# Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection



Downloaded from https://aidsinfo.nih.gov/guidelines on 4/21/2019

# Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

**(Last updated April 16, 2019; last reviewed April 16, 2019)**

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Lactic Acidosis** | NRTIs:<br>• ZDV<br>• Less likely with 3TC, FTC, ABC, TAF, and TDF<br><br>Other Drugs:<br>• See Risk Factors and Prevention/Monitoring columns for information regarding the toxicity of propylene glycol when LPV/r oral solution is used in neonates. | Onset:<br>• Generally, after years of exposure<br><br>Presentation:<br>• Lactic acidosis may be clinically asymptomatic.<br><br>*Insidious Onset of a Combination of Signs and Symptoms:*<br>• Generalized fatigue, weakness, and myalgias<br>• Vague abdominal pain, weight loss, unexplained nausea, or vomiting<br>• Dyspnea<br>• Peripheral neuropathy<br><br>**Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure). | Lactic acidosis is associated with use of ddI and d4T. Cases are rare now that these NRTIs **are no longer recommended**.<br><br>3TC, FTC, ABC, TAF, and TDF are less likely to induce clinically significant mitochondrial dysfunction than ZDV. | Adults:<br>• Female sex<br>• High BMI<br>• Chronic HCV infection<br>• African-American race<br>• Coadministration of TDF with metformin<br>• Overdose of propylene glycol<br>• CD4 cell count <350 cells/mm$^3$<br>• Acquired riboflavin or thiamine deficiency<br>• Possibly pregnancy<br><br>Preterm Infants or Any Neonates Who Have Not Attained a Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days:<br>• Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution). A diminished ability to metabolize propylene glycol may lead to accumulation and potential adverse events. | Prevention:<br>• Due to the presence of propylene glycol as a diluent, LPV/r oral solution **should not be used** in preterm neonates or any neonate who has not attained a postmenstrual age of 42 weeks and a postnatal age of ≥14 days.<br>• Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.<br><br>Monitoring<br>*Asymptomatic Patients:*<br>• Measurement of serum lactate **is not recommended**.<br><br>*Patients with Clinical Signs or Symptoms Consistent with Lactic Acidosis*:<br>• Obtain blood lactate level.[a]<br>• Additional diagnostic evaluations should include serum bicarbonate, anion gap, and/or arterial blood gas; amylase and lipase; serum albumin; and hepatic transaminases. | Lactate 2.1–5.0 mmol/L (Confirmed with a Second Test):<br>• Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic workup.<br><br>Lactate >5.0 mmol/L (Confirmed With a Second Test)[b] or >10.0 mmol/L (Any One Test):<br>• Discontinue all ARV drugs.<br>• Provide supportive therapy (e.g., IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues).<br><br>Anecdotal (Unproven) Supportive Therapies:<br>• Administer bicarbonate infusions, THAM, high doses of thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C)<br><br>Following the resolution of clinical and laboratory abnormalities, resume therapy, either with a NRTI-sparing regimen or a revised NRTI-containing regimen. Institute a revised NRTI-containing regimen with caution, using NRTIs that are less likely to induce mitochondrial dysfunction (ABC, TAF, or TDF preferred; possibly FTC or 3TC). Lactate should be monitored monthly for ≥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 receiving 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; ZDV = zidovudine

## References


**General Reviews**

1. Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S36-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25629891.

2. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. *J Med Toxicol*. 2014;10(1):26-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23963694.

3. Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr*. 2012;59(3):274-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22126740.

**Risk Factors**

4. Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivanis P. Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection. *J Ren Care*. 2011;37(1):25-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21288314.

5. Lipinavir/ritonavir [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021251s055,021906s050lbl.pdf.

6. Firnhaber C, Smeaton LM, Grinsztejn B, et al. Differences in antiretroviral safety and efficacy by sex in a multinational randomized clinical trial. *HIV Clin Trials*. 2015;16(3):89-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25979186.

7. Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PLoS One*. 2017;12(2):e0169762. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28192529.

8. Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. *J Pediatr Pharmacol Ther*. 2014;19(4):277-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25762872.

9. Mamiafo CT, Moor VJ, Nansseu JR, Pieme CA, Tayou C, Yonkeu JN. Hyperlactatemia in a group of HIV patients living in Yaounde-Cameroon. *AIDS Res Ther*. 2014;11(1):2. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24428886.

10. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS One*. 2011;6(4):e18736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21494566.

11. Moren C, Noguera-Julian A, Garrabou G, et al. Mitochondrial evolution in HIV-infected children receiving first- or second-generation nucleoside analogues. *J Acquir Immune Defic Syndr*. 2012;60(2):111-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22362155.

12. Tetteh RA, Nartey ET, Lartey M, et al. Association between the occurrence of adverse drug events and modification of first-line highly active antiretroviral therapy in Ghanaian HIV Patients. *Drug Safety*. 2016;39(11):1139-1149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27638659.

13. Wester CW, Eden SK, Shepherd BE, et al. Risk factors for symptomatic hyperlactatemia and lactic acidosis among combination antiretroviral therapy-treated adults in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses*. 2012;28(8):759-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22540188.

**Monitoring and Management**

14. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS*

*Soc*. 2013;16:18600. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782481.

15. Claessens YE, Cariou A, Monchi M, et al. Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with L-carnitine. *Crit Care Med*. 2003;31(4):1042-1047. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12682470.

16. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371(24):2309-2319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25494270.

17. Marfo K, Garala M, Kvetan V, Gasperino J. Use of Tris-hydroxymethyl aminomethane in severe lactic acidosis due to highly active antiretroviral therapy: a case report. *J Clin Pharm Ther*. 2009;34(1):119-123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125910.