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THERAPY WITH EFAVIRENZ+RITONAVIR BOOSTED INDINAVIR, WITH OR WITHOUT STAVUDINE AFTER 24 WEEKS DOES NOT DECREASE MTDNA AND MTRNA CONTENT OF PBMC ASSESSED BY SINGLE TUBE DUPLEX REAL-TIME NASBA

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BACKGROUND: Several adverse effects of antiretroviral therapy (ART) may result from inhibition of mitochondrial DNA (mtDNA) polymerase gamma by nucleoside analogue reverse transcriptase inhibitors (NRTIs). We have previously shown that antiviral therapy with zidovudine+zalcitabine or zidovudine+didanosine may result in a decline of mtDNA in PBMCs. The effect of an ART-related change in mtDNA levels on expression of mtRNA is as yet unknown.

OBJECTIVE: Investigate the effect on mtDNA and mtRNA content in PBMCs after starting first line ART which does or does not include NRTI.

METHODS: A subset of 36 ART-naïve patients participated in a randomized trial comparing an NRTI-sparing strategy (ritonavir 100 mg/indinavir 800 mg twice daily + efavirenz 600 mg once daily) with the same regimen plus stavudine (40 mg twice daily) (the EASIER trial). PBMCs were obtained at start of therapy and at 4, 8, 12, 16 and 24 weeks thereafter. Using duplex realtime NASBAs assaying both nuclear DNA and mtDNA or mtRNA respectively, the mtDNA and mtRNA content of PBMCs was determined.

RESULTS: After 24 weeks of therapy, a transient increase in mtDNA content of the PBMCs was seen in the arm without stavudine, compared with a stable increase of 24% in the stavudine arm ($P=0.049$). The rise in mtDNA was delayed by 4 to 8 weeks in

patients receiving stavudine ($P=0.01$). After 24 weeks, mtRNA content had increased equally and approximately twofold ($P<0.01$) in both arms.

DISCUSSION AND CONCLUSIONS: In contrast to what may have been expected, inclusion of stavudine in an NRTI-sparing therapy did not decrease mtDNA content of PBMC. Instead, a 24% increase of mtDNA was observed in the stavudine arm accompanied by a significant increase of mtRNA levels in both arms. This may possibly be explained by recovery of mitochondrial suppression resulting from HIV-1 infection per se, following effective suppression of viral replication by ART.

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