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The Effect of Rosiglitazone on PPARγ Expression in Human Adipose Tissue Is Limited by Continued Exposure to Thymidine NRTI

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Background: Decreases in peroxisome proliferators-activated receptor gamma (PPAR-γ) expression in subcutaneous adipose tissue may be important in the pathogenesis of lipoatrophy. Despite this, rosiglitazone (RSG), a PPAR-γ agonist, has not been shown to increase limb fat in lipoatrophic HIV-infected patients.

Methods: We completed a sub-study of a randomized, placebo-controlled, 48-week trial examining the effect of RSG 4 mg twice daily on limb fat in 100 HIV-infected adults with lipoatrophy. We examined changes in mRNA expression in subcutaneous fat biopsies, performed at weeks 0, 2, and 48. RNA was extracted and real-time RT-PCR performed for mitochondrial and lipid metabolism genes, with results presented relative to β-actin expression, which did not change. Non-parametric analyses were applied.

Results: We recruited 44 men (RSG n = 21, placebo n = 23) to this sub-study of which 21 were receiving the thymidine analogues (tNRTI) zidovudine (AZT) (n = 3) or stavudine (d4T) (n = 18) at baseline. Although groups were matched for baseline PPAR-γ expression ($p = 0.8$), limb fat was lower in the RSG group (1.9 kg vs 2.3kg). Mitochondrial-encoded cytochrome-b expression was significantly lower in those treated with tNRTI (median 2.53 [IQR 4.45] vs 6.04 [4.54] for the no-tNRTI group, $p = 0.001$). At week 2, only those randomized to RSG in the no-tNRTI group experienced a significant rise in PPAR-γ expression ($p = 0.046$). Similar significant increases in PPAR-γ co-activator 1 (PGC-1) expression were also observed in the RSG no-tNRTI group. At week 48, PPAR-γ expression was significantly higher only in the no-tNRTI group, regardless of randomized treatment allocation ($p = 0.04$), with RSG having no effect in the tNRTI group (see the table). No significant correlations were observed between changes in PPAR-γ or PGC-1 expression and change in limb fat.

	PPARγ			
	Week 2		**Week 48**	
	tNRTI	**no tNRTI**	**tNRTI**	**no tNRTI**
RSG	12 [99]	68 [56]	–22 [154]	87 [166]
Placebo	2 [97]	7 [173]	–32 [131]	74 [181]
	PGC-1			
RSG	13 [69]	149 [341]	29 [63]	672 [976]
Placebo	35 [131]	107 [181]	119 [118]	313 [220]

Keywords: Lipodystrophy; Rosiglitazone; Mitochondrial toxicity