Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (alone and in combination)	Onset: 1–20 months after starting therapy (median onset 4 months in 1 case series). Presentation: Usually insidious onset of a combination of signs and symptoms: generalized fatigue, weakness, and myalgias; vague abdominal pain, weight loss, unexplained nausea or vomiting; dyspnea; peripheral neuropathy. Patients may present with acute multi-organ failure (such as fulminant hepatic, pancreatic, and respiratory failure).	Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L): *Adults:* 15%–35% of adults receiving NRTI therapy for longer than 6 months *Children:* 29%–32% Symptomatic severe hyperlactatemia (>5.0 mmol/L): *Adults:* 0.2%–5.7% Symptomatic lactic acidosis/hepatic steatosis: Rare in all age groups (*1.3–11 episodes per 1,000* person-years), but associated with a high fatality rate (33%–58%)	Adults: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (such as d4T, TDF, RBV, or tetracycline) • Coadminstration of TDF with metformin • Overdose of propylene glycol • CD4 T lymphocyte count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly, pregnancy Pre-term infants: • Use of propylene glycol (e.g., as an diluent for LPV/r)	Prevention: Avoid d4T and ddI in combination. Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring: *Asymptomatic:* Measurement of serum lactate is not recommended. *Clinical signs or symptoms consistent with lactic acidosis:* Obtain blood lactate level;[a] additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (confirmed with second test): Consider replacing ddI and d4T with other ARVs. As alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. Lactate >5.0 mmol/L (confirmed with second test)[b] or >10.0 mmol/L (any one test): Discontinue all ARVs. Provide supportive therapy (intravenous fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). Anecdotal (unproven) supportive therapies: bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C). Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and monthly monitoring of lactate for at least 3 months.

[a] Blood for lactate determination should be collected without prolonged tourniquet application or fist clenching into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

[b] Management can be initiated before the results of the confirmatory test.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARVs = antiretrovirals, BMI = body mass index, d4T = stavudine, ddI = didanosine, FTC = emtricitabine, HCV = hepatitis C virus, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, RBV = ribavirin, TDF = tenofovir disoproxil fumarate, THAM = tris–hydroxymethyl-aminomethane

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