

A Randomized, Placebo-Controlled Trial of Rosiglitazone for HIV-Related Lipodystrophy

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(See the editorial commentary by Grinspoon, on pages 1731–3.)

Background. Thiazolidinediones such as rosiglitazone may have benefit in ameliorating human immunodeficiency virus (HIV) lipodystrophy.

Methods. HIV-positive patients receiving stable, protease inhibitor-containing highly active antiretroviral therapy with HIV lipodystrophy were prospectively randomized to rosiglitazone (4 mg/day) or placebo. The primary end point was the 24-week percentage change in arm fat by dual-energy x-ray absorptiometry (DEXA). Clinical and anthropometric evaluations, fasting lipid parameters, oral glucose tolerance testing, CD36 expression, quality of life measures, and DEXA scanning were performed at baseline and week 24.

Results. Seventy-eight of the 96 enrolled patients were evaluated. Median age was 46.8 years, 97.4% were male, and 54% were treated with thymidine analogues. Median baseline limb fat was 3.76 and 2.99 kg in the rosiglitazone and control groups, respectively. Median changes in arm, leg, trunk, and total body fat at 24 weeks were not significantly different between groups (7.1% vs. 5.0% [$P = .94$]; 0.1% vs. -2.4% [$P = .90$]; 1.2% vs. -1.4% [$P = .81$]; and 1.7% vs. 0.4% [$P = .76$]). There were no significant changes in secondary end points. There was no correlation between changes in body fat or treatment-arm and CD36 expression.

Conclusions. This randomized, placebo-controlled trial did not show benefit of 4 mg/day of rosiglitazone on lipodystrophy or metabolic parameters in patients with HIV lipodystrophy.

Improvements in morbidity and mortality due to highly active combination antiretroviral therapy (HAART) have resulted in HIV infection becoming a chronic disease. With increased life expectancy, new problems have emerged either consequent to effects from long-term viral infection and/or to complications of HIV therapy.

An emerging complication is HIV-related lipodystrophy (HIV LD). Patients with this condition develop

a pattern of redistribution in body fat characterized by peripheral fat loss (facial and limb lipodystrophy) and central fat accumulation (buffalo hump, increased breast size, and abdominal girth). Although linked to antiretroviral therapy, its exact etiology remains unclear. HIV LD is not life threatening but has become a significant problem. It affects up to 50%–80% of patients receiving therapy [1–3] and has a negative cosmetic and psychological impact [4, 5]. Its progressive nature and disfiguring consequences adversely influence self-esteem and confidentiality [4]. Furthermore, its association with HIV therapy compromises adherence to the very agents that have so dramatically improved the prognosis of HIV infection [6].

The molecular basis of HIV LD is unknown, and, thus far, there is no effective therapy. Recent studies suggest that changes to some of the components of HAART (e.g., switching stavudine or zidovudine to abacavir or tenofovir) may slow progression or reverse lipodystrophy [7–9]. However, improvement does not occur in all patients, and it tends to be slow and incomplete. In addition, small improvements based on measures such as computed tomograph, magnetic resonance imaging, and dual-energy x-ray absorptiometry

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etry (DEXA) scanning may not be clinically relevant or apparent to the patient. Finally, beneficial changes in antiretroviral therapy may not always be possible without compromising virologic control. Consequently, many affected patients have resorted to cosmetic procedures to improve their appearance [10]. However, the long-term efficacy and potential complications of these treatments are unknown.

Rosiglitazone, a thiazolidinedione, is a selective agonist of the nuclear transcription factor peroxisome proliferator-activated receptor- γ (PPAR- γ), which influences the transcription of genes that regulate adipogenesis, glucose, and lipid metabolism [11]. It has been widely used for the treatment of type 2 diabetes and is known to improve insulin resistance [11]. In other congenital and acquired LD syndromes, a thiazolidinedione has been shown to increase peripheral fat, decrease visceral fat, and improve glycemic abnormalities [12]. Some studies of thiazolidinediones in individuals affected by HIV LD have also shown improvements in body fat and insulin resistance [13]. However, other studies have yielded conflicting results [14–17].

Given the role of PPAR- γ in adipocyte differentiation and proliferation [18], as well as fatty acid uptake and storage, thiazolidinediones have been hypothesized to have a role in ameliorating HIV LD. Furthermore, studies in animal models have shown increases in numbers of small adipocytes and subcutaneous adipose tissue with these agents [19, 20]. As well, there is evidence that HIV and antiretroviral therapy may affect adipocyte biology through PPAR- γ . For example, in previous work, we have demonstrated that protease inhibitors (PIs) can downregulate the expression of CD36 via PPAR- γ , both in vivo and in vitro [21]. This receptor mediates the uptake of modified lipoproteins by macrophages and functions as a high-affinity transporter of long-chain fatty acids in adipose and muscle tissue. Further in vitro work demonstrated that the effect of PIs on CD36 could be rescued by PPAR- γ agonists [22]. Interestingly, rodent models of CD36 deficiency exhibit dyslipidemia, abnormal fatty acid metabolism, and insulin resistance, a phenotype that parallels metabolic changes seen in HIV LD [23–25]. CD36 deficiency has been associated with hyperlipidemia and insulin resistance in humans [26]. We therefore hypothesized that rosiglitazone could potentially reverse the fat changes associated with HIV LD, at least partly through PPAR- γ activation and up-regulation of CD36. This randomized, placebo-controlled trial was designed to examine the effect of rosiglitazone on HIV LD in patients receiving PI-based HAART and to evaluate whether any effects might be mediated via CD36 expression.

PATIENTS, MATERIALS, AND METHODS

Patient population and selection criteria. Participants with documented HIV infection, at least 18 years of age, were recruited from one tertiary and several primary HIV care centers

in Toronto, Canada, between May 2002 and August 2004. They were required to have at least 1 feature of HIV LD rated at least mild, using a validated self-administered questionnaire developed by Carr et al. [27]. Self-reports were confirmed by a physician using the same questionnaire. Participants must have been receiving stable HAART consisting of ≥ 3 antiretroviral agents for at least 12 weeks before study entry, including at least 1 PI, and be deemed unlikely to change any component of HAART therapy during the study. Women of childbearing potential were required to have had a negative pregnancy test within 14 days and to use contraception during the study. Women taking oral contraceptive agents or hormone replacement therapy must have been on a stable regimen for ≥ 6 months before enrollment with no planned changes. Insulin resistance was not a required inclusion criterion. Exclusion criteria included uncontrolled hypertension or clinical evidence of heart failure or a serious medical condition that may affect patient safety, including an active AIDS-defining condition, pancreatitis, or hepatitis within the previous 6 months. Similarly, participants were not eligible if they had any significant laboratory abnormalities, including increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than twice the upper limit of normal (ULN), total bilirubin level greater than twice the ULN (unless secondary to indinavir or atazanavir and not associated with liver dysfunction), lactate level >2.5 times the ULN, hemoglobin level <95 g/L, serum creatinine level >140 μ mol/L, or international normalized ratio (INR) >2.0 . Participants must not be receiving concurrent therapy with any HMG-CoA reductase lipid-lowering agent (statin), insulin, anabolic steroid (except testosterone at replacement doses), oral corticosteroid at greater than replacement dose, growth hormone, or rifampin. Lipid-lowering therapy with fibrates was permitted. Further exclusion criteria included a history of thiazolidinedione-related hepatocellular reaction or edema, a history of hypersensitivity to thiazolidinediones or compounds with similar structures, current drug or alcohol abuse, diabetes requiring treatment, and the presence of coronary insufficiency.

All patients provided written, informed consent. The study was approved by the institutional ethics review committee.

Intervention. Participants were centrally randomized to receive either rosiglitazone (4 mg/day) or matching placebo for 24 weeks; treatment allocation was concealed. The dose was chosen with consideration of the limited clinical experience in HIV and concerns about drug interactions and hepatotoxicity found in other agents in the class.

Outcome measures. Total body scans by DEXA were performed by a trained technologist at baseline and 24 weeks of follow-up using the Hologic QDR 4500A (Hologic) fan-beam densitometer in the array mode. The cuts for defining limb areas in the DEXA results were all manually placed by an ex-

Table 1 Characteristics of patients at baseline.

Characteristic	Rosiglitazone	Placebo
Age, median (IQR), years	47 (39–53)	46 (42–53)
Male sex	38 (97)	38 (97)
White race	31 (82)	36 (92)
AIDS	12 (31)	11 (28)
Physician assessment of lipodystrophy		
Mild	8 (21)	0 (0)
Moderate	17 (44)	22 (59)
Severe	14 (34)	15 (41)
Lipodystrophy pattern		
Lipoatrophy	11 (28)	14 (36)
Lipohypertrophy	2 (5)	0 (0)
Mixed	26 (67)	25 (64)
d4T or AZT use during study	25 (64)	30 (77)
Duration of ART, median (IQR), years	8.0 (4.9–10.7)	8.1 (6.7–10.7)
Any current NNRTI	17 (44)	13 (33)
Any current NRTI	39 (100)	38 (97)
Any current PI	39 (100)	39 (100)
Single PI	12 (31)	14 (37)
Boosted PI	19 (49)	17 (45)
Double boosted PI	7 (18)	7 (18)

NOTE. Data are no. (%), unless otherwise indicated. ART, antiretroviral therapy; AZT, zidovudine; d4T, stavudine; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

perienced DEXA research technologist according to standard protocol. Analysis of overall and body site-specific fat percentages were performed on the basis of the standard protocol for body composition examination. The technologist was blinded to treatment allocation.

Height, weight, standardized circumference measures of collar size, bust, waist, hips, biceps, thighs, and calves, as well as calculations for waist:hip ratio and waist:thigh ratio, were measured at baseline and weeks 12 and 24. Additionally, each participant completed a self-administered questionnaire rating severity of LD by body site [27] and a quality of life questionnaire [28].

Metabolic parameters. A standard 75-g oral glucose tolerance test (OGTT) and measurements of proinsulin and insulin, hemoglobin A1C, cortisol, anti-islet antibody, and C-peptide levels were performed at weeks 0 and 24. Fasting total cholesterol, high-density lipoprotein (HDL)-C, triglycerides, low-density lipoprotein-C, and free fatty acids were measured at weeks 0, 4, 12, and 24. AST, ALT, alkaline phosphatase, γ -glutamyl transferase, INR, complete blood counts, amylase, creatinine, and lactate levels, HIV RNA load, and CD4 cell count were measured at weeks 0, 4, 8, 12, 16, 20, and 24. Homeostatic model assessment indices of insulin resistance were calculated from fasting insulin and glucose results [29]. CD36 levels in peripheral monocytes were measured using flow cytometry.

Peripheral monocytes were isolated from 30-mL heparinized blood, fixed with 4% paraformaldehyde, and stained for CD36 expression as described elsewhere [21, 22]. Surface-associated CD36 was quantitated by flow cytometry using the Epics Elite flow cytometer (Beckman-Coulter) on at least 10,000 monocytes. Data were analyzed using Elite software (Beckman-Coulter). CD36 levels were expressed as fluorescence intensity over secondary antibody only-stained controls.

CD36 levels in peripheral monocytes were measured by flow cytometry at baseline, 1, 3, and 6 months. Repeated measurements allowed for the assessment of changes in CD36 expression in response to rosiglitazone therapy and for correlation with anthropometric and biochemical measurements.

The primary outcome measure was the percentage decrease in arm fat by DEXA over a 24-week period, chosen on the basis of cohort data suggesting that this site would show the greatest change over time [30]. A sample size of 126 patients/group was required to detect a difference of 2.6% in the change in arm fat between treatment groups with 80% power and a significance level of .05, assuming an SD of 6.6% in the change in arm fat. Secondary outcome measures included changes in other DEXA regional fat measures and anthropometric, quality of life, and metabolic parameters as outlined above. Outcome assessors were blinded to treatment allocation.

Statistical methods. Baseline characteristics were compared between treatment groups using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Wilcoxon rank sum tests were used to compare primary and secondary outcomes between treatment groups at 24 weeks of follow-up.

RESULTS

One hundred thirteen patients were screened for entry into the study. Seventeen failed screening because of withdrawal of consent ($n = 10$), failure to meet screening laboratory parameters ($n = 5$), or a need to change antiretrovirals ($n = 2$).

Ninety-six patients were enrolled into the study between May 2002 and August 2004; 48 in the rosiglitazone arm and 48 in the placebo arm. The study follow-up was completed by December 2004. Nine rosiglitazone recipients discontinued the study prematurely: 3 were lost to follow-up, 3 withdrew consent, 2 withdrew for adverse events, and 1 withdrew for non-adherence to the study drug. Nine placebo recipients ceased treatment: 7 because they withdrew consent, 1 because of death unrelated to the study drug, and 1 because of an adverse event. The timing of the dropouts was similar between treatment groups: 7 patients in the rosiglitazone arm and 6 patients in the placebo arm dropped out of the study within 8 weeks. The 78 patients who completed 24 weeks of follow-up (39 in each arm) are included in the analysis. One patient in the rosiglitazone arm discontinued therapy at week 16 because of ab-

normal lipids but did complete the follow-up assessments. Follow-up was delayed for 1 patient in 2003 because of the severe acute respiratory syndrome (SARS) epidemic in Toronto and the restriction of clinic visits.

The baseline characteristics of patients are outlined in tables 1 and 2. The majority (97%) of participants were male, and 23 (29%) had a prior AIDS diagnosis. Patients had been receiving antiretroviral therapy for a median duration of 8 years. Overall, 55 (71%) were receiving either stavudine (d4T) or zidovudine (AZT) at baseline, with a greater proportion in the placebo group (77% vs. 64%, $P = .22$). All patients were receiving a PI at baseline. All patients had LD at baseline, classified as mild, moderate, or severe. Patients who did not complete the study were similar to patients who completed the trial with regard to CD4 cell count, viral load, arm fat, and arm circumference at baseline (data not shown).

Over the course of the study, 8 (10%) subjects began lipid-

lowering therapy (6 randomized to rosiglitazone and 2 to placebo), with a statin in 5 patients and a fibrate in 3. Three (4%) subjects changed antiretroviral therapy during the study. One placebo group patient was taken off d4T at week 7. Another placebo group patient started a new antiretroviral regimen at week 20. One rosiglitazone group patient replaced indinavir with atazanavir at week 11.

As shown in table 2, the mean DEXA arm fat at baseline was 1.3 kg in the rosiglitazone group and 1.0 kg in the placebo group. At week 24, there was no difference in the primary outcome (change in arm fat) between treatment groups (7.1% in the rosiglitazone group vs. 5.1% in the placebo group; $P = .94$). There were also no significant differences between treatment groups in the absolute or percentage changes in leg fat, limb fat, trunk fat, and total body fat or in the percentage of participants who had a 5% decrease in arm fat (table 2).

Table 2 shows the distribution of changes in arm fat, leg fat,

Table 2. Changes in primary and secondary end points.

Parameter	Week 0		Change from weeks 0 to 24		P
	Rosiglitazone	Placebo	Rosiglitazone	Placebo	
Body composition and lipodystrophy					
Weight, kg	76 (64 to 83)	76 (70 to 83)	0.5 (−0.8 to 2.9)	−0.4 (−1.7 to 1.8)	.12
Body mass index	25 (22 to 28)	24 (22 to 26)	0.2 (−0.3 to 0.9)	−0.1 (−0.6 to 0.6)	.12
Arm fat, kg	1.28 (0.84 to 2.12)	1.02 (0.79 to 1.40)	0.07 (−0.05 to 0.02)	0.05 (−0.07 to 0.16)	.63
Leg fat, kg	2.27 (1.62 to 2.74)	1.93 (1.62 to 2.33)	0.002 (−0.20 to 0.15)	−0.04 (−0.13 to 0.08)	.94
Limb fat, kg	3.76 (2.74 to 4.84)	2.99 (2.40 to 3.71)	0.07 (−0.21 to 0.39)	0.03 (−0.13 to 0.21)	.60
Trunk fat, kg	6.81 (5.12 to 10.64)	6.29 (4.82 to 8.55)	0.14 (−0.70 to 0.94)	−0.07 (−0.70 to 0.54)	.60
Total body fat, kg	12.18 (8.17 to 16.24)	10.20 (8.20 to 13.28)	0.18 (−0.96 to 1.04)	0.03 (−0.69 to 0.79)	.59
% change in arm fat	7.1 (−5.3 to 15.3)	5.1 (−6.5 to 15.0)	.94
% change in leg fat	0.1 (−8.7 to 9.2)	−2.4 (−5.9 to 6.3)	.90
% change in limb fat	1.7 (−5.4 to 11.5)	1.3 (−4.1 to 5.6)	.85
% change in trunk fat	1.2 (−10.6 to 11.6)	−1.4 (−11.4 to 14.5)	.81
% change in total body fat	1.7 (−8.8 to 10.4)	0.4 (−8.6 to 7.2)	.76
5% decrease in arm fat	10 (26)	10 (26)	.99
Glycemic indices					
Glucose, mmol/L	4.9 (4.5 to 5.3)	5.1 (4.4 to 5.6)	0.0 (−0.4 to 0.5)	0.2 (−0.3 to 0.6)	.31
2-h glucose, mmol/L	5.8 (4.6 to 7.0)	6.3 (4.8 to 7.5)	−0.1 (−0.9 to 1.3)	0.6 (−1.3 to 2.0)	.57
Insulin, mIU/L	67 (43 to 118)	68 (58 to 109)	3 (−18 to 16)	4 (−21 to 25)	.77
2-h insulin, mIU/L	274 (136 to 468)	297 (190 to 570)	22 (−201 to 112)	40 (−107 to 187)	.33
HOMA index	1.99 (1.56 to 3.76)	2.29 (1.76 to 3.59)	0.08 (−0.66 to 0.65)	0.12 (−0.62 to 0.96)	.81
Lipid levels					
Total cholesterol, mmol/L	5.8 (5.0 to 6.7)	5.4 (4.5 to 6.3)	0.2 (−0.5 to 0.9)	0.1 (−0.3 to 0.9)	.54
LDL, mmol/L	3.1 (2.1 to 3.8)	2.9 (2.1 to 3.6)	0.1 (−0.3 to 0.5)	0.2 (−0.1 to 0.8)	.27
HDL, mmol/L	1.2 (1.0 to 1.4)	1.1 (0.9 to 1.4)	−0.0 (−0.1 to 0.1)	0.1 (−0.1 to 0.2)	.12
Triglycerides, mmol/L	3.4 (2.0 to 4.4)	2.8 (1.8 to 4.3)	0.3 (−1.0 to 0.9)	−0.2 (−0.8 to 0.4)	.58
Immunologic and virologic					
CD4 cell count, cells/mm ³	417 (352 to 577)	466 (384 to 779)	−9.5 (−66 to 68)	0 (−93 to 98)	.87
CD36 mean fluorescent intensity	36.1 (20.9 to 44.1)	26.6 (18.4 to 54.1)	−7.5 (−25.6 to 15.0)	1.5 (−17.5 to 31.6)	.30
HIV RNA <50 copies/mL ^a	33 (85)	26 (67)	32/38 (84)	24 (62)	.03

NOTE. Data are median (interquartile range) values, unless otherwise indicated. HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein.

^a Data are the proportions of patients with HIV RNA <50 copies/mL at baseline and 24 weeks, not the change in proportions.

and trunk fat at 24 weeks of follow-up by treatment group. Median total cholesterol, triglyceride, and HDL levels are shown by treatment group and week of follow-up in figure 1. There were no significant differences in these lipid levels, in serum glucose levels, or in indices of insulin resistance either at baseline or in changes from baseline to 24 weeks of follow-up between treatment groups.

The effect of rosiglitazone on limb and arm fat showed a favorable trend in those not receiving concomitant thymidine analogue therapy (d4T or AZT), although not statistically significant (figure 2). Rosiglitazone resulted in smaller changes than placebo in limb and arm fat among patients taking thymidine analogues at baseline but in larger changes than placebo in patients not taking these drugs.

As shown in table 2, there were no significant differences between treatment groups in CD4 cell count at baseline (417 vs. 466 cells/mm³; $P = .16$) or change in CD4 cell count at 24 weeks of follow-up (-9 vs. 0 cells/mm³; $P = .87$). At baseline, more patients in the rosiglitazone group had an undetectable viral load (85% vs. 67%; $P = .06$). These proportions were similar at 24 weeks of follow-up (84% vs. 62%; $P = .03$).

The median monocyte CD36 levels were not significantly different between treatment groups at baseline (36.1 vs. 26.6; $P = .87$) and 24 weeks of follow-up (16.1 vs. 21.8; $P = .44$). At week 24, changes in CD36 were similar between groups (-7.5 vs. 1.5; $P = .30$). Results were unchanged when CD36 levels were normalized by CD14 values.

Thirty-three (85%) rosiglitazone recipients had at least 1 adverse event, with 11 (14%) adverse events considered related to the study drug. Similarly, 30 (77%) placebo recipients had

at least 1 adverse event, with 5 (7%) likely related to the study drug. Eleven (16%) patients had grade 3 or greater adverse events; in the rosiglitazone arm, this included 2 patients with elevated triglyceride levels, 1 with low platelet levels, 1 with cholecystitis, and 1 patient with pneumonia; in the placebo arm, 1 patient had an elevated ALT level, and 5 patients had unrelated clinical events.

DISCUSSION

Because of its negative cosmetic and metabolic effects, HIV LD continues to be a significant clinical barrier to the effective treatment of HIV infection. We sought to determine whether rosiglitazone, a PPAR- γ agonist, would slow peripheral fat loss in HIV-infected individuals receiving PI-containing HAART.

Our study failed to demonstrate an impact of 24 weeks of rosiglitazone (4 mg/day) on lipoatrophy, when compared with placebo. Similarly, we found no significant impact on any of our secondary end points including other body fat measures, measures of glucose metabolism, lipid profiles, or adverse effects.

Despite the lack of difference in body fat measures between treatment groups, there was significant intersubject variability in body fat changes over the course of the study in both groups. Part of this variability may be due to differences in the components of antiretroviral therapy as suggested by the subgroup analysis of patients receiving thymidine analogue therapy (figure 2). However, research is needed to further characterize factors affecting the natural history of HIV LD.

Although our in vitro work suggested a possible role for CD36 in the LD syndrome, this study did not show an impact

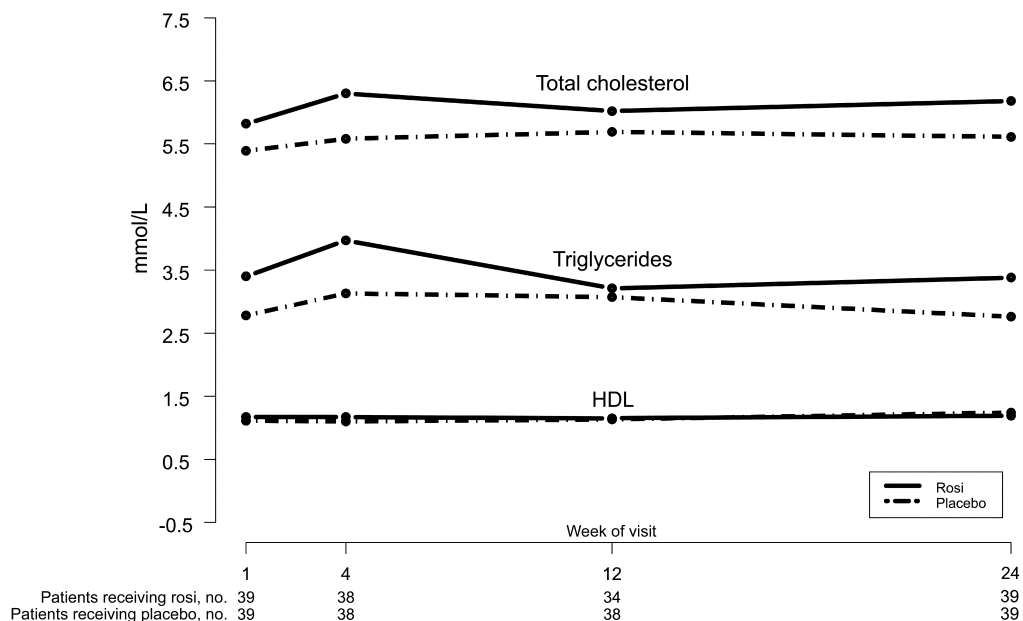


Figure 1. Median lipid levels by treatment and follow-up. HDL, high-density lipoprotein; rosi, rosiglitazone.

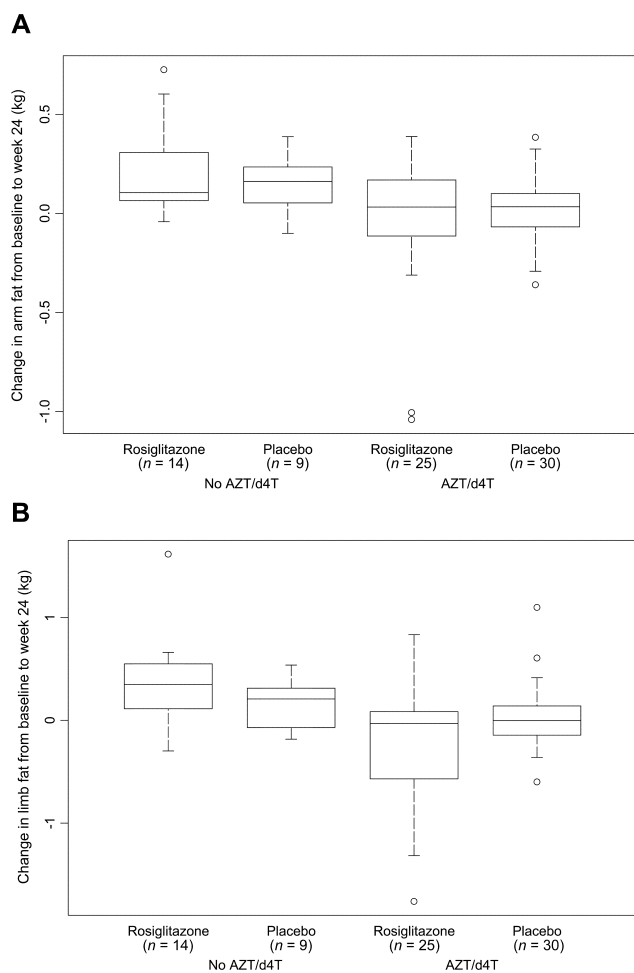


Figure 2. Effect of rosiglitazone on changes in arm fat (A) and in limb fat (B), by nucleoside reverse-transcriptase inhibitor use.

of monocyte CD36 expression on changes in fat loss or an effect of rosiglitazone on monocyte CD36 expression. Whether CD36 expression is modified by rosiglitazone in adipose tissue remains to be determined.

Previous studies of thiazolidinediones for treatment of HIV lipoatrophy have found conflicting effects on measures of body fat [13–17, 31]. Carr et al. [15] studied 108 lipoatrophic HIV-infected subjects. They found no differences in fat distribution between therapy with rosiglitazone (8 mg/day) and placebo over 48 weeks, regardless of PI or nonnucleoside reverse-transcriptase inhibitor exposure. Both arms showed gains in the primary end point of limb fat mass over the course of the study, which may have been related to changes in nucleoside therapy before or during the study. Indeed, rosiglitazone caused a greater increase in limb fat at week 24 in those not receiving stavudine or zidovudine; however, this difference was not maintained at 48 weeks. An *in vitro* substudy by the same group suggested that the impact of rosiglitazone could be limited by the continued use of thymidine analogues [32], a finding based on

observations that mitochondrial-encoded cytochrome b and PPAR- γ expression in fat tissue was lower in those treated with a nucleoside reverse-transcriptase inhibitor (NRTI). An earlier, smaller randomized, controlled trial [14] similarly found no benefit from 24 weeks of rosiglitazone (8 mg/day) on subcutaneous or intraabdominal fat mass. Treatment did, however, reduce insulin resistance and liver fat content.

In contrast, Hadigan et al. [13], studying a group of 28 hyperinsulinemic subjects affected by HIV LD, showed significant gains in subcutaneous leg fat over 3 months with rosiglitazone (4 mg/day). The mean percentage of body fat increased 1.38% in treated patients, compared with a 0.83% loss in control patients. The major impact of rosiglitazone in this study was improved insulin sensitivity.

Finally, 3 recent trials support a benefit of thiazolidinediones. In a randomized trial in men with HIV LD, rosiglitazone (8 mg/day) showed significant increases in both subcutaneous and visceral abdominal fat [17], compared with metformin. Another trial, recently presented in abstract form, demonstrated average increases in limb fat of 330 g among 130 HIV-infected men and women with HIV LD, treated with pioglitazone versus placebo over 48 weeks [33]. Mulligan et al. similarly found improvements in lower extremity fat with 4 mg/day of rosiglitazone [34].

The current study is the only trial examining this question exclusively in individuals concurrently receiving PI-containing HAART. Because we have demonstrated *in vitro* that PI drugs interfere with the expression of PPAR- γ , we hypothesized that individuals receiving this class of compound would stand to benefit the most from any potential effect of thiazolidinediones on adipose tissue. Despite its negative outcome, the present study may have been underpowered and missed a small effect of rosiglitazone, especially because we did not achieve our planned sample size. The study was terminated early because of slow enrollment based on publication of other studies showing no impact, the SARS epidemic in Toronto and concerns regarding attendance at the study center, and the increased recognition of the role of d4T in lipoatrophy and the risks of changing regimens contaminating the primary outcome. Post hoc power calculations, based on the observed SD of 16% in the primary end point, demonstrated that we achieved 80% power to detect a 10% difference in arm fat, whereas our trial results showed a 2% between-group difference. However, despite using maximal doses of rosiglitazone for 48 weeks, Carr et al. [15] found no difference in body fat between those receiving and not receiving PI therapy.

It is possible that concomitant thymidine analogue therapy might negate any positive effects of rosiglitazone on PPAR- γ . Subgroup analyses of our data performed post hoc suggest a trend toward greater improvement in peripheral body fat with rosiglitazone among patients not receiving thymidine analogues

(figure 2). This is in keeping with the results observed by van Wijk et al. [17]. Accumulating data points toward a role of thymidine analogues in the pathogenesis of lipoatrophy [35, 36], and it is possible that, in the absence of this class of drugs, beneficial effects from rosiglitazone may be more apparent. Identification of a subgroup of lipodystrophic patients that may benefit from rosiglitazone therapy will require a meta-analysis of the completed and ongoing studies.

In contrast to previous studies [13, 14, 17], we found no significant differences between treatment and control groups with regards to OGTT results or measures of insulin resistance. These differences may relate to choice of end points. For example, Hadigan et al. [13] measured insulin resistance using a euglycemic insulin clamp technique, a resource-intensive but more accurate method. Additionally, the lack of significant dysglycemia or hyperinsulinemia at baseline in the present study may account for the lack of difference between treatment and control groups. Similarly, median changes in lipid profiles in our trial were not affected by rosiglitazone therapy, whereas previous studies have documented lipid profile changes [13–15, 17]. It is unclear why this was not observed in the present study; however, the slightly higher use of lipid-lowering agents in the rosiglitazone group (6 vs. 2 patients) may have contributed to this result.

In conclusion, our results did not show a benefit of rosiglitazone in slowing or reversing lipoatrophy in patients receiving PI-containing HAART. Further research is needed to establish whether there is a role for thiazolidinediones in certain HIV-positive patients, such as those not receiving thymidine analogues. Although thiazolidinediones have a role in treating HAART-related dysglycemia, switches in NRTI therapy may be more effective strategy for treating lipoatrophy [36–38]. Finally, the wide variability in body fat composition and changes in both groups over the course of the present study underscores the need for future research into factors affecting the natural history of this syndrome.

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