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## Increased long-term mitochondrial toxicity in pyrimidine nucleoside combinations

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**BACKGROUND:** Some nucleoside reverse-transcriptase inhibitors (NRTIs) cause depletion of mitochondrial (mt)DNA in liver and other tissues by inhibiting polymerase- $\gamma$ . This may provoke clinically relevant lactic acidosis, steatohepatitis and liver failure.

**OBJECTIVE:** To evaluate the long-term mitochondrial toxicity of NRTI-combinations.

**METHODS:** The HepG2 human hepatoma cell line was cultivated in the presence of zalcitabine, didanosine, stavudine, lamivudine and zidovudine at three different concentrations (equivalent to steady-state peak plasma levels in humans, 1/3 or 10-fold of peak plasma levels). The NRTIs were added to the medium alone, or in combination. Controls cells were incubated without any NRTI or with efavirenz. Cell growth, lactate production, intracellular lipid droplets, mtDNA and the mtDNA-encoded respiratory chain subunit COX II were monitored over a period of up to 30 days.

**RESULTS:** MtDNA-depletion was most rapid and pronounced with zalcitabine and declined in the order of didanosine > stavudine > lamivudine = zidovudine. Zidovudine and the zidovudine/lamivudine combination behaved peculiarly in increasing lactate and cell death independent of a decline of mtDNA and without dramatically augmenting intracellular lipids. The toxicity of all the other NRTIs and their combinations was largely related to mtDNA depletion, which preceded or coincided with a decline in COX II-expression, a decrease in cell growth, increased lactate production and increased intracellular lipids. The effects of the lamivudine/zidovudine, lamivudine/stavudine and zalcitabine/stavudine combinations were more pronounced than those of either component alone. The combination of didanosine and stavudine was not more toxic than

didanosine alone. In some assays the steady-state levels of mitochondrial damage were not reached at day 30. At some concentrations of didanosine, of stavudine and of virtually all tested NRTI-combinations lactate, cell growth and mtDNA depletion continued to worsen. No effects were observed with efavirenz. Using a Southern blot technique, mtDNA deletions were never observed.

**CONCLUSIONS:** The *in vitro* data indicate possible additive or synergistic long-term mitochondrial toxicity of the pyrimidine nucleoside combinations. Mitochondrial damage due to some NRTI-concentrations/combinations can worsen beyond 1 month of incubation.

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