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THE ROLE OF TUMOUR NECROSIS FACTOR ALPHA AND ANTIRETROVIRALS IN ADIPOCYTE APOPTOSIS *IN VITRO*

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BACKGROUND: Subcutaneous adipocyte apoptosis is a prominent feature in patients with HIV-associated fat redistribution syndromes (FRS). Tumour necrosis factor alpha (TNF- α), which is elevated in patients with FRS, is known to potentially promote preadipocyte and adipocyte apoptosis.

METHODS: MTT method was used to assess the cellular viability of 3T3-L1 adipocytes in presence of antiretroviral drugs [stavudine (d4T), lamivudine (3TC) and indinavir, either alone or in combination]. DNA fragmentation associated with apoptotic cell death was studied by TUNEL (TdT-mediated dUTP nick-end labelling) assay. Adipocyte cells (1×10^6 /ml) placed in 6-well plates were processed according to the ApoAlert DNA fragmentation kit protocol supplied by the manufacturer (Clontech Laboratories, Inc., Palo Alto, CA, USA). Briefly, cells were incubated with TdT digoxigenin-labelled dUTP followed by incubation with FITC-labelled anti-digoxigenin antibody. The FITC-labelled positive cells were identified by flow cytometry. A total of 10,000 cells per sample were analysed and FACS analysis was performed using a FACScan flow cytometer (Becton Dickinson) equipped with a 488 nm Argon laser. CellQUEST software (Becton Dickinson) was used for data analysis.

RESULTS: The adipocyte apoptotic index did not significantly increase with respect to controls, in the presence of indinavir, d4T+3TC and d4T+3TC+indinavir, either in the absence or presence of TNF- α . However, it significantly increased for indinavir ($P=0.0001$), d4T+3TC ($P=0.01$) and d4T+3TC+indinavir ($P=0.0001$) when TNF- α was added with respect to antiretroviral drugs either alone or combined. The apoptotic index

induced by d4T+3TC+indinavir combined with TNF- α was significantly greater than that induced by indinavir ($P=0.03$) and d4T+3TC ($P=0.0001$), when combined with TNF- α .

CONCLUSIONS: Our results suggest that TNF- α is the driving force in subcutaneous adipocyte apoptosis, which occurs in the setting of FRS in HIV-1-infected patients on highly active antiretroviral therapy.

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