Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### Table 13g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

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| Lactic Acidosis | NRTIs, in particular, d4T and ddI (highest risk when co-administered) | 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  
**Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure). | Chronic,  
Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L)  
Adults:  
• 15% to 35% of adults receiving NRTI therapy for longer than 6 months  
Children:  
• 29% to 32%  
Symptomatic Severe Hyperlactatemia (>5.0 mmol/L)  
Adults:  
• 0.2% to 5.7%  
Symptomatic Lactic Acidosis/Hepatic Steatosis:  
• Rare in all age groups (1.3–11 episodes per 1000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%) | Adults:  
• Female gender  
• High BMI  
• Chronic HCV infection  
• African-American race  
• Prolonged NRTI use (particularly d4T and ddI)  
• Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline)  
• Co-administration of TDF with metformin  
• Overdose of propylene glycol  
• CD4 count <350 cells/mm³  
• Acquired riboflavin or thiamine deficiency  
• Possibly pregnancy  
Preterm Infants or Any Neonates before Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days has Been Attained:  
• Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution) due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. | Prevention:  
• d4T and ddI should both be avoided individually; co-administration of d4T and ddI is contraindicated (no exception).  
• Due to the presence of propylene glycol as a diluent, LPV/r oral solution should not be used in preterm neonates or any neonate before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days has been attained.  
• Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.  
**Asymptomatic:**  
• Measurement of serum lactate is not recommended.  
**Clinical Signs or Symptoms Consistent with Lactic Acidosis:**  
• Obtain blood lactate level.  
• 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):  
• Replace ddI and d4T with other ARVs.  
• As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.  
Lactate >5.0 mmol/L (Confirmed with Second Test) or >10.0 mmol/L (Any 1 Test):  
• Discontinue all ARVs.  
• Provide supportive therapy (IV 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 Q10, 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. |

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**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 Acronyms:**  
3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane

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References

General Reviews


Risk Factors


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**Monitoring and Management**


