



# 1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

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## EFFECT OF HIV PROTEASE INHIBITORS ON *IN VITRO* ADIPOGENESIS AND *IN VIVO* FAT DEPOSITION

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**BACKGROUND/OBJECTIVES:** Patients using HIV protease inhibitors (PIs) often suffer from lipodystrophy or dyslipidaemia. As the cause of these adverse reactions is unknown, the effects of PIs on (i) adipocyte differentiation and retinoic acid (RA) signalling *in vitro* and (ii) fat metabolism *in vivo* were tested.

**DESIGN/RESULTS:** (i) C3H10T1/2 mesenchymal stem cells were treated with various PIs under conditions that promote adipogenesis and in the presence or absence of RA. Amprenavir had little effect on adipogenesis or retinoid signalling *in vitro*. Unlike the other PIs, indinavir inhibited adipogenesis in the presence, but not the absence, of RA. Moreover, indinavir stimulated the retinoid-responsive gene alkaline phosphatase, suggesting that indinavir therapy may alter RA signalling. In the absence of RA nelfinavir, saquinavir and ritonavir inhibited lipogenesis and expression of the adipose markers, aP2 and LPL. Further, these three PIs increased lipolysis in adipocytes, indicating decreased adipogenesis and increased fat catabolism may contribute to lipodystrophy. (ii) In contrast to these *in vitro* observations, saquinavir and indinavir treatment of mice fed a low-fat diet increased epididymal fat mass by 40% and 48%, respectively. Likewise, saquinavir and nelfinavir treatment increased intrascapular fat mass by 28% and 32%, respectively. Amprenavir did not have a significant effect on fat mass. Serum triglycerides decreased in low-fat and increased in high-fat fed mice treated with nelfinavir and saquinavir. Similarly, intrascapular fat mass negatively correlated ( $r = -0.89$ ) in low- and high-fat fed mice treated with PIs.

**CONCLUSIONS:** The results suggest that (i) the various PIs affect distinct metabolic pathways and (ii) environmental factors, such as retinoids and dietary fat, can influence the effects of PIs on fat metabolism.

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