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Mitochondrial toxicity of antiretrovirals in non-HIV-infected patients

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Purpose of the study

Antiretroviral (ARV) toxicity, especially of nucleoside-analogues, together with HIV-infection have both been demonstrated to induce mitochondrial DNA (mtDNA) depletion and mitochondrial dysfunction. The contribution of each mechanism (either HIV or ARV) to the observed mitochondrial damage present in HIV-infected patients on highly active ARV treatment (HAART) is difficult to elucidate. HIV-induced mitochondrial lesion has been studied in HIV-infected but non-HAART-treated individuals, but ARV-related mitochondrial damage has been poorly explored in non-infected subjects. The aim of the present study is to assess in vivo mitochondrial toxicity of HAART without HIV-infection effects.

Methods

We included six healthy patients under one month of prophylactic ARV treatment consisting of FTC+TDF+SQVr to prevent HIV-infection after risk exposure. All of them remained uninfected 6 months after HAART withdrawal. Mitochondrial studies were performed in mononuclear cells before and after the ARV treatment to assess mtDNA content using real time PCR and mitochondrial function trough the spectrophotometric measurement of the enzymatic activity of both mitochondrial respiratory chain (MRC) complex II (non-mitochondrial encoded) and complex IV (partially encoded in the mitochondrial genome). Statistical analysis compared mitochondrial results before and after ARV therapy by the t-test for repeated measures.

Summary of results

Mitochondrial DNA content was 20% reduced along the ARV treatment in the studied patients (2.17+2.52 a 1.73+1.01, p = 0.5). MRC complex IV enzymatic activity was 24% reduced in these subjects after HAART (55.2+15.9 a 42+6.3, p = 0.1), although MRC complex II enzymatic activity remained unchanged after therapy discontinuation and with respect to baseline (26.5+10.5 a 27.8+9.4, p = 0.98).

Conclusion

In non-HIV-infected patients, one month of ARV treatment induced mitochondrial damage, even when considering the HAART consisting of FTC+TDF+SQV/r with theoretical low mitochondrial toxic profile. Mitochondrial changes consisted of slight mtDNA depletion and moderated mtDNA-encoded-MRC complex IV dysfunction, although none of these changes were statistically significant. These findings validate HAART-induced mitochondrial toxicity, even in the absence of HIV infection. Further studies should be performed to assess mitochondrial toxicity of different HAART schedules in non-infected individuals to elucidate toxic effects of antiretrovirals without HIV or previous ARV interference.