

## ***LACTIC ACIDOSIS AND HEPATIC STEATOSIS***

Lactic acidosis represents a rare but potentially fatal complication of antiretroviral therapy that has been linked to NRTIs and to HIV infection. NRTIs can inhibit human mitochondrial DNA polymerase gamma, an enzyme crucial for normal mitochondrial DNA replication. This inhibition results in depletion of mitochondrial DNA that compromises cellular oxidative phosphorylation. Evidence of mitochondrial DNA depletion can also be found in HIV-infected persons who have never received antiretroviral therapy, suggesting that HIV infection itself may contribute to mitochondrial dysfunction.

Clinically, this syndrome can range from asymptomatic hyperlactataemia to fatal lactic acidosis, often associated with hepatic steatosis. Development of this disorder appears to depend on the duration of NRTI exposure and on the specific ARVs used. d4T appears to be most commonly associated with lactic acidosis, followed by ddI and AZT, followed by 3TC and ABC. TDF appears to carry a low risk of mitochondrial toxicity as well. Pregnant women appear to be at greater risk for developing lactic acidosis, and deaths have been reported in women taking the combination of d4T plus ddI.

Physicians should maintain a high clinical suspicion for this syndrome, as symptoms are usually non-specific. Symptoms may include nausea, vomiting, abdominal pain and distension, diarrhoea, fatigue, myalgias, weight loss, and dyspnoea. An elevated lactic acid level establishes the diagnosis but requires sampling without a tourniquet, rapid transportation to a laboratory on ice, and processing within a few hours. Other helpful laboratory indicators include elevated CPK, LDH, amylase, and aminotransferases, and low serum bicarbonate.

Lactic acidosis is treated with supportive care and discontinuation of ARVs until the syndrome resolves. Case reports have suggested that supplementation with high doses of vitamins involved in oxidative phosphorylation, such as riboflavin or L-carnitine, may hasten the recovery process. Consultation with an HIV expert is strongly recommended. Following resolution of the syndrome, HAART should be re-initiated cautiously and in consultation with an HIV expert, avoiding NRTIs such as d4T and ddI that are strongly associated with mitochondrial toxicity.