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### ANTI-OXIDANTS RESCUE NRTI-INDUCED METABOLIC CHANGES IN AKR/J MICE

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**BACKGROUND:** NRTI therapies are sometimes associated with lactate acidosis, which may result from increased oxidative stress.

**OBJECTIVES:** To determine if NRTIs cause oxidative stress and if anti-oxidants can rescue the stress response.

**DESIGN:** AKR/J mice were treated with placebo or NRTIs for 2 weeks in the presence or absence of antioxidants, ascorbate and  $\alpha$ -tocopherol. Postprandial serum chemistries, liver weights and micro array analysis of oxidative-stress genes from liver were measured from each treatment group.

**RESULTS:** Compared to placebo-treated mice, zidovudine-treated mice had lower serum glucose levels (9%,  $P=0.04$ ) whereas cholesterol, fatty acids, glycerol, hydroxybutyrate and alkaline phosphatase levels remained unchanged. Mice treated with stavudine had significantly ( $P<0.05$ ) greater serum levels of lactate (10%), triglyceride (40%), fatty acids (52%), glycerol (54%) and alkaline phosphatase (26%) and increased liver weight compared to controls. Microarray analysis of oxidative stress genes revealed a significant change in 86/144 genes from liver RNA of stavudine-treated mice. Treatment with stavudine also altered expression of fatty acid binding protein (FABP) and peroxisome proliferator activated receptor  $\alpha$  (PPAR $\alpha$ ), two genes involved in lipid metabolism. Glucose and hydroxybutyrate levels were unchanged in these mice. Ascorbate and tocopherol treatment reversed the effects of stavudine on liver weight, lactate, fatty acid, glycerol and alkaline phosphatase. Similarly, these antioxidants reduced the effects of stavudine on expression of FABP, PPAR $\alpha$  and 71% of the oxidative stress genes.

**CONCLUSIONS:** Zidovudine and stavudine had different effects on metabolism in mice, indicating these agents affect distinct metabolic pathways. Moreover, ascorbate and tocopherol reversed various effects of stavudine, indicating some metabolic changes associated with NRTIs may be due to increased oxidative stress.

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