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***IN VIVO* NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS ALTER EXPRESSION OF BOTH MITOCHONDRIAL AND LIPID METABOLISM GENES INDEPENDENT TO HIV INFECTION**

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PWG Mallon¹⁻³, P Unemori^{1,3}, R Sedwell^{1,3}, A Morey⁴, M Rafferty⁵, K Williams⁵, D Chisholm⁶, K Samaras⁶, S Emery¹, A Kelleher¹⁻³, DA Cooper¹⁻³ and A Carr^{2,3} for the SAMA investigators

¹ National Centre in HIV Immunology and Clinical Research, University of New South Wales, Sydney, Australia; ² HIV, Immunology and Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney, Australia; ³ HIV Immunovirology Research Laboratory, Centre for Immunology, St Vincent's Research Campus, Sydney, Australia; ⁴ Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia; ⁵ Clinical Trials Centre, St Vincent's Hospital Sydney, Australia; and ⁶ Garvan Institute of Medical Research, Sydney, Australia.

Mitochondria play an important role in lipid homeostasis, with mitochondrial dysfunction implicated in obesity and insulin resistance. The mitochondrial dysfunction induced by nucleoside analogue reverse transcriptase inhibitors (NRTIs) used to treat HIV infection, has been implicated in the development of lipodystrophy. How this mitochondrial dysfunction affects lipid metabolism at a molecular level has not been prospectively described *in vivo*. We examined early changes (2 weeks) in mitochondrial and nuclear gene expression in adipose tissue from 20 HIV-negative volunteers exposed to 6 weeks of dual-NRTI therapy. We observed inhibition of mitochondrial RNA (mtRNA) transcription without significant mitochondrial DNA depletion. Decreases in mtRNA coincided with simultaneous up-regulation of nuclear genes involved in the regulation of mtRNA transcription (NRF1 and mtTFA) and fatty acid oxidation (PPAR α and LPL), while PPAR γ , important for adipose differentiation and insulin responses, was down-regulated. Many nuclear changes correlated with changes in PPAR γ co-activator-1 (PGC1) expression, suggesting a central role for this transcriptional co-activator in nuclear responses to mitochondrial dysfunction. Peripheral blood monocyte COX1 expression also decreased, suggesting that monocytes may be surrogates for drug-induced mitochondrial dysfunction. These results characterize the central role of mitochondrial function in adipose tissue metabolism *in vivo*, provide evidence to support the presence of feedback mechanisms between mitochondria and the nucleus in humans, and offer an explanation for NRTI-induced lipodystrophy.

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