Table 17g. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Lactic Acidosis

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic Acidosis	NRTIs • ZDV • Less likely with 3TC, FTC, ABC, TAF, and TDF Other Drugs • See the Risk Factors and Prevention/ Monitoring columns for information regarding the toxicity of propylene glycol when LPV/r oral solution is used in neonates.	Onset • Generally after years of exposure Presentation • Lactic acidosis may be clinically asymptomatic. *Lactic Acidosis May Also Present With 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 multiorgan failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure).	3TC, FTC, ABC, TAF, and TDF are less likely to induce clinically significant mitochondrial dysfunction than ZDV.	Adults • Female sex • High BMI • Chronic HCV infection • African American race • Coadministration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possible pregnancy • Overdose in setting of renal insufficiency (e.g., 3TC) Preterm Infants or Any Neonates Who Have Not Attained a Postmenstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days • Exposure to propylene glycol, which is used as a diluent in LPV/r oral	Prevention • 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. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring *Asymptomatic Patients* • Routine measurement of serum lactate **is not recommended.** *Patients With Clinical Signs or Symptoms Consistent With Lactic Acidosis* • Obtain blood lactate level.[a] • Additional diagnostic evaluations should include serum bicarbonate, anion gap, and/or arterial blood gas; amylase and lipase;	For Patients With Lactate 2.1–5.0 mmol/L (Confirmed With a Second Test) • Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic work-up. For Patients With Lactate >5.0 mmol/L (Confirmed With a Second Test)[b] or >10.0 mmol/L (Any One Test) • Discontinue all ARV drugs. • 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). Anecdotal (Unproven) Supportive Therapies • Administer bicarbonate infusions, THAM, high doses of thiamine and riboflavin, and oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C).

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				solution, because these newborns have a diminished ability to metabolize propylene glycol may lead to accumulation, increasing the risk of adverse events.	serum albumin; and hepatic transaminases.	Following the resolution of clinical and laboratory abnormalities, resume therapy either with an 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, TDF, 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: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; 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[1-21]

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: https://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: https://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: https://www.ncbi.nlm.nih.gov/pubmed/22126740.

4. Bartlett AW, Mohamed TJ, Sudjaritruk T, et al. Disease- and treatment-related morbidity in adolescents with perinatal HIV infection in Asia. *Pediatr Infect Dis J*. 2019;38(3):287-292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30281549.

5. Tshamala HK, Aketi L, Tshibassu PM, et al. The lipodystrophy syndrome in HIV-infected children under antiretroviral therapy: a first report from the Central Africa. *Int J Pediatr*. 2019;2019:7013758. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30941184.

6. Smith ZR, Horng M, Rech MA. Medication-induced hyperlactatemia and lactic acidosis: a systematic review of the literature. *Pharmacotherapy*. 2019;39(9):946-963. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31361914.

Risk Factors

7. 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: https://www.ncbi.nlm.nih.gov/pubmed/21288314.

8. Konala VM, Adapa KP, Dinesh KP. et al. Lamivudine-associated lactic acidosis. *Am J Ther*. 2022;29(4):449-451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35622009.

9. Kaletra (lopinavir/ritonavir) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021251s059,021906s054lbl.pdf.

10. 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.

11. 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.

12. 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.

13. Kirmse B, Hobbs L, Aaron L, et al. Acylcarnitines and genetic variation in fat oxidation genes in HIV-infected, antiretroviral-treated children with and without myopathy. *Pediatr Infect Dis J*. 2022;41(8):e306-e311. Available at https://www.ncbi.nlm.nih.gov/pubmed/35622436.

14. 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: https://www.ncbi.nlm.nih.gov/pubmed/24428886.

15. 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.

16. 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: https://www.ncbi.nlm.nih.gov/pubmed/22362155.

17. 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 Saf*. 2016;39(11):1139-1149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27638659.

18. 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: https://www.ncbi.nlm.nih.gov/pubmed/22540188.

Monitoring and Management

19. Arnouk S, Whitsett M, Papadopoulos Z, et al. Successful treatment of tenofovir alafenamide-induced lactic acidosis: a case report. *J Pharm Pract*. 2022;8971900221105042. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35635046.

20. 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(1):18600. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23782481.

21. 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: https://www.ncbi.nlm.nih.gov/pubmed/12682470.

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

23. 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: https://www.ncbi.nlm.nih.gov/pubmed/19125910.

24. Jung B, Martinez M, Claessens YE, et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care*. 2019;9(1):92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31418093.