Table 17b. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Dyslipidemia

Updated: April 11, 2022
Reviewed: April 11, 2023

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Dyslipidemia	PIs • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV, with or without RTV NRTIs • Lower incidence reported with TDF than with TAF NNRTIs • Lower incidence reported with NVP, RPV, and ETR than with EFV INSTIs • EVG/c	Onset • As early as 2 weeks to months after beginning therapy Presentation *PIs* • ↑ LDL-C, TC, and TG *NRTIs* • ↑ LDL-C, TC, and TG. Significant increase in plasma lipid values was observed in adults switching from TDF to TAF, regardless of third agent or presence of a boosting agent.	Reported frequency varies with specific ARV regimen, duration of ART, and the specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% of young children receiving LPV/r will have lipid abnormalities. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Pooled dyslipidemia prevalence of 39.5% and an incidence of 32% (191 per 1,000 person-years) reported in a	Advanced-stage HIV disease High-fat, high-cholesterol diet Sedentary lifestyle Obesity Hypertension Smoking Family history of dyslipidemia or premature ASCVD Metabolic syndrome Fat maldistribution	Prevention • Low-fat diet • Exercise • Smoking-prevention counseling • Use of ARVs is associated with a lower prevalence of dyslipidemia, such as INSTIs, and to a lesser extent, newer PIs (e.g., ATV, DRV). • When considering a TDF-based or TAF-based regimen, the lipid-lowering beneficial effect of TDF should be weighed against its potential for increased renal and bone toxicities. Monitoring[a] • Obtain fasting (or non-fasting) lipid profile (TC, HDL-C, non-HDL-C, LDL-C, and TG) twice (>2 weeks but ≤3 months apart) and average these results. Monitor every 6 months (for abnormal results) or every	Assess all patients for additional ASCVD risk factors. Patients with HIV are considered to be at moderate risk for ASCVD.[b] ARV regimen changes should be considered, especially when the patient is receiving older PIs (e.g., LPV/r) and/or RTV boosting. Switching to a PI-sparing regimen, a PI-based regimen with a more favorable lipid profile, or COBI boosting causes a decline in LDL-C or TG values. The lipid-lowering effect of an ARV regimen switch on LDL-C is less pronounced than with statin therapy but may be enough to re-establish a healthy lipid profile. Refer patients to a lipid specialist early if LDL-C is ≥250 mg/dL or TG is ≥500 mg/dL. If LDL-C is ≥130 mg/dL but <250 mg or TG is ≥150 mg/dL but <500 mg/dL, the following staged treatment approach is recommended by the NHLBI guidelines[b]:

Table 17b. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Dyslipidemia

		NNRTIs • ↑ LDL-C, TC, and HDL-C	recent meta-analysis and a recent review of a large consortium of prospective observational cohorts, respectively.		12 months (for normal results). • If TG or LDL-C is elevated or if a patient has additional risk factors, obtain FLP. *Children With Lipid Abnormalities and/or Additional Risk Factors* • Obtain 12-hour fasting lipid profile (FLP) before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy With Statins or Fibrates* • Obtain 12-hour FLP, LFT, and CK at 4 weeks, 8 weeks, and 3 months after starting lipid therapy. • If minimal alterations in AST, ALT, and CK are indicated, monitor every 3–4 months during the first year and every 6 months thereafter (or as clinically indicated). • Repeat FLP 4 weeks after increasing doses of antihyperlipidemic agents.	• Implement diet, nutrition, and lifestyle management for 6–9 months. Consult with a dietician if one is available. • If a 6- to 9-month trial of lifestyle modification fails and the patient is aged ≥10 years, consider implementing lipid-lowering therapy after consulting a lipid specialist. • Statin therapy should be considered for patients with elevated LDL-C levels. NHLBI guidelines provide recommendations for statin therapy in patients with specific LDL-C levels and risk factors.[b] Concurrent substitution—preferably to ARVs with no inhibitory or inducing effect on CYP3A4 or OATP1B1 (e.g., INSTI)—also should be considered as appropriate to limit drug–drug interaction potential. • Drug therapy can be considered in cases of severe hypertriglyceridemia (TG ≥500 mg/dL). Fibrates (gemfibrozil and fenofibrate) may be used. The long-term risks of lipid abnormalities in children who are receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature ASCVD.

Table 17b. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Dyslipidemia

[a] Because of the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and TG from nonfasting blood samples and follow-up abnormal values with a test done in the fasted state.

[b] Refer to the NHLBI guidelines: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.

Key to Symbol:
↑ = increase

Key: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; CYP3A4 = cytochrome P450 3A4; DRV = darunavir; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FLP = fasting lipid profile; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OATP1B1 = organic anion transporter polypeptide 1B1; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides

References

1. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-672. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19279441.

2. Arpadi S, Shiau S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child*. 2013;98(4):258-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23220209.

3. 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: https://www.ncbi.nlm.nih.gov/pubmed/23782481.

4. Blazquez D, Ramos-Amador JT, Sainz T, et al. Lipid and glucose alterations in perinatally-acquired HIV-infected adolescents and young adults. *BMC Infect Dis*. 2015;15:119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25880777.

5. Bwakura-Dangarembizi M, Musiime V, Szubert AJ, et al. Prevalence of lipodystrophy and metabolic abnormalities in HIV-infected African children after 3 years on first-line antiretroviral therapy. *Pediatr Infect Dis J*. 2015;34(2):e23-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25068287.

6. Casado JL, de Los Santos I, Del Palacio M, et al. Lipid-lowering effect and efficacy after switching to etravirine in HIV-infected patients with intolerance to suppressive HAART. *HIV Clin Trials*. 2013;14(1):1-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23372109.

7. Cid-Silva P, Fernandez-Bargiela N, Margusino-Framinan L, et al. Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine. *Basic Clin Pharmacol Toxicol*. 2019;124(4):479-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30388308.

8. Courlet P, Livio F, Alves Saldanha S, et al. Real-life management of drug-drug interactions between antiretrovirals and statins. *J Antimicrob Chemother*. 2020;75(7):1972-1980. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32240298.

9. Dejkhamron P, Unachak K, Aurpibul L, Sirisanthana V. Insulin resistance and lipid profiles in HIV-infected Thai children receiving lopinavir/ritonavir-based highly active antiretroviral therapy. *J Pediatr Endocrinol Metab*. 2014;27(5-6):403-412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24259240.

10. Echecopar-Sabogal J, D'Angelo-Piaggio L, Chaname-Baca DM, Ugarte-Gil C. Association between the use of protease inhibitors in highly active antiretroviral therapy and incidence of diabetes mellitus and/or metabolic syndrome in HIV-infected patients: a systematic review and meta-analysis. *Int J STD AIDS*. 2018;29(5):443-452. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28956700.

11. Echeverria P, Bonjoch A, Puig J, Ornella A, Clotet B, Negredo E. Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia. *HIV Med*. 2017;18(10):782-786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28671337.

12. Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128 Suppl 5(Suppl 5):S213-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22084329.

13. Food and Drug Administration. FDA drug safety communication: interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. 2012. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-interactions-between-certain-hiv-or-hepatitis-c-drugs-and-cholesterol

14. Grand M, Bia D, Diaz A. Cardiovascular risk assessment in people living with HIV: a systematic review and meta-analysis of real-life data. *Curr HIV Res*. 2020;18(1):5-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31830884.

15. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1046-e1081. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30565953.

16. Hazra R, Cohen RA, Gonin R, et al. Lipid levels in the second year of life among HIV-infected and HIV-exposed uninfected Latin American children. *AIDS*. 2012;26(2):235-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22008654.

17. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on antiretroviral therapy. *Pediatr Infect Dis J*. 2015;35(1):e1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26421804.

18. Irira ME, Philemon RN, Mmbaga JY, et al. Dyslipidemia in HIV-infected children and adolescents on antiretroviral therapy receiving care at Kilimanjaro Christian Medical Centre in Tanzania: a cross-sectional study. *Infect Dis (Auckl)*. 2020;13:1178633720948860. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32922028.

19. Jacobson DL, Williams P, Tassiopoulos K, Melvin A, Hazra R, Farley J. Clinical management and follow-up of hypercholesterolemia among perinatally HIV-infected children enrolled in the PACTG 219C study. *J Acquir Immune Defic Syndr*. 2011;57(5):413-420. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21602698.

20. Jao J, Yu W, Patel K, et al. Improvement in lipids after switch to boosted atazanavir or darunavir in children/adolescents with perinatally acquired HIV on older protease inhibitors: results from the Pediatric HIV/AIDS Cohort Study. *HIV Med*. 2018;19(3):175-183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29159965.

21. Kauppinen KJ, Kivela P, Sutinen J. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide significantly worsens the lipid profile in a real-world setting. *AIDS Patient Care STDS*. 2019;33(12):500-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31742421.

22. Lagoutte-Renosi J, Flammang M, Chirouze C, et al. Real-life impact on lipid profile of a switch from tenofovir disoproxil fumarate to tenofovir alafenamide in HIV-infected patients. *Curr HIV Res*. 2021;19(1):84-89. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32838719.

23. Langat A, Benki-Nugent S, Wamalwa D, et al. Lipid changes in Kenyan HIV-1-infected infants initiating highly active antiretroviral therapy by 1 year of age. *Pediatr Infect Dis J*. 2013;32(7):e298-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23385950.

24. Lazzaretti RK, Kuhmmer R, Sprinz E, Polanczyk CA, Ribeiro JP. Dietary intervention prevents dyslipidemia associated with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected individuals: a randomized trial. *J Am Coll Cardiol*. 2012;59(11):979-988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22402068.

25. Lee FJ, Monteiro P, Baker D, et al. Rosuvastatin vs. protease inhibitor switching for hypercholesterolaemia: a randomized trial. *HIV Med*. 2016;17(8):605-614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26987376.

26. Melvin AJ, Montepiedra G, Aaron L, et al. Safety and efficacy of atorvastatin in human immunodeficiency virus-infected children, adolescents and young adults with hyperlipidemia. *Pediatr Infect Dis J*. 2017;36(1):53-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27749649.

27. O'Gorman CS, O'Neill MB, Conwell LS. Considering statins for cholesterol-reduction in children if lifestyle and diet changes do not improve their health: a review of the risks and benefits. *Vasc Health Risk Manag*. 2011;7:1-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21339908.

28. Patel K, Lindsey J, Angelidou K, Aldrovandi G, Palumbo P, IMPAACT P1060 Study Team. Metabolic effects of initiating lopinavir/ritonavir-based regimens among young children. *AIDS*. 2018;32(16):2327-2336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30102656.

29. Ramteke SM, Shiau S, Foca M, et al. Patterns of growth, body composition, and lipid profiles in a South African cohort of human immunodeficiency virus-infected and uninfected children: a cross-sectional study. *J Pediatric Infect Dis Soc*. 2017;7(2):143-150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28481997.

30. Rhoads MP, Lanigan J, Smith CJ, Lyall EG. Effect of specific ART drugs on lipid changes and the need for lipid management in children with HIV. *J Acquir Immune Defic Syndr*. 2011;57(5):404-412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21499114.

31. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25890673.

32. Singh S, Willig JH, Mugavero MJ, et al. Comparative effectiveness and toxicity of statins among HIV-infected patients. *Clin Infect Dis*. 2011;52(3):387-395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21189273.

33. Strehlau R, Coovadia A, Abrams EJ, et al. Lipid profiles in young HIV-infected children initiating and changing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012;60(4):369-376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22134152.

34. Taramasso L, Tatarelli P, Ricci E, et al. Improvement of lipid profile after switching from efavirenz or ritonavir-boosted protease inhibitors to rilpivirine or once-daily integrase inhibitors: results from a large observational cohort study (SCOLTA). *BMC Infect Dis*. 2018;18(1):357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30064371.

35. Tassiopoulos K, Williams PL, Seage GR, 3rd, et al. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2008;47(5):607-614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18209684.

36. Vieira ADS, Silveira G. Effectiveness of n-3 fatty acids in the treatment of hypertriglyceridemia in HIV/AIDS patients: a meta-analysis. *Cien Saude Colet*. 2017;22(8):2659-2669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28793080.