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ASSESSMENT OF MITOCHONDRIAL TOXICITY OF DIVERSE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY REGIMENS BY A SIMULTANEOUS GENETIC AND BIOCHEMICAL APPROACH

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OBJECTIVES: Nucleoside reverse transcriptase inhibitors are being increasingly associated with mitochondrial (mt) toxicity. We aimed to assess mt content and function in peripheral blood mononuclear cells (PBMCs) of HIV-infected patients previous to the development of clinically evident body fat changes.

METHODS: We studied one control group of antiretroviral-naïve patients ($n=25$) and four ($n=42$) on different highly active antiretroviral therapies (HAART) consisting on zidovudine+lamivudine or stavudine+didanosine plus either nelfinavir or nevirapine for at least 6 months. The relative mitochondrial/nuclear (mt/n) DNA ratio was determined by real time PCR, and mt abundance was estimated by citrate synthase activity. Enzyme activity of complexes III and IV of the electron transport chain (ETC) was spectrophotometrically determined; oxygen consumption was polarographically measured in intact PBMCs and in the presence of complex I and III substrates. The decrease of *cis*-parinaric acid fluorescence due to lipid peroxidation reactions was used to indirectly monitor the oxidative damage of PBMCs membranes.

RESULTS: Only those groups of HIV-infected patients on HAART, including stavudine+didanosine exhibited significant mtDNA depletion. Mitochondrial abundance was significantly lower in all treated groups, nelfinavir-containing HAART groups showing the greatest decrease. Antiretroviral regimens containing either stavudine+didanosine or nelfinavir were associated with a significant decrease of enzyme activity of complex IV of ETC, the greatest decline was found when both

stavudine+didanosine and nelfinavir were combined in the same schedule. All oxidative activities remained normal. No HAART regimen was associated with increased lipid peroxidation; even those groups receiving stavudine+didanosine exhibited less oxidative damage than others groups.

CONCLUSIONS: PBMCs can be used to detect different degrees of mitochondrial toxicity of HAART regimens, even before adverse effects occur. All HAART regimens seem to exert toxic effects on mitochondria and different patterns are observed, suggesting the presence of different HAART pathogenic mechanisms on mitochondria. Despite mtDNA depletion being present in asymptomatic patients on stavudine+didanosine-containing HAART, functional capacity of MRC remained normal and the oxidative damage was not increased. Accordingly, we recommend caution on interpreting isolated abnormal genetic mitochondrial analyses and encourage simultaneous genetic and functional approaches before attributing any pathogenic conclusion.

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