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MITOCHONDRIAL DNA DEPLETION IN ASYMPTOMATIC HIV-INFECTED PATIENTS RECEIVING DIDANOSINE PLUS STAVUDINE-BASED HAART REGIMEN SEEMS TO BE COMPENSATED BY UP-REGULATORY MECHANISMS

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OBJECTIVES: The use of nucleoside analogues is uniformly associated with mitochondrial DNA (mtDNA) depletion, but diverse studies in asymptomatic patients have reported functional indemnity of mitochondria. We determined whether homeostatic mechanisms are able to compensate this mtDNA depletion in patients receiving stavudine plus didanosine (d4T+ddI), an antiretroviral association with great *in vitro* and *in vivo* capacity to decrease mtDNA.

METHODS: We included 28 symptom-free HIV-infected individuals: 17 on first-line antiretroviral regimen consisting of d4T+ddI for at least 6 months (case group) and 11 naïve subjects (control group). In peripheral blood mononuclear cells we assessed: 1) the quantity of mitochondria by citrate synthase activity, 2) the content of mtDNA by quantitative real-time PCR, 3) COX-II expression [subunit II of cytochrome c oxidase (COX), encoded by mtDNA] by Western blot, and 4) COX activity by spectrophotometry.

RESULTS: The quantity of mitochondria and the mtDNA content of cases (d4T+ddI) were decreased when compared with controls, whether calculated by cells or by mitochondria. The expression of COX-II and COX activity were similar in cases and controls. The expression of COX-II was found to be constant and independent of the mtDNA content, whereas it was closely related to COX activity.

CONCLUSIONS: Decreased mitochondrial mass and mtDNA content are associated with ddI+d4T treatment, but the expression of COX-II and COX activity remains unaltered. These data suggest that, at least during the initial phases of treatment, up-regulatory transcriptional or post-transcriptional mechanisms compensate mtDNA depletion caused by ddI+d4T.

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