Nucleoside reverse transcriptase inhibitors induce endothelial dysfunction and compromise mitochondrial function

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Nucleoside reverse transcriptase inhibitors (NRTIs) are an important component of highly active antiretroviral therapy for HIV patients. Though they are effective, long-term use of NRTIs leads to cardiovascular complications likely resulting from drug-induced mitochondrial toxicity. Our prior studies demonstrated that NRTIs impair endothelial cell function in the vasculature via an increased production of mitochondria-derived reactive oxygen species. In this study, we investigated the effects of three subclasses of NRTIs: the thymidine analogues azidothymidine (AZT) and stavudine (d4T), the cytidine analogue lamivudine (3TC), and the adenosine analogue didanosine (ddI). In mice that were orally administered pharmacologically relevant doses of these NRTIs for 2 weeks, endothelium-dependent vasorelaxation following acetylcholine administration and endothelium-independent relaxation by sodium nitroprusside were determined. In addition, we examined the mitochondrial locus of injury by measuring the activity of mitochondrial electron transport chain complexes in human umbilical vein endothelial cells (HUVEC) treated with equimolar doses of NRTI or their phosphorylated metabolites. Our *in vivo* data suggests that all three subclasses of NRTI impaired endothelium-dependent vasodilation, with the cytidine analog lamivudine having the most profound effect. The *in vitro* experiments showed direct inhibition for one or more mitochondrial complexes, and this effect was observed across all NRTI subclasses. Ongoing studies are aimed at determining the mechanism by which NRTIs mediate mitochondrial electron transport.