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A Meta-Analysis of Six Placebo-Controlled Trials of Thiazolidinedione Therapy for HIV Lipoatrophy

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Keywords

Meta-analysis; Rosiglitazone/Pioglitazone; Lipoatrophy; HIV; HAART

INTRODUCTION

Highly active antiretroviral therapy (HAART) has resulted in improvements in morbidity and mortality for HIV-infected individuals but is associated with lipodystrophy characterized by body fat redistribution and metabolic changes. The characteristic body fat changes include the loss of subcutaneous fat in the limbs, face and buttocks (lipoatrophy) and /or a relative increase or conservation of fat in the trunk, breast, neck and abdomen (lipohypertrophy).[1] The predominant metabolic changes include dyslipidemia with increased triglyceride levels and disorders of glucose homeostasis including insulin resistance. Lipodystrophy can be a psychologically devastating consequence of HAART and can result in poor compliance or reluctance to initiate HAART. There is no proven, effective therapy for lipoatrophy.

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Conflicts of Interest

Andrew Carr has received research funding from Abbott, Merck and Roche; consultancy fees from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck and Roche; lecture sponsorships from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck and Roche; and has served on advisory boards for Abbott, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck and Roche.

Dominique Costagliola has received travel grants, consultancy fees and honoraria from Abbott, BMS, Boehringer-Ingelheim, Gilead, Janssen, Merck, GSK and Roche.

Steven Grinspoon has previously served as a consultant and received research funding from Theratechnologies and Serono and receives research support from Bristol-Meyers Squibb.

Kathleen Mulligan has served on advisory boards for Abbott, Theratechnologies, and Serono; has consulted for Amylin and Amgen; and has received research support from Theratechnologies.

Jussi Sutinen has received lecture sponsorships from Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Roche and Tibotec; has consulted for GlaxoSmithKline; and served on advisory board for Tibotec.

Sharon Walmsley has received lecture sponsorships and has served on advisory boards for GlaxoSmithKline, Boehringer-Ingelheim, Bristol-Meyers Squibb, Abbott, Roche, Merck, Tibotec, Gilead and Phizer.

The pathogenesis of these abnormalities remains unclear. Proposed mechanisms for the role of antiretroviral agents initially focused on the impact of protease inhibitors in increasing lipolysis[2] and decreasing lipogenesis[3]. One hypothesis implicates decreased activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), an important regulator of adipocyte differentiation and proliferation, in patients on protease inhibitors (PI).[4] As this enzyme is preferentially expressed in peripheral fat, this may account for the fat redistribution seen in the syndrome. PPAR-γ stimulation also improves insulin sensitivity and hyperlipidemia, and its decreased activity in the setting of PI, could account for the metabolic changes.[5,6]

An alternative hypothesis for the lipoatrophic changes implicates the nucleoside analogue reverse transcriptase inhibitors (NRTIs).[7] The thymidine analogues stavudine (d4T) and zidovudine (AZT) have been thought to play a key role both on the basis of *in vitro* inhibition of mitochondrial DNA polymerase gamma,[8] decreased transcription of mitochondrial RNA and changes in oxidation phosphorylation[9] and multiple clinical trials showing higher rates of lipoatrophy with NRTI-based therapy.[10,11,12,13]

Rosiglitazone and pioglitazone are both agents in the class of thiazolidinediones (TZDs) and are agonists for PPAR-γ activation and influence the transcription of genes that regulate adipogenesis, glucose and lipid metabolism. *In vitro*, TZDs promote adipogenesis. In HIV uninfected populations, TZDs have been used to treat type 2 diabetes and are known to improve insulin resistance, and increase limb fat. In congenital lipodystrophy syndromes, troglitazone increased peripheral fat, decreased visceral fat and improved glycemic abnormalities.[14,15,16] TZDs may also dose-dependently increase mRNA expression and secretion of adiponectin, which could impact on insulin resistance and fat redistribution. In a meta-analysis of randomized trials of TZDs in diabetic patients, pioglitazone and rosiglitazone were shown to have different impacts on lipid levels.[17]

Given these observations, six randomized trials were conducted to compare changes in body fat or insulin among HIV positive individuals randomized to TZD or placebo.[18,19,20,21,22,23] The results have been mixed. Rosiglitazone was associated with a significant increase in total body fat and subcutaneous leg fat area in one study[22] and with increased leg fat in another.[21] Other trials failed to show any significant effects on limb fat.[18,19,20] As thymidine analogues could counteract the impact of TZDs on PPAR-γ, subset analyses of individual trials have hypothesized that rosiglitazone may be useful to increase limb fat in patients not receiving a thymidine analogue.[18] The single placebo-controlled trial of pioglitazone demonstrated that pioglitazone marginally improved limb fat mass, particularly among patients not receiving d4T.[23]

This meta-analysis of the six randomized trials was undertaken to better determine the overall effect of TZD therapy on peripheral fat in HIV positive adults, to compare the effects of rosiglitazone and pioglitazone and to conduct subset analyses defined by the use at baseline of a thymidine analogue or a protease inhibitor.

METHODS

Randomized, placebo-controlled trials of a thiazolidinedione in HIV positive individuals which were published at the time of the analysis and had an outcome measure of body fat were identified through PubMed and consultation with experts in the field. Principle investigators of the identified trials were contacted and all agreed to participate in the meta-analysis.

The meta-analysis was conducted with the use of the original, individual-patient data from the six participating, randomized, placebo-controlled trials investigating the effects of

rosiglitazone (n=5) or pioglitazone (n=1) on changes in body fat and insulin resistance in HIV positive patients (Table 1). [18,19,20,21,22,23] From the study with a factorial design in which patients were randomly assigned to receive either metformin or placebo and to receive either rosiglitazone or placebo,[22] only patients randomized to either active rosiglitazone and metformin placebo (n=26) or to the dual placebo arm (n=27) were included in the meta-analysis.

The primary outcome of this meta-analysis was the impact of the TZD relative to placebo on changes in limb fat mass as determined by dual energy X-ray absorptiometry (DXA) scan analysis.

Statistical Methods

All data were combined into a single dataset. Baseline characteristics were summarized by treatment arm with counts and percentages for the categorical variables and with medians and interquartile ranges (IQR) for the continuous variables. Categorical variables were compared between treatment groups with chi square tests or Fisher's exact tests, as appropriate. Continuous variables were compared between treatment groups with Wilcoxon rank sum tests.

Generalized Estimating Equation (GEE) models were used to estimate the effect of TZD therapy on changes in limb fat while adjusting for covariates and correlation among multiple observations within individuals.[24] The exchangeable correlation structure was assumed. This methodology allows the number and timing of observations to vary within individuals. Covariates which had a p value of less than 0.10 in the univariate models or those believed to be possible confounding factors were candidates for inclusion in the multivariable regression model. Prespecified interaction terms between the use of d4T or AZT at baseline, the use of PIs at baseline, and treatment variables (TZD vs placebo, and dummy variables for rosiglitazone and pioglitazone compared to placebo) were tested for significance in the multivariate model.

At each follow-up visit, patients were classified as limb fat "responders" if they had an increase in limb fat mass from baseline of at least 10%; otherwise they were classified as "non-responders". GEE logistic regression models were used to identify predictors of a significant limb fat response by this definition.

The outcome variables of change in limb fat mass and increase in limb fat mass from baseline of at least 10% were chosen to adjust for possible imbalances in baseline limb fat between treatment groups.

Data were analyzed with SAS Version 9.1.

RESULTS

Participant Characteristics

Four hundred and twenty-seven patients were included in the meta-analysis. In total, 213 (50%) patients were randomized to the TZD therapy and 214 (50%) were randomized to placebo. Of the patients allocated to TZD therapy, 149 (70%) received rosiglitazone and 64 (30%) received pioglitazone.

Table 2 describes the baseline characteristics of the patients by treatment arm and for the whole population. Patients randomized to TZD therapy had marginally higher limb fat at baseline than patients randomized to placebo (3.1 vs 2.7 kg, p=.06). There was no significant difference between the TZD and placebo groups in any of other characteristics tested.

Limb Fat Changes

Measures of limb fat from DXA scans were available for 393 patients from five trials at baseline and for 373 patients at both baseline and at least one follow-up visit.[18,20,21,22,23] Figure 1 shows the median limb fat change from baseline by study center, treatment group and baseline use of AZT or d4T. The median limb fat change was not statistically significantly different between TZD and placebo for any of the subgroups in Figure 1.

Table 3 describes the results of univariate GEE models for limb fat changes from baseline. Smoking status, use of d4T or AZT at baseline and use of d4T at baseline were associated with lower limb fat mass change while weeks of follow-up and NNRTI use were associated with higher limb fat mass change. The overall effect of TZD therapy was statistically significant (GEE regression coefficient = 0.14 kg, p=.04). Patients receiving pioglitazone had significantly higher changes in limb fat mass compared to patients receiving placebo (coeff=0.33 kg, p<.01) while patients on rosiglitazone had changes in limb fat mass that were not significantly greater than those in patients receiving placebo (coeff=0.07 kg, p=0.36).

In a multivariable GEE model controlling for study, week of follow-up, NNRTI use and thymidine analogue use, there was a benefit of TZDs relative to placebo on limb fat mass gains (coeff=.13, p=.05) but no difference in the efficacy of TZDs according to thymidine analogue use in a separate model with an interaction term (p=0.64).

In a multivariable GEE model examining the effects of each TZD separately after adjusting for study, NNRTI use and d4T use (Table 4), patients receiving pioglitazone had higher changes in limb fat mass (coeff=0.35 kg, p<0.01) than patients receiving placebo while patients receiving rosiglitazone had similar changes in limb fat mass as patients receiving placebo (coeff = 0.05 kg, p=0.48). Interactions between TZD use and use of AZT or d4T, between rosiglitazone and pioglitazone and use of AZT or d4T, between TZD use and NNRTI use and between rosiglitazone and pioglitazone and PI use were not statistically significant, indicating that the effectiveness of TZDs generally and rosiglitazone and pioglitazone specifically did not vary according to use of thymidine analogues or PIs.

Limb Fat Response

One hundred and fifty-three patients (41%) had an increase of at least 10% in limb fat mass at least once during follow-up. Table 3 shows the results of univariate GEE logistic regression models of the probability of a 10% increase in limb fat mass from baseline. A multivariate GEE logistic regression model to identify predictors of limb fat mass response demonstrated that patients receiving pioglitazone were significantly more likely to achieve a 10% increase in limb fat at a given visit (odds ratio [OR] = 2.28, p=0.03) than patients receiving placebo while patients receiving rosiglitazone had similar likelihood of a 10% increase in limb fat mass as patients receiving placebo (OR=1.11, p=0.63) after controlling for study, length of follow-up, use of d4T and NNRTI use.

Adverse Events

Six patients on TZD therapy and seven patients on placebo discontinued the study drug because of adverse events. Among patients on rosiglitazone, reasons for discontinuation included elevated triglycerides (n=2),[18,19] abdominal and parotid swellings (n=1),[18] diarrhea (n=1),[22] nausea (n=1),[22] and requirement for prohibited medication (n=1).[22] Among patients on placebo, reasons for discontinuation of study drug included portal hypertension with possible venous thrombosis (n=1)[18], elevated lactate (n=2),[22] elevated liver function tests (n=2),[11,22] nausea (n=1)[22] and a combination of toxicities (n=1).[22]

Grade 3 or 4 levels of ALT were reported in only one patient on rosiglitazone.[18] Grade 3 or 4 levels of AST were reported in seven patients: two on rosiglitazone, one on pioglitazone and four on placebo during the study periods. As noted above, two patients on placebo stopped study medication because of elevated AST.

Rosiglitazone increased the risk of hypercholesterolemia[18] and hypertriglyceridemia[18,19] in individual studies. In contrast, pioglitazone increased HDL cholesterol and had no deleterious effects on triglycerides, total, or LDL cholesterol.[23] One patient on pioglitazone died suddenly from an unknown cause. There was no case of new or increasing congestive heart failure or documented myocardial infarction.

DISCUSSION

This meta-analysis of individual-patient data from six randomized, placebo-controlled trials of TZD from five countries forms the largest assessment of the effect of TZD therapy on limb fat among HIV-positive individuals. Overall, there was a small impact of TZD on limb fat gains in the combined dataset, unlikely to be clinically meaningful. Sub-analysis demonstrated a significant effect of pioglitazone but not of rosiglitazone on increases in limb fat relative to placebo. There was no difference in limb fat response or in the effectiveness of TZDs according to whether or not patients were receiving protease inhibitors.

In this meta analysis, while the use of thymidine analogues was associated with poorer limb fat outcomes, the effectiveness of TZD therapy did not vary by thymidine analogue use. Our data contrast those recently presented in abstract form which showed rosiglitazone to be effective at increasing limb fat among HIV positive individuals with mild limb fat loss on thymidine-sparing regimens.[25] However, while the mean change in limb fat to week 48 was significantly higher in the rosiglitazone group than the placebo group (911g +/− 1215 vs 253g +/− 1039, p=.018), the difference between treatment groups in median changes in limb fat was more modest although still similar in magnitude to prior switch studies off of thymidine analogue NRTIs (448 vs 153, p=.02) (personal communication, Grace McComsey, August 6, 2009). Since there was no comparison group of patients on thymidine analogues in the study, it is difficult to determine if the effectiveness of rosiglitazone was due to the absence of thymidine analogues or to differences in the patient population with regard to baseline line levels of limb fat, racial background or other factors. At this time, the data from this trial is not available for inclusion in the meta-analysis.

Our data are consistent with previous studies demonstrating that patients receiving d4T or AZT have increased risks of lipoatrophy over time.[26] Since regimens containing abacavir (ABC)/lamivudine (3TC) or tenofovir (TDF)/emtricitabine (FTC) are associated with lower risks of lipoatrophy, and have been shown *in vitro* to have less mitochondrial toxicity, regimens excluding d4T and AZT are now recommended among patients initiating antiretroviral therapy.[13,27] Among patients with established lipoatrophy, switching drug regimens from those containing d4T or AZT to either ABC or TDF may result in peripheral fat gain.[28,29,30,31,32] However, since only 15 patients in the combined meta-analysis stopped d4T or AZT during the study period, this phenomenon is unlikely to have impacted changes in limb fat in our study.

Differences in the efficacy of TZD therapy among trials may have occurred because of disparities in the study populations at enrolment with respect to age, gender, baseline BMI, use of protease inhibitors, d4T and AZT and other ARVs, duration of ARV use, the presence or degree of insulin resistance or because of differences in changes in limb fat in the placebo group. In the two trials in which rosiglitazone increased limb fat, insulin resistance was an

eligibility criterion[21,22] as it was in a smaller, open-label study in which rosiglitazone increased limb fat in patients with HIV-associated lipoatrophy.[33]

In a sub-study in the Australian cohort, PPAR-γ expression in fat biopsies was not increased in subjects on thymidine analogues randomized to rosiglitazone either at week 2 or 48 but was increased in subjects not on thymidine analogues at week 2 in those on rosiglitazone and in both rosiglitazone and placebo groups at week 48.[34] This would suggest that intact mitochondrial function could be required for TZD-induced stimulation of PPAR-γ expression in human adipose tissue.

The differential efficacy between pioglitazone and rosiglitazone could be due to in part to differences in dosing, the fact that the pioglitazone study was conducted several years later than the rosiglitazone studies, unmeasured differences in the patients enrolled in the pioglitazone study or biologic differences between the agents. For example, differential impacts of rosiglitazone and pioglitazone on adiponectin could have been associated with different limb fat outcomes. However, we were not able to assess this in our meta-analysis.

Rosiglitazone was associated with increases in triglycerides[18,19] and total cholesterol[18,19,21,] in several of the studies in the meta-analysis. In another study, rosiglitazone increased LDL cholesterol and decreased HDL cholesterol[22] while pioglitazone has been shown to improve HDL cholesterol.[23] There were few documented increases in liver transaminases among participants of these studies. In a meta-analysis of randomized trials of rosiglitazone for the treatment of type 2 diabetes in non HIV populations, a significant increase in the risk of myocardial infarction and a trend towards an increase in deaths due to cardiovascular causes was demonstrated.[35] While we did not observe an increased risk of cardiovascular disease in this meta-analysis, many studies excluded patients at higher cardiovascular risk, the follow up period was short and our sample size was not large enough to rule out the possibility of this adverse event.

While use of d4T and AZT is still common in resource limited settings, the incidence of HIV lipoatrophy in the developed world is decreasing due to improved knowledge of strategies to avoid the development of this syndrome among patients on HAART. To date, trials in antiretroviral-naïve patients have shown a lower incidence of lipoatrophy with the use of abacavir or tenofovir but more long term follow up is necessary to determine whether they prevent, or simply slow the development of the problem.[36] While d4T and AZT might be avoided in first-line regimens, it may be necessary to use one of these drugs later in disease due to toxicity, virologic failure or drug resistance. If this is the case, the development of lipoatrophy may just be deferred to a later stage of disease.

The relative contributions of other agents in the HAART combination are also unclear. In ACTG 5005s, initiation of efavirenz was associated with relative less loss of limb fat, compared with nelfinavir.[12] In ACTG 5142, a randomized trial of nucleoside, non-nucleoside and protease inhibitor sparing regimens for initial HIV treatment, the risk of lipoatrophy was greater in those randomized to efavirenz than those randomized to lopinavir/r even after controlling for NRTI use.[11] In our analysis, fat gains were greater in patients on efavirenz over time. Patients in the meta-analysis were treatment experienced, on stable ARV regimens with higher CD4 counts, lower viral load and lower baseline limb fat mass than patients in ACTG 5142. Patients in the meta-analysis were attempting to reverse loss of limb fat mass whereas patients in ACTG 5142 were experiencing initial loss of limb fat mass, which may explain the difference in findings. Further, our results must be interpreted with caution, as the effect of efavirenz was not an a priori hypothesis of interest, patients were not randomized to ARV treatments and the significant association between efavirenz and limb fat mass gain may be due to an unmeasured confounder.

Strengths of our study include the large sample size which increased the statistical power to test for interactions and conduct subset analyses, the availability of individual patient data, repeated measures of limb fat over time, inclusion of trials with different doses of TZD and a broader range of patient baseline characteristics than in any single trial.

These data and concerns about cardiovascular risk from studies in non HIV-infected populations[37] suggest that the use of rosiglitazone for peripheral lipoatrophy is not justified. Further research on the use of pioglitazone is justified, as it may have a stronger and more significant impact on lipoatrophy, more favorable effects on lipids and no increased risk of cardiovascular events.[38] More data are needed on the safety of this compound and investigation of populations that might benefit most from this treatment strategy. Moreover, further research is needed as to the cardiovascular effects of these insulin-sensitizing strategies, independent of effects on fat atrophy.

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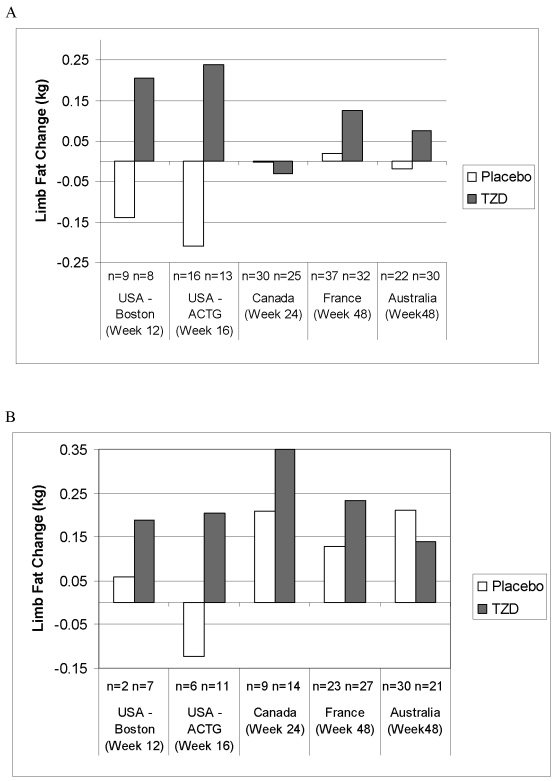

Figure 1.
Median limb fat mass change from baseline by study in (A) Patients on AZT or d4T, (B) Patients not on AZT or d4T

Table 1

Summary of Studies Included in Meta-Analysis

	Australia[18] (n=108)	USA-Boston[21] (n=28)	USA-ACTG[22] (n=53)	Finland[19] (n=30)	Canada[20] (n=78)	France[23] (n=130)
Inclusion Criteria						
Lipoatrophy	< 20% limb tissue or limb fat % at least 10% less than truncal fat %	Clinically diagnosed	waist-hip ratio > 0.95 for men or > 0.85 for women or a waist circumference > 100 cm	Clinically diagnosed	Clinically diagnosed	Clinically diagnosed
Antiretroviral therapy	Stable ≥12 weeks	Stable ≥12 weeks	Stable > 60 days	>>18 months	Stable ≥12 weeks	Stable > 6 months
Insulin resistance	Not required	Yes	Yes	Not required	Not required	Not required
HIV viral load	-	-	< 10,000 copies/mL	-	-	<400 copies/mL
CD4 Count	-	-	-	-	-	> 200 cells/mm^3
Study Characteristics						
Duration of follow-up	48 weeks	12 weeks	16 weeks	24 weeks	24 weeks	48 weeks
Timing of DXA measurements	weeks 0, 24, 48	weeks 0, 12	weeks 0, 16	-	weeks 0, 24	weeks 0, 48
Timing of Lipid Measurements	weeks 0, 8, 16, 24, 32, 40, 48	weeks 0, 12	weeks 0, 8, 16	weeks 0, 6, 12, 18, 24	weeks 0, 12, 24	weeks 0, 48
Active Drug	rosiglitazone 4mg bid	rosiglitazone 4mg qd	rosiglitazone 4mg qd	rosiglitazone 8mg qd	rosiglitazone 4mg qd	pioglitazone 30mg qd
Primary Outcome	limb fat	insulin sensitivity	change in fasting insulin	subcutaneous fat	percentage change in limb fat	limb fat
Patient Characteristics						
Male	106 (98%)	21 (75%)	34 (64%)	25 (83%)	76 (97%)	106 (82%)
Age (years)	45 (40, 50)	45 (39, 50)	45 (41, 50)	42 (39, 48)	47 (41, 53)	44 (39, 50)
CD4 count (cells/mm^3)	542 (428.5, 724)	432 (239.5, 617)	641 (400, 922)	526 (329, 707)	439 (364, 641)	582 (404, 735)
Viral Load < 50 copies/ml	58 (54%)	20 (74%)	39 (74%)	20 (67%)	59 (76%)	85 (66%)
Protease inhibitor use	66 (61%)	18 (64%)	35 (66%)	22 (73%)	76 (97%)	63 (48%)
AZT or d4T	53 (49%)	19 (68%)	34 (64%)	28 (93%)	55 (70%)	79 (61%)
Limb fat (kg)	2.3 (1.7, 3.4)	3.9 (2.4, 5.7)	6.4 (3.6, 10.6)	-	3.2 (2.5,4.3)	2.2 (1.6, 3.5)
Body mass index (kg/m^2)	22.9 (21.3,24.6)	24.3 (22.5, 28.4)	28.2 (26.1, 32.0)	23.6 (21.3,25.7)	24.3 (22.3, 26.6)	21.6 (20.1,23.4)
Glucose (mmol/L)	5.1 (4.9, 5.5)	5.3 (4.7, 6.0)	5.4 (5.1, 5.8)	5.3 (4.8, 5.8)	5.0 (4.5, 5.4)	5.1 (4.6, 5.5)
Insulin (mlU/L)	8.3 (5.6, 11.5)	16.2 (10.3,24.7)	17 (14, 26.5)	9 (6, 14)	9.6 (7.2, 15.7)	7.6 (5.6, 11.4)
Cholesterol (mmol/L)	6.0 (5.1, 6.9)	5.3 (4.5, 6.5)	5.6 (4.8, 6.6)	5.9 (5.2, 6.5)	5.5 (4.7, 6.5)	5.8 (4.7,6.8)
Triglycerides (mmol/L)	2.9 (1.9,4.2)	2.8 (1.9, 6.6)	2.9 (2.0, 5.1)	2.8 (1.9,4.3)	3.2 (1.9,4.3)	2.5 (1.5, 3.9)

DXA = dual energy X-ray absorptiometry

†All lipid measurements were done on fasting samples

Table 2

Baseline Demographic and Clinical Characteristics by Treatment Group

		Total (N=427)		Placebo (N=214)		TZD (N=213)	p value
Study Characteristics							
Clinical Center	Canada	78 (18%)		39 (18%)		39 (18%)	0.99
	Finland	30 (7%)		15 (7%)		15 (7%)	
	USA-ACTG	53 (12%)		27 (13%)		26 (12%)	
	USA-Boston	28 (7%)		12 (6%)		16 (8%)	
	France	130 (30%)		66 (31%)		64 (30%)	
	Australia	108 (25%)		55 (26%)		53 (25%)	
Demographic Characteristics							
Male		368 (86%)		185 (86%)		183 (86%)	0.87
Age (years)		45 (40-51)		45 (40-51)		44 (39-50)	0.63
Caucasian		151 (80%)		78 (84%)		73 (77%)	0.23
Clinical Characteristics							
AIDS Defining Illness		131 (31%)		61 (29%)		70 (33%)	0.31
Smoking Status	Current	138 (33%)		66 (31%)		72 (34%)	0.79
	Past	107 (25%)		55 (26%)		52 (25%)	
	Never	179 (42%)		92 (43%)		87 (41%)	
CD4 cells/mm^3		542 (383-724)		542 (384-747)		542 (382-721)	0.81
Viral Load (copies/mL)		50 (50-200)		50 (50-200)		50 (50-200)	0.94
Viral Load < 50 copies/mL		281 (66%)		141 (66%)		140 (66%)	0.97
Baseline statin use		39 (10%)		16 (8%)		23 (12%)	0.21
Baseline Body Fat							
Body Mass Index (kg/m^2)		23.2(21.3-25.7)		23.0 (21.1-25.2)		23.4 (21.5-26.4)	0.18
Arm Fat (kg)		1.0 (0.7-1.7)	132	1.0 (0.7-1.6)	133	1.0 (0.7-1.8)	0.54
Leg Fat (kg)		2.0 (1.4-3.1)	132	1.9 (1.3-2.9)	134	2.1 (1.4-3.4)	0.13
Limb Fat (kg)		2.9 (1.9-4.4)	197	2.7 (1.8-4.1)	196	3.1 (2.1-4.7)	0.06
Total Body Fat (kg)		11.5 (8.2-17.0)	147	11.1 (8.0-16.9)	148	11.9 (8.5-17.4)	0.34
Current Antiretroviral Use							
AZT or d4T Use		268 (63%)		137 (64%)		131 (62%)	0.55
AZT Use		105 (25%)		57 (27%)		48 (23%)	0.26
d4T Use		163 (38%)		80 (37%)		83 (39%)	0.81
NRTI Use		404 (95%)		202 (95%)		202 (95%)	0.99
NNRTI Use		192 (45%)		90 (42%)		102 (48%)	0.23
EFV use		103 (24%)		51 (24%)		52 (24%)	0.89
PI Use	Boosted PI	156 (37%)		78 (36%)		78 (37%)	0.99
	Unboosted PI	124 (29%)		62 (29%)		62 (29%)	
	Not Used	147 (34%)		74 (35%)		73 (34%)	
Years on ARV		6.9 (5.0-9.9)	213	6.8 (5.0-9.7)	212	7.0 (5.0-10.0)	0.50
Years on HAART		5.0 (3.4-6.3)	192	4.9 (3.6-6.3)	200	5.0 (3.2-6.3)	0.65
Changes to ARVs during study		88 (30%)		39 (26%)		49 (33%)	0.22

	Total (N=427)		Placebo (N=214)		TZD (N=213)	p value
Baseline laboratory values						
Cholesterol (mmol/L)	5.7 (4.9-6.7)	203	5.8 (4.9-6.7)	208	5.7 (4.8-6.8)	0.90
Triglycerides (mmol/L)	2.8 (1.8-4.3)	205	2.9 (1.8-4.3)	208	2.8 (1.7-4.2)	0.81
LDL (mmol/L)	3.2 (2.6-4.0)	166	3.3 (2.6-4.1)	181	3.2 (2.5-3.9)	0.28
HDL (mmol/L)	1.1 (0.9-1.3)	200	1.1 (0.9-1.3)	204	1.1 (0.9-1.3)	0.70
Glucose (mmol/L)	5.1 (4.7-5.6)	212	5.1 (4.7-5.6)	211	5.1 (4.7-5.6)	0.33
Insulin (mIU/L)	9.6 (6.4-15.7)	200	9.7 (6.5-15.6)	203	9.6 (6.2-15.9)	0.60
HOMA	2.2 (1.5-3.7)	200	2.2 (1.5-3.6)	202	2.1 (1.4-3.7)	0.45
ALT (U/L)	32 (23-48)	211	33 (23-49)	210	32 (23-47)	0.66
AST (U/L)	30 (23-39)	210	30 (23-38)	209	29 (23-40)	0.93

Values are presented as N (%) or median (interquartile range).

TZD = thiazolidinediones, ACTG = AIDS Clinical Trials Group, VL = viral load, PI = protease inhibitor, NNRTI = non nucleoside reverse transcriptase inhibitor, AZT = zidovudine, d4T = stavudine, ARV = antiretroviral therapy, HOMA = homeostasis model assessment, LDL = low density lipoprotein, HDL = high density lipoprotein, ALT = alanine transaminase, AST= aspartate transaminases

Table 3

Univariate Generalized Estimating Equation (GEE) Regression Models

	GEE Linear Regression model of Change in Limb Fat Mass			GEE Logistic Regression model of 10% Increase in Limb Fat from Baseline		
Covariates	**Estimate**	**95% CI**	**p value**	**OR**	**95% CI**	
Study Characteristics						
Week of follow-up	0.004	(0.002, 0.007)	0.0001	1.01	(1.01, 1.02)	<.0001
TZD vs. Placebo	0.14	(0.006, 0.27)	0.04	1.38	(0.95, 2.00)	0.09
Treatment						
Pioglitazone	0.33	(0.11, 0.55)	0.004	2.19	(1.23, 3.89)	0.007
Rosiglitazone	0.07	(−0.08, 0.21)	0.36	1.19	(0.79, 1.77)	0.40
Placebo (ref.)	.	.	.			
Center						
France	−0.02	(−0.18, 0.15)	0.85	1.07	(0.68, 1.68)	0.76
Canada	−0.20	(−0.35, −0.05)	0.009	0.51	(0.28, 0.92)	0.03
USA-ACTG	−0.37	(−0.68, −0.07)	0.02	0.46	(0.22, 0.97)	0.04
USA-Boston	−0.19	(−0.43, 0.05)	0.12	0.47	(0.18, 1.19)	0.11
Australia (ref.)	.	.				
Demographic Characteristics						
Male	0.03	(−0.30, 0.37)	0.84	1.32	(0.67, 2.62)	0.42
Age (per 10 years)	−0.007	(−0.10, 0.08)	0.88	0.97	(0.77, 1.21)	0.79
Caucasian	0.16	(−0.13, 0.46)	0.28	2.56	(0.83, 7.86)	0.10
Clinical Characteristics						
AIDS Defining Illness	−0.003	(−0.15, 0.14)	0.97	1.10	(0.73, 1.66)	0.64
Baseline CD4 per 100 cells/mm^3	0.01	(−0.02, 0.04)	0.40	1.03	(0.96, 1.09)	0.43
Baseline CD4 < 500 cells/mm^3	−0.07	(−0.21, 0.06)	0.27	0.87	(0.60, 1.26)	0.47
Baseline VL < 50 copies/mL	0.11	(−0.04, 0.26)	0.15	1.15	(0.79, 1.67)	0.48
Ever Smoked	−0.14	(−0.27, 0.002)	0.05	1.06	(0.73, 1.54)	0.77
Baseline Statin Use	−0.04	(−0.24, 0.16)	0.67	0.85	(0.43, 1.67)	0.63
Current Antiretroviral use						
PI Use						
Boosted PI	−0.08	(−0.24, 0.07)	0.30	0.73	(0.48, 1.12)	0.15
Unboosted PI	−0.11	(−0.30, 0.08)	0.26	0.94	(0.58, 1.54)	0.82
No PI (ref.)	.	.	.			
NNRTI use						
Efavirenz	0.31	(0.16, 0.46)	<0.0001	1.89	(1.24, 2.89)	.003
Other	0.08	(−0.10, 0.26)	0.39	0.94	(0.58, 1.52)	.80
NNRTI Use	0.20	(0.06, 0.33)	0.005	1.31	(0.91, 1.90)	0.15
AZT or d4T Use	−0.25	(−0.38, −0.12)	<.001	0.66	(0.45, 0.96)	0.03
AZT Use Only	−0.12	(−0.29, 0.05)	0.18	0.95	(0.60, 1.49)	0.81
d4T Use Only	−0.17	(−0.31, −0.03)	0.01	0.67	(0.46, 0.98)	0.04
Baseline Body Fat						

	GEE Linear Regression model of Change in Limb Fat Mass			GEE Logistic Regression model of 10% Increase in Limb Fat from Baseline		
Covariates	**Estimate**	**95% CI**	**p value**	**OR**	**95% CI**	
BMI (kg/m^2)	−0.01	(−0.04, 0.01)	0.30	0.93	(0.88, 0.98)	<.01
Limb Fat	−0.02	(−0.06, 0.02)	0.24	0.92	(0.85, 0.99)	0.02
Limb Fat >15%	−0.006	(−0.25, 0.24)	0.96	0.69	(0.41, 1.16)	0.16
Baseline HOMA	0.007	(−0.006, 0.02)	0.30	1.03	(1.00, 1.07)	0.08
$\log_{10}$ Baseline Insulin	−0.09	(−0.35,0.16)	0.48	1.06	(0.55, 2.04)	0.86

TZD = thiazolidinediones, VL = viral load, PI = protease inhibitor, NNRTI = non nucleoside reverse transcriptase inhibitor, AZT = zidovudine, d4T = stavudine, BMI = body mass index, HOMA = homeostasis model assessment

Table 4

Multivariable Generalized Estimating Equation (GEE) Regression Models

	GEE Linear Regression model of Change in Limb Fat Mass			GEE Logistic Regression model of 10% Increase in Limb Fat from Baseline		
Covariates	**Estimate**	**95% CI**	**p value**	**OR**	**95% CI**	
Week of follow-up	0.004	(0.001, 0.006)	0.0016	1.01	(1.00, 1.02)	0.0017
Treatment						
Pioglitazone	0.35	(0.11, 0.58)	0.004	2.28	(1.07, 4.88)	0.03
Rosiglitazone	0.05	(−0.10, 0.21)	0.48	1.11	(0.72, 1.72)	0.63
Placebo (ref.)	.	.	.			
Center						
France	−0.18	(−0.37, 0.01)	0.06	0.73	(0.37, 1.45)	0.37
Canada	−0.07	(−0.22, 0.08)	0.34	0.72	(0.37, 1.40)	0.33
USA-ACTG	−0.28	(−0.58, 0.03)	0.07	0.64	(0.28, 1.49)	0.30
USA-Boston	−0.09	(−0.34, 0.16)	0.47	0.65	(0.23, 1.81)	0.41
Australia (ref.)	.	.	.			
NNRTI Use - efavirenz	0.31	(0.17, 0.46)	<0.0001	1.94	(1.26, 2.99)	0.003
NNRTI use – other	0.004	(−0.18, 0.19)	0.97	0.79	(0.48, 1.30)	0.36
Stavudine use	−0.15	(−0.28, −0.02)	0.02			

TZD = thiazolidinediones, NNRTI = non nucleoside reverse transcriptase inhibitor