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Thiazolidinediones in the Treatment of HIV/HAART-Associated Lipodystrophy Syndrome

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Abstract

The treatment of HIV-1 infected patients with HAART has resulted in long-term suppression of viral replication and reduced progression to AIDS. However, the use of HAART has been associated with adverse effects, including metabolic dysregulation and changes in body fat deposition. This syndrome, known as HIV/HAART-associated lipodystrophy syndrome, is characterized by insulin resistance, dyslipidemia, lipodystrophy, and increased visceral adiposity, which contribute to an increased risk of cardiovascular disease amongst these patients. The thiazolidinediones are a class of agonists for the nuclear receptors, the peroxisome proliferator-activated receptor. Since peroxisome proliferator-activated receptor is critically involved in the regulation of insulin sensitivity and lipid metabolism, a number of clinical trials have analyzed whether thiazolidinediones could ameliorate the signs of HIV/HAART-associated lipodystrophy syndrome. Based on these trials, thiazolidinediones appear to up-regulate peroxisome proliferator-activated receptor-dependent genes such as adiponectin, an effect that could have important physiological benefits in the long-term for HIV/HAART-associated lipodystrophy syndrome patients. Critically, many of the studies were of short duration and thus the beneficial effects of thiazolidinediones might have been missed. In addition, the few studies on the thiazolidinedione pioglitazone showed a beneficial effect on limb fat mass that was not associated with a pro-atherogenic lipid profile. Based on these studies, a large-scale clinical trial of pioglitazone use in HIV/HAART-associated lipodystrophy syndrome patients is warranted. **(AIDS Rev. 2013;15:171-80)**

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Key words

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Introduction

The treatment of HIV-1-infected individuals with HAART has achieved long-term viral suppression and reduced AIDS-related fatalities[1]. Despite this success, there are problems associated with HAART, including the need for adherence to a life-long regimen of daily medication and the side-effects or toxicity of the drugs[2]. One of the most common side-effects of HAART is the development of metabolic abnormalities and changes in body composition, referred to as HIV/HAART-associated lipodystrophy syndrome (HALS; Table 1). HALS is characterized by insulin resistance, dyslipidemia, and lipodystrophy, which are thought to increase the risk of cardiovascular disease amongst these patients[3,4]. Lipodystrophy comprises peripheral lipoatrophy, visceral fat accumulation, and increased central adiposity, with lipoatrophy being the dominant feature[3]. Importantly, some of the metabolic abnormalities observed could be related to HIV-1 infection rather than to HAART alone[5], such as changes in lipid metabolism[6,7]. Nonetheless, the use of specific drugs as part of HAART has been associated with the onset of particular deleterious effects. For example, the use of protease inhibitors (PI) has been associated with elevated triglycerides, increased low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL)[7].

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Table 1. Clinical features of HIV/HAART-associated metabolic syndrome

Metabolism	Body Composition
Peripheral insulin resistance	Loss of subcutaneous adipose tissue
Hyperglycemia	Lipoatrophy in limbs, buttocks and face
Elevated serum triglycerides	Central adiposity
Elevated total and LDL-C	Adipose tissue deposition in submental and dorsocervical regions
Reduced HDL-C	
Reduced adiponectin levels	

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

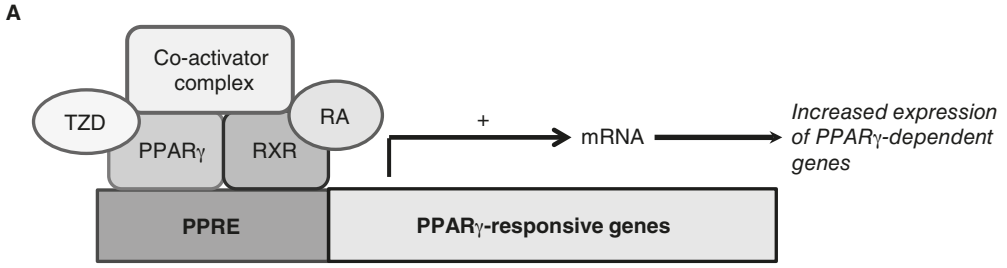
It has been hypothesized that PI could bind to cellular proteins with homology to the viral protease and that this could account for some of the effects observed in HALS[8,9]. Further, the thymidine nucleoside reverse transcriptase inhibitors (tNRTI) have been found to be toxic to the mitochondria, which could lead to increased apoptosis of adipocytes and the development of lipoatrophy[6,10]. This is underscored by studies showing that changing the HAART regimen, particularly reducing the use of tNRTI, has reduced lipoatrophy[3,7]. Thus, the development of HALS could be due to the specific agents used in the combination therapies. While a full discussion of the clinical features of HALS is beyond the scope of this review and has been discussed elsewhere[4,7,11,12], it is worth noting that there is uncertainty in the clinical definition of this disorder[3,12]. The aim of this article is to evaluate the merits of using thiazolidinediones (TZDs), a class of drugs that target the peroxisome proliferator-activated receptors (PPARs), in the treatment of HALS.

The role of peroxisome proliferator-activated receptor gamma in HIV/HAART-associated lipodystrophy syndrome

The PPARs are a class of ligand-activated nuclear receptors, which control the transcription of a variety of genes involved in lipid metabolism, adipose tissue dynamics, inflammation, and tissue repair[14,15]. In order to regulate gene expression, the PPARs form a heterodimeric complex with the retinoid X receptor (RXR)[16]. The PPAR/RXR heterodimer can then bind to a specific recognition sequence, referred to as a PPAR-response element, which is present in the regulatory regions of PPAR-inducible genes[14]. The binding and activation of gene expression by PPARs is further regulated by specific corepressor and coactivator proteins[17]. The PPARs are present in at least three isotypes (α, β/δ, and γ), each of which has been found to be expressed in different tissues and to exert distinct effects on metabolism[14]. Of these isotypes, PPARγ is expressed in adipose tissue, liver, and muscle where it is involved in adipocyte differentiation, regulation of apolipoprotein synthesis, fatty acid uptake, as well as in mediating insulin sensitivity (Fig. 1)[18].

Importantly, PPARγ expression has been found to be reduced in HAART-treated HIV-1-infected patients[19,20] and this is likely due to the action of specific HAART agents. Some PI have a potent negative effect on lipid metabolism[9] and more recent studies indicate that the tNRTI contribute greatly to the pathogenesis of HALS[7,10]. Furthermore, PPARγ expression has been found to be downregulated in patients receiving PI[6,8,21] and tNRTI[13]. Importantly, HIV-1 infection, and particularly expression of the p17 protein, is also associated with the downregulation of PPARγ[22]. One of the consequences of impaired PPARγ expression is the reduced expression of PPARγ-dependent genes, notably adiponectin[23]. Adiponectin is an important cytokine secreted by adipocytes that acts to increase fatty acid oxidation and insulin sensitivity, as well as by influencing adipogenesis[24]. Some HAART drugs implicated in HALS have been found to reduce adiponectin levels[25], potentially due to the effect of these drugs on PPARγ. In contrast, the NNRTI efavirenz and nevirapine, which have not been associated with HALS, are found to increase adiponectin levels[26]. With decreasing use of tNRTI in HAART regimens, it could be the case that in the future the incidence and severity of HALS will be reduced[12].

Given the importance of PPARγ in fat metabolism, therapeutics that upregulate and activate this receptor could ameliorate HALS. The TZDs are a class of insulin-sensitizing drugs that have been used to treat type II



B

Physiological effects of PPARγ activation by the TZDs:

Liver	↑ insulin action ↓ glucose production ↓ fatty acids
Adipocytes	↑ adipocyte differentiation ↑ fatty acid uptake and lipogenesis ↓ macrophage infiltration
Muscle	↑ insulin action ↑ glucose uptake ↓ intramuscular fat deposition
Overall	↑ insulin sensitivity ↓ reduced triglycerides and free fatty acids ↓ reduced central adiposity

TZD: thiazolidinediones; PPARγ: peroxisome proliferator-activated receptor gamma; RA: retinoic acid; RXR: retinoid X receptor; PPRE: PPAR response element.

Figure 1. *The mechanism of action of thiazolidinediones on peroxisome proliferator-activated receptor γ. (a) In the nucleus, the TZDs bind to PPARγ, which in turn heterodimerizes with retinoic acid-bound RXR. The PPARγ-RXR heterodimer is able to bind to the PPAR response element (PPRE) and to alter gene expression. There are several additional mechanisms of regulation of PPAR function, including the binding of co-activating proteins. Several genes are known to be induced by PPARγ, including adiponectin and GLUT4. Ultimately, the expression of PPARγ-dependent genes leads to physiological effects including adipogenesis, improved insulin sensitivity, and reduced triglycerides. Part B adapted from H Yki-Jarvinen[63].*

diabetes mellitus (T2DM) and that specifically target PPARγ[18]. In addition to upregulating PPAR-responsive genes, PPAR agonists such as TZDs have been shown to increase expression of the receptor itself[27]. Therefore, there is a rationale for the use of TZDs in treating HALS and here we review clinical trials that evaluate the use of TZDs as a therapy for this disorder.

Clinical trials using thiazolidinediones to treat HIV/HAART-associated lipodystrophy syndrome

Rosiglitazone

Rosiglitazone has been examined in a number of clinical trials for its efficacy in treating HALS. The studies show heterogeneity in many parameters including duration, sample size, baseline characteristics, and rosiglitazone dose (Table 2, supplementary data). Among the critical differences are variations in the HAART regimen, particularly the use of the lipoatrophic NRTI in some studies[3,7]. Also of note is that there is an unequal gender balance in all of the trials; they have mainly male participants and some of the studies exclude women altogether (Table 2). This is potentially important given the differences in body fat distribution observed between men and women generally. Despite these limitations, the studies assessing the use of rosiglitazone in the treatment of HALS have provided some insight into this disorder and possible therapeutic strategies for managing it.

A pilot study on the use of rosiglitazone in treating HALS found a 23% increase in subcutaneous adipose tissue ($p = 0.046$) and a decrease in visceral adiposity

of 21% (p = 0.04)[28]. Rosiglitazone improved insulin sensitivity by 59% (p = 0.02) using a hyperinsulinemic-euglycemic clamp and there was a mean decrease in insulin concentration of 9.76 mU/ml (p = 0.03)[28]. The rosiglitazone-treated HALS patients were compared to healthy, HIV-1-seronegative controls, not to patients receiving a placebo[28]. While this study was short (6-12 weeks), not placebo-controlled, and involved only a few patients, it provided a rationale for further trials examining rosiglitazone.

In a placebo-controlled trial, rosiglitazone was evaluated for its effect on subcutaneous fat levels, as well as several secondary endpoints, in HALS patients who were all receiving tNRTI[29]. Rosiglitazone was found to increase total cholesterol by 1.4 mmol/l (p < 0.05) and triglycerides by 2.3 mmol/l (p < 0.001)[29]. Despite these changes in plasma lipid levels, there were no significant changes in subcutaneous fat tissue, body weight, or total body fat[29]. An important secondary endpoint was insulin sensitivity; there was a 27% reduction in serum insulin levels compared to baseline (p < 0.05), while insulin levels in the placebo group increased by 70%[29]. However, the baseline values with rosiglitazone (12.6 µU/ml) and placebo (9.6 µU/ml) were not well-matched and the reduction in insulin levels observed with rosiglitazone only brought the values to within the range of those of the placebo group at baseline. Hepatic insulin sensitivity was measured by analyzing liver fat and this was reduced by 15% (p < 0.05) in the rosiglitazone group, while it increased by 26% (p < 0.05) in the placebo group[29]. A subsequent analysis of the changes in gene expression in these patients following rosiglitazone treatment found that there was an increase in adiponectin expression of 16% (p < 0.05) and there was a correlation with the aforementioned improvements in serum insulin sensitivity[30]. In addition, there was an increase in PPARγ expression in the rosiglitazone group of 9.4% compared to placebo (p = 0.05), although the rosiglitazone and control groups were poorly matched in this regard at baseline and the increase in PPARγ expression observed following rosiglitazone treatment was within the range of the placebo group at baseline[30].

A subsequent trial found that rosiglitazone had a beneficial effect on several markers of HALS[31]. This randomized, controlled trial evaluated the effect of rosiglitazone on a small number of HIV-1-seropositive men and women[31]. All of the patients in this study were on an NRTI, with 58% of the rosiglitazone group and 42% of the control group receiving the tNRTI stavudine[31]. Importantly, rosiglitazone increased total body fat by 6.3% (p = 0.03) and had a particularly beneficial effect on lipoatrophy, with a 24% increase (p = 0.02) in subcutaneous leg fat area as measured by CT scan[31]. Rosiglitazone treatment increased adiponectin levels by 72% (p = 0.006) and improved insulin sensitivity, with a 29% decrease in the area under the curve for insulin over time following a glucose challenge (p = 0.003)[31]. These improvements were observed despite a lower dose of rosiglitazone (4 mg/day)[31] than was used in most of the other trials (Table 2). In contrast to the beneficial effects are detrimental increases in total cholesterol of 0.6 mmol/l (p = 0.007) and LDL of 0.4 mmol/l (p = 0.01) in the rosiglitazone group[31]. The results were promising, but the study was limited by small sample size and short duration.

In five clinical trials, rosiglitazone was compared to metformin for the treatment of HALS. In two of these trials, patients were randomized to receive either rosiglitazone or metformin, but there were no controls[32,33]. Rosiglitazone was found to improve signs of HALS in a small study of HIV-1-seropositive men[32]. Although rosiglitazone increased subcutaneous abdominal fat by 16% (p < 0.05), the study did not measure limb subcutaneous fat levels. Only four patients in the rosiglitazone group were receiving stavudine and these patients did not show an increase in subcutaneous adipose tissue[32]. Rosiglitazone increased adiponectin levels by 84% (p < 0.05), as well as decreasing the area under the curve for both glucose (p = 0.01) and insulin (p = 0.05)[32,34]. Deterioration in the fasting lipid profile was observed in the rosiglitazone group, with increased LDL, triglycerides, and total cholesterol, as well as decreased HDL[32]. A later analysis of the same data showed that rosiglitazone increased fatty acid oxidation[34]. However, this beneficial effect on lipid metabolism was tempered by increased postprandial cholesterol remnants[34]. In another non-placebo-controlled study of 31 patients, comparing rosiglitazone to metformin, a reduction in fasting glucose was observed in the rosiglitazone group (p = 0.004), but not in the metformin group (p = 0.1)[33]. Both rosiglitazone and metformin decreased fasting insulin and the homeostasis model assessment of insulin resistance (HOMA-IR) index (p < 0.05)[33]. Fasting triglycerides increased by 1.17 mmol/l (p = 0.01) and body mass index increased by 0.7 kg/m^2 (p = 0.02) in the rosiglitazone group[33]. All of the patients in the study were receiving unspecified NRTI[33]. Given the fact that neither of these studies was placebo-controlled, it is impossible to definitively attribute the observed effects to rosiglitazone.

In three of the trials comparing rosiglitazone and metformin, there were placebo or no-treatment control groups. A study of HIV-1-seropositive men comparing rosiglitazone to metformin or to no treatment found that rosiglitazone improved fasting insulin levels by 49% ($p < 0.001$) and the sum of the insulin levels in the glucose tolerance test decreased by 37% ($p < 0.001$)[35]. There was no change in plasma triglyceride levels with rosiglitazone, but there were increases in total cholesterol of 23% ($p < 0.05$) and LDL of 28% ($p < 0.05$)[35]. The HDL cholesterol increased by 38% ($p < 0.01$)[35], suggesting that the rosiglitazone-induced increase in plasma lipids is not universally atherogenic. A later multifactorial, placebo-controlled trial (n = 105) investigating metformin and rosiglitazone found an improvement in limb fat mass and insulin sensitivity with rosiglitazone[36]. Median insulin area under the curve decreased significantly in both groups receiving rosiglitazone ($p = 0.01$ alone, $p = 0.002$ with metformin)[36]. While leg fat increased by 4.8% in subjects on rosiglitazone alone ($p = 0.034$), other measures of body composition did not change[36]. Rosiglitazone increased adiponectin by 66% ($p < 0.01$), as well as increasing LDL by 7 mg/dl ($p < 0.01$) and decreasing HDL by 5 mg/dl ($p < 0.01$)[36]. Overall, 96% of the patients were receiving NRTI, including 63% on thymidine analogues[36]. Finally, a randomized, controlled trial of HIV-1-infected men compared the effects of metformin and rosiglitazone on fasting plasma glucose and insulin levels[37]. Rosiglitazone improved insulin sensitivity, with a decrease in fasting insulin levels of 49% compared to baseline ($p < 0.001$), as well as reducing HOMA-IR by 7.3 ($p < 0.001$), and improving pancreatic beta cell function by 142 percentage points ($p < 0.001$)[37]. Adiponectin, fasting lipids, and body composition measures were not reported in this trial[37].

Additional non-controlled trials indicated a beneficial effect of rosiglitazone on body fat deposition in HALS patients. In a 24-week prospective clinical trial, patients taking rosiglitazone showed a significant increase in limb fat from baseline of 0.74 kg ($p < 0.001$) without any change in total fat mass or total weight[38]. Abdominal circumference reduced by 3% ($p = 0.03$), indicating beneficial fat redistribution, but there was an increase in serum cholesterol of 33 mg/dl ($p = 0.006$)[38]. In another non-placebo-controlled study comparing rosiglitazone, pravastatin, and recombinant human growth hormone, a beneficial effect of rosiglitazone on body fat deposition was observed, with a slow accrual of limb fat of 0.4 kg ($p = 0.019$)[39]. Rosiglitazone use was also associated with a decrease in blood glucose of 0.5 mmol/l ($p < 0.05$) along with an improvement in insulin sensitivity ($p = 0.04$)[39]. Although these trials showed promising results on limb fat mass, they were not controlled and thus their findings should be treated with caution.

In a larger placebo-controlled clinical trial, rosiglitazone did not improve lipoatrophy or body composition despite improvements in metabolic parameters[40]. Insulin sensitivity was improved with rosiglitazone treatment, with a 31% reduction in insulin concentration from baseline, and this was significant when compared to placebo ($p = 0.02$)[40]. Other measures of insulin sensitivity also improved, such as the glucose-to-insulin ratio ($p = 0.05$) and the HOMA-IR ($p = 0.03$), and there was an increase in adiponectin levels of 102% ($p < 0.0001$)[40]. Similar to other studies, there was an increase in triglycerides of 1.5 mmol/l from baseline and an increase in total cholesterol ($p = 0.001$) and LDL ($p = 0.04$), although there was no significant change observed in HDL[40]. The lack of an effect of rosiglitazone on lipoatrophy was unexpected by the authors and they hypothesized that this might have been because of the ongoing NRTI use by the study participants.

This failure of rosiglitazone to improve limb fat mass in the study by Carr, et al.[40] was analyzed for the molecular mechanism in a subgroup of the main study cohort[10]. Participants in this substudy were randomized to receive rosiglitazone or placebo, with 62% of the rosiglitazone patients taking tNRTI compared to 35% of the placebo group. Importantly, the patients not taking tNRTI during the study had previously used these drugs, with an average time since cessation of 1.5 years[10]. Irrespective of treatment designation or tNRTI use, there was a significant correlation between upregulation of *PPARG* gene expression and increased limb fat mass at week 48[10]. In the patients not receiving tNRTI, rosiglitazone treatment caused a 68% increase in *PPARG* gene expression in biopsied adipose tissue at week two[10]. Interestingly, at the end of the study, patients who were not taking tNRTI had a similar increase in *PPARG* expression, whether they were on rosiglitazone (87%) or placebo (74%), and there was no significant difference between these groups[10]. In comparison, patients receiving tNRTI did not show a significant increase in *PPARG* gene expression at either time point[10]. In addition, the NRTI were found to be toxic to adipocyte mitochondria, with baseline mitochondrial RNA being reduced by 58% ($p < 0.01$) and DNA by 53% ($p < 0.05$) in patients on tNRTI[10]. Crucially, intact mitochondria were found to be required for the stimulation of *PPARG* expression by the TZD[10].

These findings underscore the negative impact of the tNRTI on adipose tissue function.

In a subsequent placebo-controlled trial, rosiglitazone was found to improve insulin sensitivity, with a decrease in serum insulin of 21.5% ($p = 0.01$) following glucose load[41]. Despite this, no change was observed in fasting insulin sensitivity by the quantitative insulin sensitivity check index (QUICKI)[41]. Rosiglitazone increased adiponectin levels by 2.5 µg/ml ($p = 0.007$), while no difference was observed with placebo[41]. In addition, there were no differences between rosiglitazone and placebo groups in measures of body composition[41]. This finding could be due to ongoing NRTI use by 70% of patients[41]. The findings of this study are similar to those of Carr, et al.[40], in which many of the patients were on tNRTI and the use of these drugs could account for the lack of an effect on body composition, as discussed above[10,40]. In contrast to this is the most recent study of rosiglitazone, in which a significant effect on both insulin sensitivity and limb fat mass was observed with rosiglitazone despite five patients in each study arm (22.7-29.4% by group) and eight of the patients on placebo (42.1%) being on stavudine or zidovudine[42]. In the pooled data across the study arms, rosiglitazone was found to significantly improve insulin sensitivity in a glucose tolerance test ($p = 0.003$)[42]. Rosiglitazone had no effect on visceral adipose tissue, but did increase limb fat mass significantly when compared to placebo ($p = 0.044$)[42]. The smaller proportion of all patients taking tNRTI in this study (30%) compared to that of Schindler, et al.[41] (70%) could account for the differential benefit of rosiglitazone on limb fat mass in the two studies.

A few of the more recent studies have examined the effects of rosiglitazone in patients not receiving tNRTI. In a large placebo-controlled trial, no benefits of rosiglitazone on metabolism or peripheral lipid mass were observed[43]. A small and not statistically significant improvement in peripheral lipid deposition was observed in the subset of patients who were not on tNRTI[43]. Another randomized clinical trial found that rosiglitazone did not improve the metabolism of glucose and lipids or body composition despite significantly increasing adiponectin levels by 107% ($p < 0.02$)[44]. In this study, the sample size was small ($n = 13$), making it difficult to generalize the results[44]. An open-label extension of the study meant that six patients received rosiglitazone for a total of 32 weeks. In these patients, total body fat mass increased, which consisted of an increase in trunk fat mass of 1.2 kg ($p < 0.02$) and limb fat mass of 0.5 kg ($p < 0.05$)[44]. This suggests that the duration of the placebo-controlled trial might not have been long enough to observe a significant result. Critically, all of the patients in this trial had not received either PI or tNRTI for greater than six months prior to entry into the study[44].

In another randomized, placebo-controlled trial of HIV-1-seropositive men and women, patients on a tNRTI-sparing regimen showed a significant increase in limb fat mass and insulin sensitivity with rosiglitazone compared to placebo[13]. All the patients in this study had a history of tNRTI use of at least 12 months duration, with cessation of tNRTI for a minimum of 24 weeks prior to study entry[13]. The significant increase in limb fat mass in rosiglitazone patients of 448 g compared to 153 g in the placebo group ($p = 0.02$) suggested an effect due to rosiglitazone rather than simply switching from tNRTI use alone[13]. Insulin sensitivity, measured by changes in insulin levels and HOMA-IR from baseline, was improved with rosiglitazone ($p = 0.01$) and the changes were more significant with rosiglitazone compared to placebo ($p < 0.03$)[13]. Thus, the use of rosiglitazone following tNRTI cessation could ameliorate lipoatrophy in patients more effectively than switching from tNRTI alone. As observed in other studies, rosiglitazone increased total cholesterol by 22 mg/dl compared to baseline ($p = 0.008$)[13]. This study is particularly interesting in light of the earlier work that showed no benefit of rosiglitazone[10,40]; in the absence of a lipoatrophic NRTI, rosiglitazone could improve body composition in HALS patients.

Pioglitazone

Given that pioglitazone is still in clinical use[16], the effects of this TZD are of particular interest. Despite this, there have not been many studies performed on the use of pioglitazone in treating HALS (Table 3, supplementary data) and thus it is difficult to provide as detailed an analysis as with rosiglitazone. In a prospective cohort study, pioglitazone was used to treat HALS in a small number of patients, all of whom were taking stavudine[45]. This trial found total body fat increased by 3.1% ($p = 0.05$) and leg fat mass increased by 2.3% ($p = 0.05$) without changes in the serum lipid profile[45]. Further, seven of the 11 patients reported a subjective improvement in their lipoatrophy[45]. Pioglitazone increased insulin levels by 41% ($p = 0.01$) and did not improve insulin sensitivity as observed with rosiglitazone[45]. This was an open-label prospective study, with patients compared to baseline and without placebo controls[45].

A comparison of the lipid-lowering agent fenofibrate and pioglitazone found greater improvement in lipid profiles with pioglitazone in a small, placebo-controlled trial[46]. All of the patients were taking NRTI at the start of the study, although the type of NRTI is not specified[46]. Pioglitazone increased adiponectin levels by 284% ($p < 0.05$), while no change was observed with placebo. Several measures of insulin sensitivity, including HOMA-IR, QUICKI, and fasting insulin levels, improved significantly during the study. Contrary to the rosiglitazone studies, pioglitazone decreased the fasting triglyceride levels by 28% ($p < 0.05$)[46]. They also found an increase in HDL cholesterol with pioglitazone compared to placebo ($p = 0.01$), while the increase in LDL cholesterol was not statistically significant ($p = 0.07$)[46]. Abdominal skin fold thickness increased by 42% and waist circumference increased by 4% ($p < 0.05$)[46]. Measures of limb fat did not change significantly during the study. While the results of this study were promising for pioglitazone, it was limited by small sample size.

In a large randomized, placebo-controlled trial, a significant increase in limb fat with pioglitazone compared to placebo was observed[47]. The limb fat increase was 0.38 kg in the pioglitazone treatment group compared to placebo ($p = 0.051$). Crucially, in the patients who were not on stavudine, the increase was greatest at 0.45 kg and there was no significant change observed in the patients who were exposed to stavudine[47]. The study also found a significant increase in HDL cholesterol levels in patients receiving pioglitazone[47]. In comparison to the rosiglitazone studies, there was no significant increase in atherogenic lipids. There was no effect on insulin sensitivity in this study, probably due to the normal blood glucose and insulin responsiveness at baseline in the cohort[47]. The findings of this relatively large study provide further evidence supporting the role of pioglitazone in treating HALS.

In a small non-placebo-controlled study, patients taking pioglitazone alone or in conjunction with an exercise regimen showed improvements in some metabolic markers over 16 weeks[48]. The study found that the glucose disposal rate improved by 19% from baseline ($p < 0.0002$) and that there was an even greater effect when combined with exercise (37%; $p = 0.005$)[48]. Measurement of hepatic insulin sensitivity, HOMA-IR, and endogenous glucose production found an improvement in each treatment group ($p < 0.03$, $p < 0.004$, and $p = 0.01$, respectively), but there was no difference between the groups[48]. Adiponectin was found to increase with pioglitazone alone as well as with both pioglitazone and exercise ($p= 0.0001$ and $p = 0.002$, respectively); other markers of metabolism and body composition did not change significantly in either group, including: fasting triglycerides, total cholesterol, LDL, HDL, body weight, fat-free mass, and limb adipose mass[48]. Most of the patients were on an unspecified NRTI, with only 5% of the pioglitazone group on stavudine[48]. Since this study was not placebo controlled, definitive conclusions about the treatment of HALS with pioglitazone cannot be made.

Role of thiazolidinediones on HIV/HAART-associated lipodystrophy syndrome

The most prominent feature of HALS is lipoatrophy, and this review has considered whether treatment of these patients with TZDs could ameliorate this problem. It is well-known that the TZDs cause weight gain in T2DM patients, which could be due, in part, to the induction of adipocyte differentiation and the redistribution of body fat[49]. While these side-effects are not desirable in T2DM, it is possible that they could ameliorate the signs of lipodystrophy in HALS patients. On balance, the improvement in limb fat mass in the studies with rosiglitazone was small or not detectable, and this was borne out in a meta-analysis of the data[50]. In all of the clinical trials where it was measured, rosiglitazone increased adiponectin levels, but whether this change resulted in obvious clinical signs including improved limb fat mass is not universally evident. This disconnect could be due to the HAART drugs used, including the tNRTI, which are associated with reduced *PPARG* gene expression and mitochondrial toxicity[10]. The trials in which tNRTI use was taken into account in the calculations[47] or in which the study patients were on tNRTI-sparing regimens[13] found a greater improvement in limb fat mass with TZD treatment. The study by Tungsiripat, et al. is of particular interest since it was published after the most recent meta-analysis[50] and identified a beneficial effect of rosiglitazone on lipoatrophy in patients not receiving tNRTI[13].

It has been hypothesized that pioglitazone could be more favorable than rosiglitazone in reversing lipoatrophy[51,52]. A small meta-analysis of six trials of TZD in treating HALS, including one of pioglitazone[47], found that patients receiving pioglitazone had greater limb fat mass gains of 0.35 kg ($p = 0.01$) compared to placebo and this effect was not observed with rosiglitazone[53]. In this review, limb fat mass was found to improve with pioglitazone treatment in two out of the four studies analyzed[45,47]. The limb fat increase with

pioglitazone was not affected by NRTI use by all of the patients in one study[45] and was greater in the patients not taking tNRTI in the other[47]. A more comprehensive meta-analysis of the use of TZDs or metformin in treating HALS found that pioglitazone improved fasting HDL levels compared to placebo ($p = 0.04$), but did not significantly ameliorate measures of body composition or insulin sensitivety[50]. Critically, this study only analyzed two trials of pioglitazone, one of which showed a beneficial effect on limb fat mass[47] while the other did not[46]. Since the meta-analyses were published, an additional trial on pioglitazone has been reported[48]. While this study has found improvements in insulin sensitivity and adiponectin levels with pioglitazone, no increase in limb fat mass was reported[48]. The improved insulin sensitivity observed with pioglitazone[46,48] was not found in the other placebo-controlled trial[47]. The dearth of trials on pioglitazone makes it difficult to conclude further.

The mechanism by which the TZDs could ameliorate HALS likely involves activation of PPARγ, with the consequent increase in expression of PPARγ and upregulation of PPARγ-responsive genes. Importantly, this could also be influenced by changing the HAART regimen, specifically by reducing tNRTI use[10]. When tNRTI use has been avoided for the duration of the study (48 weeks), there was an increase in *PPARG* gene expression in the placebo group that was comparable to that observed in the rosiglitazone group[10]. Further, there was a positive correlation between improved limb fat mass and increased *PPARG* expression[10,52]. This is logical given the recognized importance of PPARγ in peripheral adipose tissue[7] and that PPARγ functions in promoting adipogenesis, such as by increasing the expression of adiponectin[23]. Several of the trials measured adiponectin levels as a secondary endpoint, with increased adiponectin observed in seven of the 12 trials of rosiglitazone and in two of the four of pioglitazone. Stimulation of PPARγ is known to increase adiponectin expression[51,54] so the finding that the TZDs increase adiponectin levels is not surprising. Importantly, elevated adiponectin is inversely correlated with measures of obesity and T2DM, and thus adiponectin levels could be a marker of improved metabolism in HALS, even in the absence of increased limb fat mass. In addition, expression of other genes involved in lipid metabolism and adipogenesis are stimulated by PPARγ[55], including the very low density lipoprotein receptor (VLDLR), which is required for lipid accumulation in adipocytes and for adipogenesis[56]. Thus, treatment with the TZDs is thought to lead to lipid accumulation via upregulation of expression of the VLDLR, thereby promoting weight gain[56].

In addition to effects of the TZDs on limb fat mass, these drugs have been examined for their effects on insulin sensitivity and glucose metabolism. While pioglitazone increased insulin sensitivity in 50% of the trials, rosiglitazone improved insulin sensitivity and glucose metabolism in 80% of the trials compared to placebo ($p = 0.03$) and to metformin (not significant, $p = 0.5$), while most of the other measures of metabolism and body composition favored metformin over rosiglitazone[50]. Rosiglitazone is thus particularly effective at improving insulin sensitivity and could still have clinical relevance in treating insulin resistance in HALS patients. The induction of insulin resistance depends upon complex factors, including reduced adiponectin and impaired GLUT4 function[55]. Since adiponectin and GLUT4 are PPARγ-responsive genes, the TZDs could improve insulin sensitivity by increasing the expression of these genes and this was observed in the clinical trials. Both rosiglitazone and pioglitazone increased adiponectin levels and this could be associated with improved insulin sensitivity[54,55]. One PPARγ-responsive gene is the glucose transporter GLUT4[57], and it is feasible that PPARγ improves insulin sensitivity by increasing the uptake of glucose into skeletal muscle[58]. The PI used as part of HAART have been found to reduce GLUT4 expression, which could contribute to insulin resistance in HALS[7], and this could be counteracted by treatment with TZDs. Thus, the improvement in insulin sensitivity following TZD treatment likely results from the activation of PPARγ and the consequent upregulation of PPARγ-responsive genes. Rosiglitazone use could be associated with significant changes in the expression of such genes even in the absence of altered PPARγ expression[58].

Of further interest is the possible benefit of TZDs in blocking HIV-1 replication as a number of studies have found that PPARγ agonists inhibit HIV-1 replication in several cell types[59], notably in macrophages and dendritic cells[60,61]. Since HIV-1 is known to contribute to HALS[5,22], the inhibition of viral replication by the TZDs could be an additional mechanism by which these drugs ameliorate HALS, although this was not examined in the clinical trials discussed. The fact that study participants were on stable HAART regimens with low viral loads would likely preclude analysis of this effect in these patients. Nonetheless, this effect of the TZDs is noteworthy and could provide a means of suppressing HIV-1 reactivation from latency in viral reservoirs.

Rosiglitazone was associated with increased total and LDL cholesterol in seven of the studies discussed[13,31,33-36,40], thereby increasing the atherogenic lipid profile in patients who are already at greater risk of cardiovascular disease. Indeed, concern for the safety of TZDs in the treatment of T2DM has resulted in the discontinuation of rosiglitazone from clinical use[16]. Safety concerns of rosiglitazone include hepatotoxicity and edema[49], as well as an increased risk of myocardial infarction[62]. Pioglitazone is still in general use, although it has been withdrawn in two countries due to a link with cholangiocarcinoma[16]. In comparison to rosiglitazone, pioglitazone was not found to increase atherogenic lipid levels[45,47,48] and was associated with a beneficial increase in HDL[46]. There were few reported adverse events in the studies discussed, with none recorded in any of the pioglitazone trials[45-48]. It is thus feasible that pioglitazone is a safer TZD that could be used to treat HALS. Given the promising findings in the few studies on pioglitazone, as well as the conclusion of the meta-analyses, it is apparent that a large randomized, placebo-controlled trial of pioglitazone in the treatment of HALS would be beneficial[45,50].

Conclusions

Given the changes in HAART, particularly the reduction in tNRTI use, it is feasible that the incidence of HALS could be decreasing, at least in the northern hemisphere[12]. However, the reversal of lipoatrophy following tNRTI discontinuation was found to be slow and incomplete[13] and the use of TZDs in conjunction with a tNRTI-sparing regimen could lead to greater improvements in HALS. Thus, even where the change in HAART combinations prevents a worsening of HALS, the use of TZDs could enhance the improvement in clinical signs of the disorder. Given the safety concerns and withdrawal of rosiglitazone, it is unlikely that further clinical trials of this drug will be pursued. In contrast, the beneficial effect of pioglitazone on lipoatrophy and better safety profile compared to rosiglitazone warrant additional clinical trials on the use of this TZD in the treatment of HALS. These trials should include participants who are on stable, comparable HAART regimens and should be of sufficient duration in order to observe improvements in lipoatrophy that could emerge slowly, particularly following tNRTI cessation.

Search strategy and selection criteria

The search terms 'HIV PPARs' were used in PubMed and the results were then filtered by randomized clinical trials. Further clinical trials were identified from additional searches for 'HAART and PPARs', 'pioglitazone HIV' and 'rosiglitazone HIV', as well as by manual searches of references given in the papers and the meta-analyses.

Disclosure statement

The authors declare that they do not have any conflicts of interest.

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Supplementary Data

Supplementary data is available at AIDS Reviews journal online (http://www.aidsreviews.com). This data is provided by the author and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

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