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ADDITION OF TENOFOVIR TO A DIDANOSINE-BASED HAART DOES NOT INCREASE MITOCHONDRIAL DNA DEPLETION BUT DECREASES CYTOCHROME C OXIDASE FUNCTION AND MITOCHONDRIAL MASS

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PURPOSE OF THE STUDY: The nucleotide analogue tenofovir disoproxil fumarate (TDF) has been reported to be free of mitochondrial toxicity. In the present study, we evaluate the effects of the introduction of TDF on a HAART schedule containing didanosine (ddI) on mitochondrial mass, mitochondrial DNA (mtDNA) content and cytochrome c oxidase (COX) activity.

METHODS: Fifty HIV-infected patients receiving a ddI-based HAART schedule were recruited, and changed to ddI plus TDF (300 mg/d) and nevirapine (400 mg/d) ($n=25$, cases) or maintained with the same HAART scheme ($n=25$, controls). All patients were symptom-free with undetectable viral load along the study. Peripheral blood mononuclear cells (PBMCs) were obtained at 0 (baseline), 6 and 12 months. The quantity of mitochondria was assessed by the spectrophotometric measurement of the citrate synthase activity, the content of mtDNA by quantitative real-time PCR and the activity of COX (complex IV of the mitochondrial respiratory chain) by spectrophotometry.

RESULTS: Cases and controls maintained unchanged in all mitochondrial parameters at 6 months with respect to baseline. Conversely, at 12 months we found that mtDNA content was reduced in both cases (24%, $P<0.01$) and controls (18%, $P<0.05$), while mitochondrial mass and COX activity were found to be significantly decreased only in cases (28%, $P<0.05$ and 47%, $P<0.001$; respectively).

CONCLUSIONS: A decrease in mitochondrial mass, mtDNA content and COX activity is detected after 12 months of the addition of TDF to HAART schedules containing ddI. This diffuse deterioration of mitochondrial parameters could be due to the effects of TDF itself, the increase of ddI concentrations caused by TDF or both. The relevance of these biochemical findings in clinical practice remains to be determined.

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