isozymes. Participants continued all antiretroviral therapy when possible and were advised to maintain their current diet and exercise pattern. Randomisation was done by statisticians at the National Centre in HIV Epidemiology and Clinical Research (NCHECR), Sydney, and minimised by current protease inhibitor use, current global lipoatrophy severity on combined physical examination and patient report, and study site. Minimisation by protease inhibitor use was used since we were mindful of the possible different pathogenesis of lipoatrophy with protease inhibitors

	Rosiglitazone n=53	Placebo n=55
<b>Patient</b>		
Age (years)	45 (7)	46 (8)
Sex (male)†	52 (98)	54 (98)
AIDS (category C disease)†	11 (21)	8 (15)
CD4-positive lymphocyte count (cells/mm <sup>3</sup> )	586 (239)	567 (260)
HIV RNA <50 copies per mL plasma†	40 (75)	40 (73)
<b>Body composition</b>		
Limb fat (kg)	2.69 (1.28)	2.69 (1.45)
Limb fat (%)	9.7 (3.7)	10.1 (4.9)
Right mid-thigh subcutaneous fat (cm <sup>2</sup> )	11 (8)	13 (11)
Subcutaneous abdominal fat (cm <sup>2</sup> )*	69 (40)	80 (47)
Intra-abdominal fat (cm <sup>2</sup> )*	134 (65)	116 (69)
Abdominal fat accumulation†	17 (32)	13 (24)
Dorso-cervical fat pad†	3 (6)	3 (5)

Numbers are mean (SD) unless otherwise indicated. \*The mean of values at the L2, L3, and L4 vertebrae. †Values are n (%).

Table 1: Baseline patients' characteristics: body composition

	Rosiglitazone n=53		Placebo n=55	
	n (%)	Duration (years)	n (%)	Duration (years)
<b>Antiretroviral treatment</b>				
Any previous nucleoside analogue therapy	..	4.8 (2.3)	..	4.9 (3.0)
Any previous protease inhibitor therapy	..	2.5 (1.3)	..	2.5 (1.6)
Time since cessation of stavudine	..	2.4 (1.5)	..	2.0 (1.3)
Current nucleoside analogue	47 (89)	..	49 (89)	..
Stavudine	26 (53)	4.0 (0.6)	16 (29)	4.2 (2.0)
Zidovudine	5 (9)	1.1 (0.9)	6 (11)	1.7 (1.2)
Lamivudine	28 (53)	4.0 (2.0)	32 (58)	4.1 (2.3)
Abacavir	17 (32)	1.6 (1.1)	18 (33)	1.7 (1.0)
Didanosine	15 (28)	3.0 (1.6)	13 (24)	3.6 (2.2)
Tenofovir	2 (4)	1.1 (1.2)	2 (4)	0.6 (0.1)
Current non-nucleoside analogue	32 (60)	..	30 (55)	..
Nevirapine	17 (32)	3.3 (1.2)	23 (42)	3.3 (1.9)
Efavirenz	13 (25)	2.3 (1.0)	5 (9)	1.8 (1.1)
Delavirdine	2 (4)	..	2 (4)	..
Current protease inhibitor	32 (60)	..	34 (62)	..
Indinavir*	11 (21)	3.9 (1.8)	16 (29)	3.6 (1.8)
Nelfinavir	5 (9)	3.0 (1.0)	2 (4)	3.3 (1.3)
Saquinavir*	5 (9)	4.3 (2.2)	7 (13)	4.8 (1.6)
Lopinavir	14 (26)	1.3 (0.6)	9 (16)	1.0 (0.5)
Ritonavir	1 (2)	4.0 (..)	4 (7)	2.9 (0.5)

\*Most individuals were receiving low-dose ritonavir (generally 100 mg twice daily) as a pharmacological booster. Duration is shown as mean (SD).

Table 2: **Baseline patients' characteristics: antiretroviral treatment**

compared with nucleoside analogues. Lipoatrophy severity was a surrogate for limb fat mass, because we postulated that more severe fat loss might be associated with less fat gain. Minimisation based on limb fat mass would have needed central reading of each baseline scan within 4 weeks, something that could not be achieved for all 17 sites nationwide. Each lipoatrophy severity score was the sum of patient and physician scores for the face, arms, legs, and buttocks, a score known to correlate with peripheral fat mass; in each region, a score of 0 for nil, 1 for mild, 2 for moderate, or 3 for severe was assigned, and so the maximum lipoatrophy score was 24.<sup>10,25,26</sup> Participants were minimised based on a final score less than or equal to 12 or greater than 12. Minimisation by site was used so that subjective assessments of lipo-dystrophy (a secondary endpoint) would be less prone to bias.

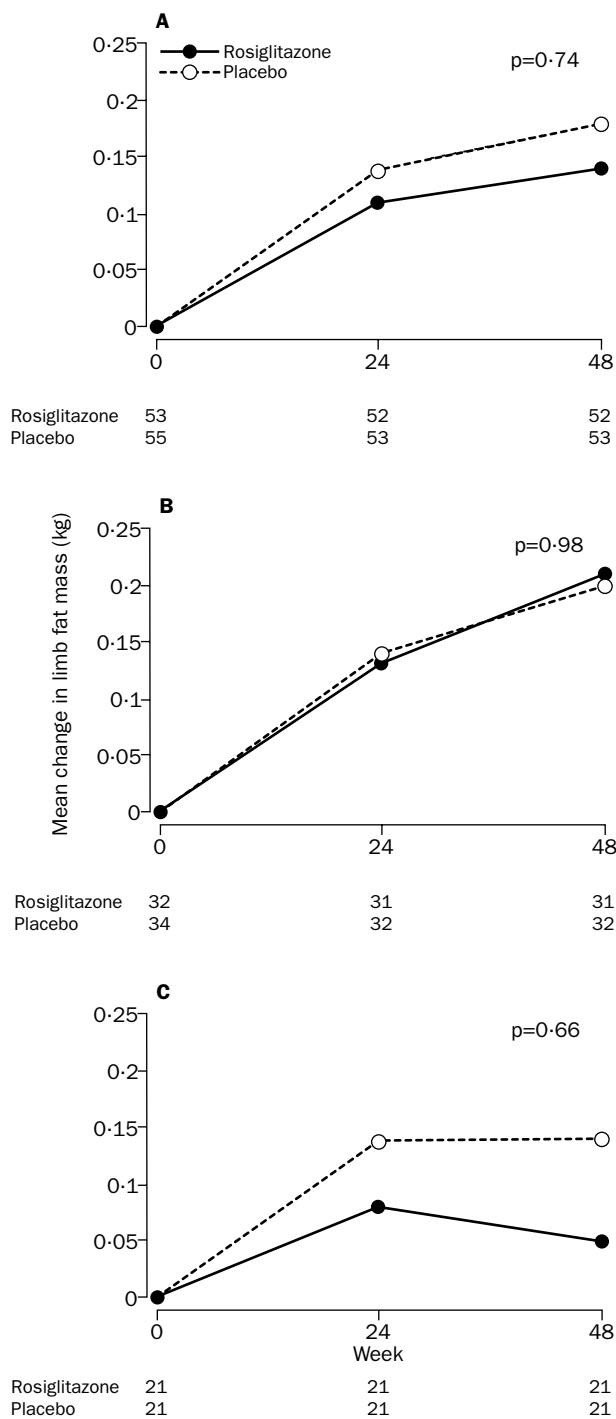
To ensure masking, only the study statistician had access to treatment allocation; lipid and glycaemic parameters, which could have been affected by active rosiglitazone, were measured at a central laboratory and were unavailable to participants or doctors for the duration of the trial. Emergency procedures were established to unmask study drug in the event of severe adverse reactions, but this did not happen.

Management guidelines for elevated hepatic transaminases, hyperglycaemia, hypoglycaemia, and anaemia included the potential toxicity profile of thiazolidinediones (including troglitazone, a drug withdrawn because of hepatotoxicity). These guidelines are not shown since none of these events occurred. Permanent cessation of study drug was mandatory for other grade 3 or 4 adverse events, pregnancy, or use of proscribed therapy. Grade 1 or 2 study drug-related adverse events were managed

Week	Event	SAE	Study drug	
			Association*	Ceased
<b>Rosiglitazone</b>				
-2	Gonococcal arthritis	Yes	No	No
8	Abdominal bloating	No	No	Yes
18	Grade 4 triglycerides	Yes	Definite	Yes
20	Abdominal and parotid swellings	Yes	Possible†‡	Weeks 25-43
23	Bilateral achilles tendon xanthomatosis and rupture	Yes	Possible†‡	Weeks 25-43
24	Patient choice, no event	No	No	Weeks 24-38
26	Depression	No	No	Yes
27	No event; withdrawn for non-adherence	No	No	Yes
30	Deep venous thrombosis	Yes	No†	Weeks 25-43
37	Epididymo-orchitis	Yes	No†	Weeks 25-43
48	Avascular necrosis hip	Yes	Remote	No
<b>Placebo</b>				
-2	Vagal episode	Yes	No	No
12	Abdominal bloating	No	No	Yes
14	Patient choice, no event	No	No	Yes
16	Portal hypertension possible venous thrombosis	Yes	Possible	Yes
16	Moved overseas	No	No	Yes
20	Surgery to resect laryngeal tumour	Yes	No	No
26	Patient choice, no event	No	No	Yes
31	<i>Clostridium difficile</i> enteritis	Yes	No	No
35	Patient choice, no event	No	No	Yes
48	Infected surgical wound needing IV antibiotics	Yes	No	No

\*Association between study drug and adverse event was determined by investigator before unblinding. †Adverse events occurred in the same patient; therapy was ceased because of the abdominal and parotid swellings. ‡Initially possibly attributed to study drug; resolved after rosiglitazone and antiretroviral therapy were ceased concurrently and recurred when the same antiretroviral therapy was recommenced without rosiglitazone. Masked rosiglitazone subsequently recommenced without recurrence.

Table 3: **Serious adverse events (SAE) and study drug discontinuations**



**Figure 2: Changes in body composition**

Mean changes from baseline in limb fat mass in all individuals (A), and in those receiving (B) or not receiving (C) a protease inhibitor at baseline. Numbers under graphs refer to patients in each group with available data at baseline, week 24, and week 48. p values are for comparisons at week 48 with the t test.

according to the treating clinician's assessment. Substitution of antiretroviral drugs was mandatory for related and recurrent grade 3 or 4 adverse events and optional for other adverse events or for virological failure.

#### Assessments

Demographical characteristics, previous antiretroviral treatment, and concomitant therapies were recorded at

screening. Participants were seen at weeks 0, 4, 8, and 12 weeks, and then every 6 weeks to week 48, including nine of the 12 participants who ceased randomised treatment but agreed to follow-up.

Safety assessments included clinical adverse events, use of concomitant medications, physical examination, full blood count, biochemistry (electrolytes, liver enzymes, urea, creatinine, creatine phosphokinase, amylase), plasma HIV-1 RNA and CD4-positive lymphocyte count, and serum  $\beta$ -human chorionic gonadotropin (pregnancy test) in women. Quality of life was self-assessed with a visual analogue scale.<sup>10</sup>

Fasting metabolic indices included glucose and insulin (including 2 h after 75 g oral glucose loading), C-peptide, estimated insulin resistance (by homoeostasis model assessment [HOMA]), total cholesterol, direct low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and lactate.<sup>10,13,25</sup> Participants and clinicians were masked to all lipid and glycaemic results after screening unless fasting triglycerides rose above 15.0 mmol/L (because of the small risk of pancreatitis) or fasting glucose rose above 7.0 mmol/L (diagnostic of diabetes) or fell below 3.0 mmol/L. Plasma adiponectin and leptin, markers of adipocyte function, were measured by radioimmuno assays (Linco Research, St Charles, USA) at baseline, week 24, and week 48.

Body composition was quantified at screening, week 24, and week 48 by DEXA and CT.<sup>10,13,25</sup> DEXA measured total and regional body fat and lean tissue. CT measured the mean intra-abdominal and subcutaneous fat areas at the intervertebral spaces immediately below the L2, L3, and L4 vertebrae and subcutaneous fat area at the right mid-thigh. We did not undertake CT of the face because there are no validated landmarks for this measurement. Quality assurance programmes were instituted for DEXA and CT, and all scans were analysed centrally. Patients' physical activity and diet (food frequency questionnaires) were recorded to determine whether either of these measures affected body composition.

Other objective body fat measures included the lipodystrophy case definition score,<sup>22</sup> total and trunk fat with DEXA, weight, body-mass index, and waist and hip circumferences. Subjective lipodystrophy presence and severity overall were measured by clinicians and participants every 24 weeks (every participant was assessed by the same clinician at all timepoints) with a standardised scoring system; a score of 0 for nil, 1 for mild, 2 for moderate, or 3 for severe was assigned for every region.<sup>10,25,26</sup>

#### Statistical analysis

The study had 80% power to detect a 0.5 kg difference in changes in limb fat (by DEXA) between groups at week 48 by intention-to-treat analysis, and to detect a 0.7 kg difference within each protease inhibitor stratum. On the basis of previous studies, we judged that an effect less than 0.5 kg over 12 months would not be clinically meaningful. Analyses were done after all randomised participants had completed 48 weeks' follow-up or were permanently lost to follow-up. Baseline characteristics were summarised without formal between-group comparison. Changes from baseline in efficacy endpoints were summarised at each nominal study week by randomised group, both overall and separately for each protease inhibitor stratum. Time windows were defined by the mid-point between nominal study weeks, except for body composition studies which were done within 4 weeks of weeks 24 and 48; if more than one measurement of a parameter were available in a time window, the mean value was used.

	Week 0		Week 48				
	Mean		Change from baseline		Between-group difference		
	Rosiglitazone	Placebo	Rosiglitazone	Placebo	Mean	95% CI	p
<b>Body composition/lipodystrophy</b>							
Weight (kg)	73.4 (10.6)	71.5 (9.1)	0.5 (3.3)	1.2 (2.7)	-0.7	-1.9 to 0.5	0.24
Body-mass index (kg/m <sup>2</sup> )	23.3 (2.8)	22.1 (2.4)	0.2 (1.1)	0.4 (0.9)	-0.2	-0.6 to 0.1	0.22
Total fat (kg)	10.8 (4.7)	10.9 (5.0)	0.5 (2.1)	0.6 (2.0)	-0.1	-0.9 to 0.7	0.81
Trunk fat (kg)	7.5 (3.4)	7.6 (3.6)	0.3 (1.7)	0.4 (1.4)	-0.1	-0.7 to 0.5	0.78
Total lean mass (kg)	58.3 (7.0)	56.6 (6.4)	-0.2 (2.0)	0.1 (2.2)	-0.3	-1.1 to 0.5	0.41
Hip circumference (cm)	89.8 (6.0)	89.8 (5.0)	-0.5 (5.4)	0.8 (2.7)	-1.3	-3.0 to 0.4	0.13
Subcutaneous right mid-thigh fat (cm <sup>2</sup> )	11 (8)	13 (11)	1 (3)	0 (4)	0	-1 to 2	0.60
Subcutaneous abdominal fat (cm <sup>2</sup> )	69 (40)	80 (47)	5 (34)	7 (22)	-2	-13 to 10	0.79
Intra-abdominal fat (cm <sup>2</sup> )	134 (65)	116 (69)	-17 (50)	-11 (28)	-6	-22 to 10	0.46
Waist circumference (cm)	86.6 (7.2)	86.4 (8.0)	0.3 (3.5)	0.6 (3.2)	-0.3	-1.6 to 1.0	0.65
Waist to hip ratio	0.97 (0.07)	0.96 (0.06)	0.01 (0.07)	0.00 (0.04)	0.01	-0.01 to 0.03	0.36
Lipodystrophy case definition score	4.9 (17.7)	3.2 (15.0)	7.7 (12.1)	8.1 (11.4)	-0.5	-5 to 4	0.85
Subjective lipoatrophy (patient)	9.9 (3.9)	9.1 (3.7)	-3.7 (3.9)	-3.3 (3.8)	-0.4	-2.0 to 1.2	0.62
Subjective lipoatrophy (physician)	9.6 (3.2)	9.6 (3.8)	-1.9 (3.3)	-2.6 (3.7)	0.6	-0.8 to 2.0	0.40
Subjective fat accumulation (patient)	2.0 (1.9)	1.8 (2.2)	0.7 (3.1)	0.5 (2.5)	0.2	-1.0 to 1.3	0.78
Subjective fat accumulation (physician)	1.7 (1.9)	1.8 (1.6)	0.4 (1.6)	-0.5 (1.4)	0.8	0.2 to 1.4	0.01
<b>Blood pressure</b>							
Systolic	120 (13)	122 (12)	1 (13)	0 (14)	1	-5 to 6	0.77
Diastolic	77 (10)	77 (11)	-2 (9)	0 (11)	-2	-6 to 2	0.32
<b>Adipocytokines</b>							
Leptin (mmol/L)	2.9 (1.4)	3.1 (1.8)	0.0 (0.9)	0.2 (1.1)	-0.2	-0.6 to 0.2	0.26
Adiponectin (mmol/L)	4.1 (3.3)	4.5 (3.7)	4.1 (4.3)	-0.1 (1.4)	4.2	2.0 to 5.4	<0.0001
<b>Glycaemic</b>							
Glucose (mmol/L)	5.2 (0.5)	5.2 (0.5)	-0.2 (0.5)	-0.2 (0.5)	-0.2	-0.3 to 0.1	0.45
2-hour glucose (mmol/L)	6.0 (1.9)	6.3 (1.9)	-0.2 (1.7)	-0.1 (2.0)	-0.1	-0.9 to 0.7	0.79
Insulin (mIU/L)	11.4 (12.0)	9.7 (6.1)	-3.5 (12.4)	0.7 (4.6)	-4.2	-7.8 to -0.6	0.02
2-hour insulin (mIU/L)	51.3 (52.3)	54.2 (47.1)	-13.6 (48.2)	3.9 (53.9)	-17.5	-38 to 3	0.09
C-peptide (ng/mL)	2.9 (1.6)	3.1 (1.5)	-0.1 (1.5)	0.2 (1.2)	-0.3	-0.8 to 0.2	0.33
Glucose:insulin ratio	0.8 (0.5)	0.7 (0.3)	0.1 (0.5)	-0.1 (0.3)	0.2	0 to 0.3	0.05
HOMA score (mIUmmol/L <sup>2</sup> )	2.7 (3.1)	2.3 (1.7)	-1.0 (3.2)	0.04 (1.3)	-1.0	-2.0 to 0.1	0.03
<b>Lipid</b>							
Total cholesterol (mmol/L)	6.0 (1.4)	6.2 (1.8)	0.9 (1.6)	0.0 (1.6)	1.0	0.4 to 1.5	0.001
LDL cholesterol (mmol/L)	3.2 (1.0)	3.4 (0.8)	0.8 (1.0)	0.4 (0.8)	0.4	0 to 0.8	0.04
HDL cholesterol (mmol/L)	1.1 (0.3)	1.2 (0.4)	0.0 (0.3)	0.0 (0.2)	0.0	-0.1 to 0.1	0.55
Triglycerides (mmol/L)	3.9 (3.3)	3.4 (2.6)	1.5 (3.7)	1.3 (0.1)	1.3	0.1 to 2.5	0.04
<b>Safety</b>							
Quality of life (0-100)	81 (16)	77 (12)	-6 (15)	-5 (12)	-1	-6 to 5	0.80
CD4+ lymphocyte count (cells/mm <sup>3</sup> )	586 (239)	567 (260)	14 (197)	32 (171)	-17	-93 to 59	0.65
HIV-1 RNA (log copies/ml plasma)	2.44 (0.99)	2.31 (0.93)	0.28 (1.01)	0.18 (0.92)	-0.11	-0.27 to 0.48	0.58
Haemoglobin (g/L)	151 (11)	150 (11)	-6 (10)	0 (9)	-6	-10 to -3	0.001
Alanine aminotransferase (U/L)	35 (14)	34 (16)	-5 (15)	7 (26)	-12	-20 to -4	0.005
Aspartate aminotransferase (U/L)	31 (12)	29 (8)	1 (12)	4 (21)	-3	-10 to 3	0.33
Alkaline phosphatase (mmol/L)	90 (27)	87 (27)	-12 (17)	-1 (19)	-11	-18 to -4	0.002
Lactate (mmol/L)	1.6 (0.5)	1.7 (0.6)	-0.1 (0.4)	-0.1 (0.7)	0	-0.2 to 0.3	0.80
<b>Daily dietary intake</b>							
Energy (kJ)	10023 (3636)	9948 (2972)	-456 (2501)	377 (3239)	-833	-1959 to 293	0.15
Fat (g)	82.7 (36.4)	79.4 (27.2)	-4.2 (23.8)	6.2 (35.1)	-10.4	-22 to 1.3	0.08
Fat (%)	30.3 (5.7)	29.7 (5.5)	0.1 (5.3)	1.1 (5.5)	-1.0	-3.0 to 1.0	0.34
Mono-unsaturated fat (g)	33.6 (18.0)	30.6 (11.3)	-2.3 (12.2)	3.9 (14.5)	-6.1	-11.0 to -0.9	0.02
Mono-unsaturated fat (%)	44.1 (4.4)	42.3 (3.7)	-0.4 (3.7)	0.9 (5.1)	1.3	-3.0 to 0.4	0.13
Saturated fat (g)	29.5 (12.8)	29.4 (11.9)	-0.2 (8.9)	1.7 (14.2)	-1.9	-6.0 to 3.0	0.42
Saturated fat (%)	39.6 (5.2)	40.6 (5.6)	1.2 (4.4)	-0.2 (6.2)	1.4	-0.7 to 3.5	0.20

HOMA=homeostasis model assessment. LDL=low-density lipoprotein. HDL=high-density lipoprotein. Numbers are mean (SD).

Table 4: Changes in secondary endpoints

All efficacy analyses compared randomised groups in terms of change from baseline at weeks 24 and 48 on an intention-to-treat basis, including all participants with data at baseline and at least one follow-up assessment, and without adjustment for any baseline covariate. Primary efficacy analyses used a last value carried forward approach for participants lost to follow-up. Secondary analyses used only available data. Continuous endpoints were assessed through analysis of variance or non-parametric equivalents and binary endpoints by use of  $\chi^2$  tests or logistic regression. We did not adjust p values for multiple comparisons.

There was one protocol-defined interim efficacy analysis after all participants had completed 6 months of randomised therapy, in addition to 3-monthly safety

reviews by a data and safety monitoring board. The pre-defined threshold stopping rule for this analysis was a highly significant difference ( $p < 0.001$ ) in limb fat mass between groups and a consistent trend for differences in peripheral fat with all other imaging and clinical lipoatrophy endpoints (p values all  $< 0.1$ ), with no evidence of toxicity or reduced antiretroviral efficacy.

Serious adverse events, adverse events leading to cessation of study drug, and all clinical and all laboratory adverse events were summarised by randomised group. Factors associated with grade 3 or 4 hypertriglyceridaemia during the first 6 months were explored, since this was the main adverse event detected by 3-monthly safety review. Factors analysed by logistic regression were baseline demographical characteristics, antiretroviral treatment,

		Rosiglitazone		Placebo		p	
		n	Change in limb fat mass (kg)	n	Change in limb fat mass (kg)	Between groups	Interaction*
<b>Baseline</b>							
Protease inhibitor use†	Yes	32	0.21	34	0.20	0.89	
	No	21	0.05	21	0.14	0.74	0.70
Stavudine or zidovudine use	Yes	37	0.04	27	0.00	0.76	
	No	16	0.34	27	0.39	0.84	0.72
Insulin resistance (HOMA score)	Top quartile	15	0.12	12	0.20	0.68	
	Lower quartiles	38	0.14	43	0.17	0.74	0.86
Limb fat mass	<2.36 kg‡	27	0.06	27	0.10	0.93	
	≥2.36 kg‡	25	0.22	28	0.26	0.93	0.98
<b>On therapy</b>							
Triglyceride change to week 12	≤1.3 mmol/L‡	18	-0.07	35	0.21	0.18	
	>1.3 mmol/L‡	35	0.25	10	0.13	0.71	0.13

HOMA=homeostasis model assessment. \*Testing whether the magnitude of the treatment effect between commencing rosiglitazone or placebo is significantly different between the two strata. †Randomisation was stratified by use of protease inhibitor therapy at baseline. ‡Median value.

Table 5: Subgroup analyses comparing effect of rosiglitazone and placebo on changes in limb fat mass at week 48

lipid and glycaemic variables, limb fat mass, visceral fat area, and randomised treatment.

There was one protocol-defined subgroup analysis based on strata defined by protease inhibitor use at baseline. We postulated that rosiglitazone would increase limb fat more in participants not receiving a protease inhibitor than in those who did. Additional subgroup analyses were developed after study inception, but before database closure. These strata were defined by: baseline use of the nucleoside analogues stavudine or zidovudine; baseline estimated insulin resistance, defined by the upper

quartile of HOMA values; baseline median limb fat mass; and median increases in triglyceride levels to week 12. Our hypothesis was that rosiglitazone would increase limb fat more in those not receiving stavudine or zidovudine than in those who were not given these drugs, with higher HOMA scores, more limb fat, and larger early increases in triglycerides. Differences in outcomes between randomised treatments in the strata were assessed with tests for interaction between treatment and strata. The protocol for this study was peer-reviewed and accepted by *The Lancet*; a summary of the protocol (01PRT/32) was

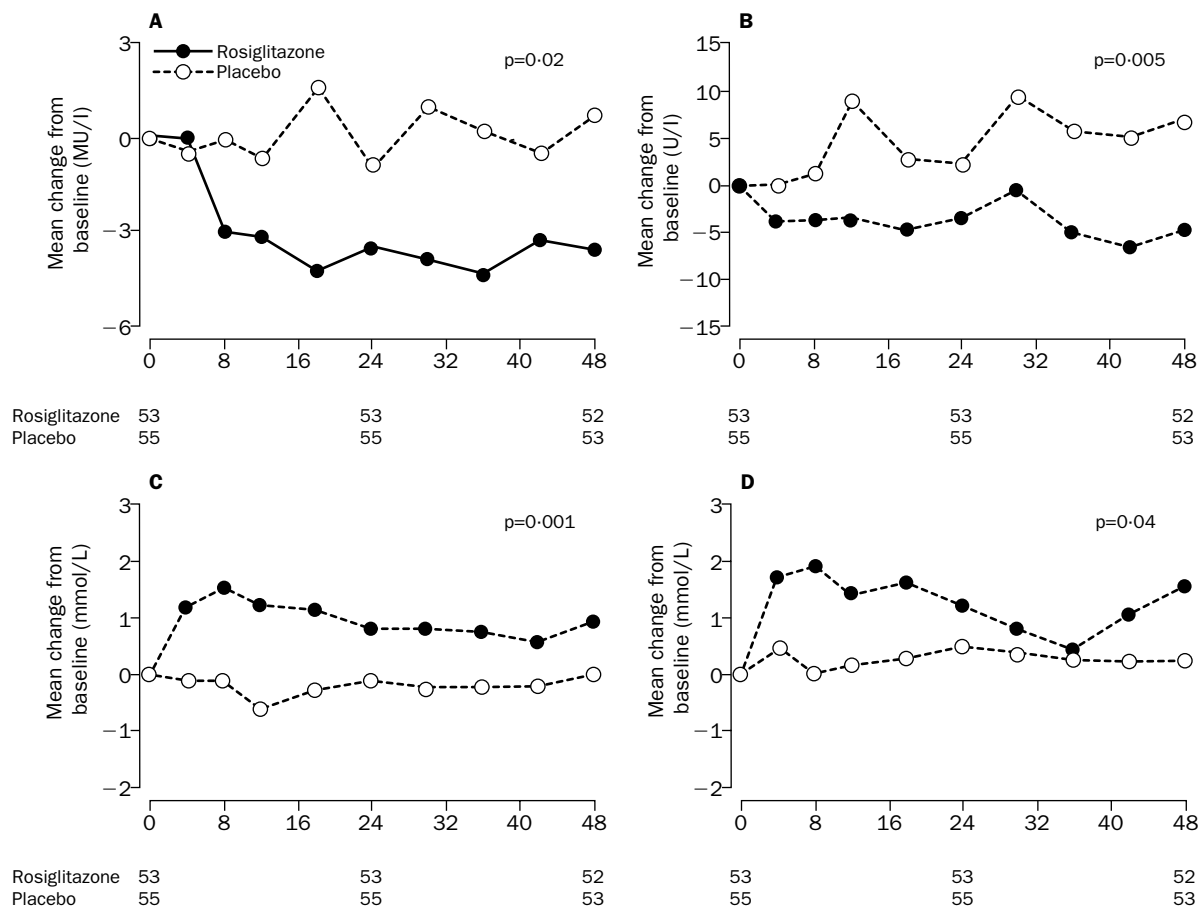


Figure 3: Changes in metabolic indices

Mean changes from baseline in fasting plasma insulin (A), alanine aminotransferase (B), total cholesterol (C), and triglycerides (D). Numbers under graphs refer to patients in each group with available data at baseline, week 24, and week 48. p values are for comparisons at week 48 with the rank-sum test.

published on the journal's website (<http://www.thelancet.com>), and the journal then made a commitment to peer-review the primary clinical manuscript.

### Role of the funding source

The study was investigator initiated and undertaken independently by NCHECR, which maintained the database and undertook all analyses. All investigators had access to all study data and hold final responsibility for the decision to submit the manuscript for publication. Bristol-Myers Squibb supported the study financially. GlaxoSmithKline supplied study drug. Both companies reviewed the protocol and manuscript but did not attempt to substantially change the study design, assessments, data analysis, or data interpretation.

### Results

Between December, 2001, and June, 2002, 149 patients were screened and 108 (72%) participants were randomised (figure 1). All patients had lipoatrophy on physical examination and self-report. Almost all (98%) participants were male, 18 (17%) had AIDS, and 66 (61%)

were receiving a protease inhibitor (tables 1 and 2). More participants in the rosiglitazone group than in the placebo group were receiving stavudine or zidovudine. The mean durations of all previous nucleoside analogue and protease inhibitor treatments, however, were similar. Six participants (four on rosiglitazone and two controls) were receiving lipid-lowering treatment at baseline.

Six (11%) rosiglitazone recipients interrupted therapy (four permanently), two for adverse events and four because of patient choice (table 3). Six (11%) placebo recipients ceased treatment, one for an adverse event and five out of their own choice. Dose of study drug was not reduced in any participant. The only lipid-lowering therapy commenced was gemfibrozil in one rosiglitazone participant.

14 antiretroviral drugs were stopped in each group (eight [15%] participants receiving rosiglitazone and nine [16%] participants receiving placebo). The most common drugs ceased were stavudine (three participants per group [weeks -2, 24, and 38 in the rosiglitazone group; weeks 24, 44, and 48 in the placebo group] and lamivudine (two participants per group). Five (9%) and three (5%)

	Rosiglitazone		Placebo	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
<b>Clinical adverse events</b>				
Constitutional				
Fatigue	9 (17)	0	3 (6)	0
Flu-like illness	5 (9)	0	1 (2)	0
Night sweats	3 (6)	0	2 (4)	0
Fever	2 (4)	0	2 (4)	0
Gastro-intestinal				
Diarrhoea	13 (25)	1 (2)	11 (20)	0
Nausea	6 (11)	0	6 (11)	0
Bloating	5 (9)	0	0	0
Vomiting		0	5 (9)	0
Gastro-enteritis	2 (4)	0	1 (2)	1 (2)
Respiratory				
Upper respiratory tract infection	21 (40)	1 (2)	22 (40)	1 (2)
Lower respiratory tract infection	2 (4)	0	5 (9)	1 (2)
Neurological				
Headache	7 (13)	1 (2)	6 (11)	1 (2)
Insomnia	6 (11)	0	3 (5)	0
Dizziness	4 (8)	0	2 (4)	0
Cutaneous				
Rash	4 (8)	1 (2)	2 (4)	0
Eczema	4 (8)	0	1 (2)	0
Mycosis	3 (6)	0	5 (9)	0
Warts	0	0	4 (7)	0
Herpes simplex	3 (6)	0	2 (4)	0
Basal cell carcinoma	1 (2)	0	0	0
Musculoskeletal				
Myalgia/arthralgia	8 (15)	0	7 (13)	0
Back pain	1 (2)	0	3 (5)	0
Cardiovascular	4 (8)	1 (2)	8 (15)	1 (2)
Ophthalmological	4 (8)	0	3 (6)	0
<b>Laboratory adverse events</b>				
Biochemical				
Creatine phosphokinase	45 (85)	19 (36)	43 (78)	8 (15)
Amylase	19 (36)	3 (6)	10 (18)	2 (4)
Lactate	21 (40)	0	20 (36)	0
Triglycerides	51 (96)	30 (57)	53 (96)	20 (36)
Total cholesterol	45 (85)	11 (21)	44 (80)	4 (7)
Glucose	2 (4)	0	4 (7)	0
Creatinine	7 (13)	0	10 (18)	0
Haematological				
Neutropenia	28 (53)	3 (6)	24 (44)	3 (5)
Anaemia	5 (9)	0	3 (5)	0
Thrombocytopenia	9 (17)	1 (2)	2 (4)	0
Hepatic				
Alanine aminotransferase	40 (75)	0	42 (76)	1 (2)
Aspartate aminotransferase	38 (72)	1 (2)	38 (69)	3 (5)
Bilirubin	12 (23)	1 (2)	11 (20)	1 (2)
Alkaline phosphatase	4 (8)	0	10 (18)	0

Table 6: Adverse events to week 48

participants in the rosiglitazone and placebo groups, respectively, stopped taking a protease inhibitor. No participant died or developed a new AIDS-defining or cardiovascular event.

There were 35 protocol violations (18 in the rosiglitazone group, 17 in the placebo group) in 25 participants (13 and 12 participants, respectively), the most common being non-study lipid or glycaemic measurements (10 participants per group). No participant commenced lipid-lowering therapy as a result, however.

Rosiglitazone had no beneficial effect on limb fat (figure 2). The mean changes in limb fat mass at week 48 were 0.14 (SD 0.58) kg with rosiglitazone and 0.18 (0.68) kg with placebo, a difference of  $-0.04$  (95% CI  $-0.29$  to  $0.21$ ) kg ( $p=0.74$  by *t* test). There was no significant effect on any other body composition or lipodystrophy endpoint (table 4). No difference in exercise intensity (data not shown), energy intake, or fat intake between the groups explained the lack of benefit. There was no significant effect noted in any subgroup at week 48 (table 5). Rosiglitazone caused a greater increase in limb fat at week 24 in those not receiving stavudine or zidovudine (rosiglitazone 0.48 kg, placebo 0.19 kg;  $p=0.06$ ) than in those receiving stavudine or zidovudine (rosiglitazone  $-0.06$  kg, placebo 0.09 kg;  $p=0.31$ ; *p* value for interaction 0.05), but this difference was not maintained at week 48.

Rosiglitazone improved fasting insulin levels (figure 3), HOMA scores, and glucose to insulin ratios, even though no participant was diabetic or developed diabetes. Rosiglitazone increased plasma adiponectin at week 24 (3.6 mmol/L [ $+93\%$ ];  $p<0.0001$ ) and week 48 (4.2 mmol/L [ $+102\%$ ];  $p<0.0001$ ), but not plasma leptin at either timepoint. Alanine aminotransferase and alkaline phosphatase levels fell with rosiglitazone after 4 weeks and these declines were sustained.

Triglycerides, total cholesterol, and LDL cholesterol levels increased from week 4. 30 (57%) participants receiving rosiglitazone and 20 (36%) receiving placebo developed grade 3 or 4 hypertriglyceridaemia ( $p=0.0001$ ), and 11 (21%) and four (7%) participants, respectively, developed grade 3 or 4 hypercholesterolaemia ( $p=0.0001$ ). Increases in triglycerides over the first 12 weeks of therapy were significantly associated with use of rosiglitazone (odds ratio 7.3 [95% CI 2.0–27.0];  $p=0.003$ ) and higher baseline triglycerides (odds ratio 5.0 [2.6–9.9];  $p<0.0001$ ).

Adverse events are shown in table 6. Haemoglobin concentrations fell significantly with rosiglitazone, but no participant developed grade 2 or greater anaemia. There was no grade 2 or higher increase in alanine or aspartate aminotransferase levels with rosiglitazone, and rosiglitazone had no significant effect on CD4-positive lymphocyte counts or plasma HIV viral load. There were 12 serious adverse events, seven in the rosiglitazone group (four participants) and five in the placebo group (five participants). Of these 12 events, one was definitely associated with rosiglitazone, two possibly associated with rosiglitazone, one possibly associated with placebo, and one remotely associated with rosiglitazone.

## Discussion

Rosiglitazone 4 mg twice daily did not improve lipodystrophy in HIV-infected adults receiving antiretroviral therapy. This result is in contrast to the sustained improvements in lipodystrophy that are seen after switching from a thymidine nucleoside analogue reverse transcriptase inhibitor (mainly stavudine), and in contrast to the benefit of troglitazone in congenital lipodystrophy.<sup>10–13,19</sup> No sustained, significant trend was

recorded in the five subgroups in which we postulated that rosiglitazone might be more active. The only possible benefit was seen in participants that were not receiving a thymidine nucleoside analogue, but this was seen only at week 24. As such, this result most likely represents a type 1 error or perhaps a true effect that is not sustained for 48 weeks and so of no clinical relevance. Although insulin sensitivity appeared to improve, hyperlipidaemia was observed, also reported by Sutinen and colleagues.<sup>23</sup>

Our findings are in keeping with those of two small randomised studies that yielded negative outcomes,<sup>23,24</sup> despite our study being substantially longer and, unlike the investigation done by Sutinen and colleagues, being powered for far less than a 40% change in subcutaneous fat mass. The possible beneficial effect reported by Hadigan and co-workers<sup>24</sup> was not significant; it is not known whether their finding was affected by inclusion of only lipotrophic patients with insulin resistance or by changes in antiretroviral treatment, diet, or exercise after baseline. The modest increases in limb fat seen in both groups in our study may be the result of thymidine nucleoside analogue cessation before baseline, but we cannot prove this. That almost all individuals in the study reported by Sutinen and co-workers were receiving stavudine might be relevant.

Since HIV lipodystrophy is associated with some residual PPARG expression in adipocytes,<sup>5</sup> the lack of response to rosiglitazone was unexpected. There are several possible reasons for this. Perhaps the most likely is that stimulation of residual PPARG cannot adequately promote adipogenesis in the presence of antiretroviral treatment. Specifically, although rosiglitazone can reverse the lipotrophic effect of protease inhibitors in isolated cell lines,<sup>6</sup> whether rosiglitazone can reverse nucleoside analogue-induced lipodystrophy *in vivo* is unknown. Although the rosiglitazone group had a greater proportion of participants receiving stavudine or zidovudine at baseline than did the placebo group, the absence of a sustained, significant difference in outcome between the subgroups receiving or not receiving stavudine or zidovudine argues somewhat against such a possibility. Second, recovery of key genes that are also depleted in lipodystrophy such as glucose transporter 4 might be necessary; PPARG does not always upregulate these genes *in vitro*.<sup>27</sup> Third, PPARG depletion in lipotrophic fat and *in vitro* could be a by-product and not part of the pathogenetic pathway, even though rosiglitazone can both reverse and prevent adipocyte toxicity and PPARG deficiency with protease inhibitors.<sup>6</sup> Fourth, PPARG agonists stimulate pre-adipocyte growth but can arrest growth in mature adipocytes *in vitro*.<sup>28</sup> Poor absorption or cellular activity of rosiglitazone were less likely as seen by the low rate of participant withdrawal and its multiple metabolic effects. Lastly, it is remotely possible, but in our view unlikely, that the outcome was specific to rosiglitazone and that another thiazolidinedione such as pioglitazone might prove effective.

One explanation for the discordant effects of rosiglitazone on body fat and insulin sensitivity may lie in the finding that thiazolidinediones affect insulin sensitivity not only in adipocytes but also in skeletal muscle and the liver; PPARG expression in these latter organs is not known to be reduced in HIV lipodystrophy. Thiazolidinediones can also have discordant effects on adipocyte insulin sensitivity and growth *in vitro*.<sup>29,30</sup> Our data argue against the suggestion that peripheral fat is critical for the insulin-sensitising effect of thiazolidinediones.<sup>31</sup>

Mechanisms for the discordant leptin and adiponectin responses to rosiglitazone are unknown, although factors controlling the expression of each gene might differ.<sup>32</sup> It is also possible that leptin but not adiponectin secretion is dependent upon adipocyte growth. No adipokine specific to subcutaneous adipocytes has been identified that could be measured to test whether rosiglitazone was active in the remaining lipotrophic subcutaneous fat. Ongoing analysis of subcutaneous fat biopsies from some participants might clarify this.

Hypertriglyceridaemia is rare in HIV-uninfected diabetics treated with thiazolidinediones. PPAR $\gamma$  is expressed in hepatocytes, the site of triglyceride synthesis, albeit to a lesser extent than in fat.<sup>33</sup> Lipotrophic mice receiving rosiglitazone have increases in hepatic triglyceride synthesis and steatosis,<sup>34</sup> whereas HIV-infected and uninfected lipotrophic adults receiving thiazolidinediones have reductions in liver fat.<sup>16,23</sup> In our investigation, rosiglitazone treatment also reduced the marginally elevated alanine aminotransferase levels, a common feature of hepatic steatosis. Collectively, these data suggest that rosiglitazone increases hepatic triglyceride synthesis and secretion in human beings, and that diabetics with normal fat and those with congenital lipotrophy, but not those with HIV lipotrophy, are able to store this triglyceride within adipocytes.

Rosiglitazone cannot be recommended for the treatment of HIV lipotrophy in adults receiving antiretroviral therapy, even though it has insulin-sensitising effects in this population (despite paradoxically increasing triglyceride levels). Its efficacy for lipotrophy in participants receiving neither a thymidine nucleoside analogue nor a protease inhibitor remains unknown, as does any effect in women or children, and studies in these populations could be useful. Any use for insulin resistance or type 2 diabetes in lipotrophic HIV-infected patients will need to take into consideration the adverse lipid effects we noted.

Our results have substantial implications for antiretroviral therapy of HIV infection. If lipotrophy can only be improved partially and only by modifying antiretroviral treatment, then avoidance of implicated drugs will be critical for those patients wishing to avoid this complication. Promising preliminary results in this respect have been seen with abacavir or tenofovir in combination with lamivudine and a non-protease inhibitor.<sup>35,36</sup>

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#### Contributors

A Carr conceived the study, participated in study design, overview of the project, patient enrolment, analysis, and drafted the manuscript. C Workman, G Rogers, and D Baker participated in study design, patient enrolment, and manuscript preparation. D Carey participated in study design, study initiation and coordination, and manuscript preparation, and oversaw site initiations and monitoring. A Martin participated in study initiation, coordination and manuscript preparation, and oversaw site initiations, and data monitoring. S Emery participated in study design, overview of the project, analysis, and manuscript preparation. H Wand undertook the statistical analyses and participated in manuscript preparation. M Law contributed to study design and manuscript preparation, and did the statistical analyses. K Samaras conceived the study, served as medical adviser for rosiglitazone, and participated in analysis and manuscript preparation. D Cooper conceived the study, participated in study design, patient enrolment, manuscript preparation, and secured funding. All investigators contributed to study design, patient recruitment, and reviewed the final manuscript.

#### Conflict of interest statement

A Carr has received research grants or funding from Boehringer-Ingelheim, Roche, Schering-Plough and the National Institutes of Health (NIH); consultancy fees from Boehringer-Ingelheim, Bristol-Myers Squibb, and GlaxoSmithKline; lecture sponsorships from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, and GlaxoSmithKline; and has served on advisory boards for Bayer, Bristol-Myers Squibb, GlaxoSmithKline, and Roche. C Workman receives research grant support from Abbott, Boehringer-Ingelheim, GlaxoSmithKline, Merck, and the National Health and Medical Research Council (NHMRC); honoraria from Abbott, Gilead Sciences, and GlaxoSmithKline; lecture sponsorship from Abbott, Boehringer-Ingelheim, GlaxoSmithKline, and Merck; and has served on advisory boards for Merck and Roche. D Carey has received research grant funding from Bristol-Myers Squibb, GlaxoSmithKline, Merck, and Roche, and an honorarium from GlaxoSmithKline. G Rogers has been given a consultancy payment from Merck and a scholarship from the NHMRC. D Baker has received honoraria from Boehringer-Ingelheim, Gilead Sciences, Merck, and Roche. M Law has received honoraria from GlaxoSmithKline, consultancy payment from Johnson and Johnson, and research support from the NHMRC and the American Foundation for AIDS Research. S Emery has received research grant support from Bristol-Myers Squibb, Chiron, GlaxoSmithKline, Merck, and the NIH. D Cooper has received research support from Boehringer-Ingelheim, Bristol-Myers Squibb, Chiron, Gilead Sciences, GlaxoSmithKline, Merck, Roche, NIH and NHMRC, honoraria from Boehringer-Ingelheim, Bristol-Myers Squibb, Chiron, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Roche, and consultancies from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Roche. A Martin, H Wand, and K Samaras have no conflicts of interest to declare.

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