



## 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

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### ALTERED TNF- $\alpha$ AND IL-6 LEVELS AND THE ANTIADIPOGENIC EFFECTS OF ANTIRETROVIRALS ON CULTURED ADIPOCYTES: POSSIBLE MECHANISMS FOR THEIR ROLE IN LIPODYSTROPHY IN HIV-INFECTED PATIENTS

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**BACKGROUND:** The use of highly active antiretroviral therapy (HAART) has improved the morbidity and mortality of HIV-infected patients. However, it has been associated with the debilitating metabolic syndrome of lipodystrophy, characterized by fat redistribution, hyperlipidaemia and insulin resistance. Both protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) have been implicated as potential causative agents of this syndrome. Their contribution (singly, or in combination) to dysregulated fat metabolism remains to be characterized.

**METHODS:** We incubated differentiating murine 3T3-F442A adipocytes in the presence (20  $\mu$ M) or absence of the NRTIs zidovudine, stavudine and the PIs indinavir, ritonavir, saquinavir and nelfinavir. The effects of the drugs either singly or in combination on adipogenesis was assessed by measuring glycerol-3-phosphate dehydrogenase (GPDH) activity after 8 days. Additionally the influence of drug treatment on TNF- $\alpha$  and IL-6 levels (ELISA) was determined.

**RESULTS:** Nelfinavir, saquinavir and ritonavir markedly inhibited adipogenesis. A combination of any of the PIs led to a much greater decrease in GPDH activity compared to single drugs alone ( $P < 0.005$ ). Nelfinavir combined with indinavir was found to have the greatest inhibitory effect (-80% vs control,  $P < 0.001$ ). However, the inhibition profile seen with the NRTIs was minimal (and often non-existent) when compared to the effect of PIs. Interestingly, when either of these NRTIs were combined with indinavir, a synergistic effect was noted (-28% combined stavudine/indinavir vs -0.8% stavudine alone,  $P < 0.001$ ). We found that the secretion of TNF- $\alpha$  and IL-6 was enhanced by PI

treatment. The order of potency of increased TNF- $\alpha$  secretion was nelfinavir > saquinavir > ritonavir > indinavir (90, 71, 21 and 5% respectively).

**CONCLUSIONS:** In conclusion, our data show that the protease inhibitors nelfinavir, saquinavir and ritonavir exert potent inhibitory effects on adipocyte differentiation, by inhibiting GPDH activity. Interestingly, the order of potency of inhibition of GPDH corresponded to the increase in TNF- $\alpha$  and IL-6 levels caused by these treatments. Taken together, the data show that antiretrovirals have complex effects on adipocytes, their effects often being enhanced by use of combinations, and in addition, they increase TNF- $\alpha$  and IL-6 levels, adipokines known to have marked effects on adipocyte metabolism.

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3

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