**Nucleoside reverse transcriptase inhibitors of all subclasses induce endothelial dysfunction and compromise mitochondrial function**

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Nucleoside reverse transcriptase inhibitors (NRTI) are a critical component of highly active antiretroviral therapy for HIV patients. Despite their effectiveness, however, long-term use of NRTIs leads to cardiovascular complications likely resulting from drug-induced mitochondrial toxicity. Our prior in vitro studies demonstrated that NRTIs impair endothelial function in the vasculature, likely via an increase production of mitochondria-derived reactive oxygen species. In this study, we investigated the effects of three subclasses of NRTIs: thymidine analogues like zidovudine (AZT) and stavudine (d4T); cytidine analogues, such as lamivudine (3TC); and adenosine analogues like didanosine (ddI). In mice orally administered pharmacologically relevant doses of NRTI for 4-6 weeks, endothelium-dependent vasorelaxation following acetylcholine administration and endothelium-independent relaxation by sodium nitroprusside were assessed. In addition, we determined 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. Our in vivo data suggests that all three subclasses of NRTIs 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 NRTI mediate mitochondrial electron transport.