

## 2nd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV



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### EFFECTS OF NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS AND HIV PROTEASE INHIBITORS ON ADIPOGENESIS AND ADIPOCYTE METABOLISM

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**BACKGROUND:** Lipodystrophy (LD) has been associated with nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) therapy in HIV-AIDS. Effects on adipocyte mitochondrial function by NRTIs, and glucose transport by PIs, have been proposed as potential mechanisms underlying LD.

**OBJECTIVES:** Evaluate and compare the direct effects of NRTIs and PIs on adipogenesis and metabolism in adipocyte cell culture.

**DESIGN:** Differentiating murine CB1 and 3T3-L1 adipocytes were incubated with drugs for 6 days and assayed for intracellular triglyceride accumulation (TG). Fully differentiated cells were treated with drugs for 4 days and assayed for lipolysis (glycerol release). Mitochondrial function (ATP) was measured after 5 days' incubation with differentiating cells.

**RESULTS:** TG IC<sub>50</sub> values (μM) in CB1 adipocytes were, for PIs: 7.0 (nelfinavir), 24 (saquinavir), 67 (ritonavir), 140 (indinavir) and 150 (amprenavir); and for NRTIs: 84 (fialuridine), 100 (abacavir), 110 (azidothymidine) and 120 (stavudine, lamivudine). Similar patterns were obtained for increases in lipolysis. ATP IC<sub>50</sub> values (μM) for PIs were: 76 (saquinavir), 92 (nelfinavir), 260 (ritonavir) and >1000 (indinavir, amprenavir); and for all NRTIs, IC<sub>50</sub> >1000 μM. Incubation with both ritonavir plus stavudine or azidothymidine augmented effects on TG and lipolysis versus either drug' alone.

**CONCLUSIONS:** Over 4-6 days' exposure, PIs suppressed TG accumulation and promoted lipolysis at lower concentrations than those affecting mitochondrial function. Nelfinavir, saquinavir and ritonavir were more potent inhibitors of adipogenesis than indinavir and amprenavir. In contrast, NRTIs weakly affected adipogenesis and lipolysis with minimal effects on ATP levels under these conditions. These data do not support direct NRTI-induced mitochondrial toxicity in adipocytes as a main mechanism for LD, but are consistent with a multifactorial etiology of LD in HIV-AIDS, including previous or current exposure to certain PIs.

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