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Mitochondrial nephrotoxicity, a potential mechanism of kidney dysfunction in HIV-infected patients on HAART

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BACKGROUND: Tenofovir disoproxil fumarate (TDF) use has been associated with renal dysfunction. Mitochondrial nephrotoxicity was investigated as a potential mechanism. Given the known pharmacokinetic interaction between TDF and didanosine (ddI), the effect of their concurrent use was also investigated.

METHODS: Relative kidney mitochondrial DNA (mtDNA) to nuclear DNA ratios were measured retrospectively in diagnostic kidney biopsies divided into three groups: HIV-infected individuals who received TDF within 6 months preceding the biopsy (HIV+/TDF+, $n=21$, 13 with acute tubular necrosis [ATN]); HIV+ individuals who never received TDF (HIV+/TDF-, $n=10$, 3 ATN); HIV-uninfected controls (HIV-, $n=22$, 12 ATN). Twelve HIV+/TDF+ individuals received concurrent ddI, 10 of them at unadjusted dose. Tubular mitochondria morphology was also examined by electron microscopy. Statistical analyses were done on log-transformed mtDNA ratios, using non-parametric tests.

RESULTS: Relative kidney mtDNA levels were different among the three groups ($P=0.046$). Median [IQR] mtDNA ratios were lower in HIV+/TDF+ subjects (7.5 [2.0–12.1]) than in HIV-uninfected ones (14.3 [6.0–16.5], $P=0.014$), but not lower than HIV+/TDF- controls (6.4 [2.8–11.9], $P=0.82$). Among HIV+ subjects, there was a difference between TDF-, TDF+/ddI- and TDF+/ddI+ ($P=0.005$), as concurrent use of TDF/ddI was associated with lower mtDNA (2.1 [1.9–5.5]; $n=12$) than TDF use without ddI (13.8 [7.5–16.4]; $n=9$, $P=0.003$), with a similar prevalence of ATN in both groups.

No TDF⁻/ddI⁺ biopsies were available. In regression analyses adjusting for age, gender, HIV, ATN and the use of TDF±ddI, only HIV infection ($P=0.03$), and TDF/ddI use ($P=0.003$) were associated with lower mtDNA. Ultrastructurally, abnormal tubular mitochondrial morphology was more prevalent in HIV⁺/TDF⁺ biopsies than HIV⁺/TDF⁻ and HIV⁻ ones together ($P<0.001$) but not more so in TDF⁺/ddI⁺ biopsies than TDF⁺/ddI⁻ ones ($P=0.67$). None of the co-variables tested were significantly associated with abnormal mitochondria.

CONCLUSIONS: Renal dysfunction in patients receiving TDF can be mediated through mitochondrial nephrotoxicity, influenced by both HIV infection and concurrent TDF/ddI therapy, two drugs that are cleared renally. The current clinical relevance of these findings needs to be further evaluated given the recommendation for lower doses of ddI when used with TDF.



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