



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

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**Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia**

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Dyslipidemia</b>	<p><u>PIs:</u></p> <ul style="list-style-type: none"> <li>All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV.</li> </ul> <p><u>NRTIs:</u></p> <ul style="list-style-type: none"> <li>Especially d4T</li> </ul> <p><u>NNRTIs:</u></p> <ul style="list-style-type: none"> <li>EFV &gt; NVP, RPV, and ETR</li> </ul>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>As early as 2 weeks to months after beginning therapy</li> </ul> <p><u>Presentation</u></p> <p><u>PIs:</u></p> <ul style="list-style-type: none"> <li>↑LDL-C, TC, and TG</li> </ul> <p><u>NNRTIs:</u></p> <ul style="list-style-type: none"> <li>↑LDL-C, TC, and HDL-C</li> </ul> <p><u>NRTIs:</u></p> <ul style="list-style-type: none"> <li>↑LDL-C, TC, and TG</li> </ul>	<p>Reported frequency varies with specific ARV regimen, duration of ART and specific laboratory parameters used to diagnose lipid abnormalities.</p> <p>10% to 20% in young children receiving LPV/RTV</p> <p>40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities.</p> <p>In studies of treatment naive adults, 38% and 32% receiving EVG/COBI/FTC/TAF developed abnormal fasting TC and LDL-C (respectively) after 48 weeks compared with 21% and 20% receiving EVG/COBI/FTC/TDF, difference mainly attributable to TAF</p> <p>In 48 adolescents treated with EVG/COBI/FTC/TAF median change from baseline to</p>	<p>Advanced-stage HIV disease</p> <p>High-fat, high-cholesterol diet</p> <p>Lack of exercise</p> <p>Obesity</p> <p>Hypertension</p> <p>Smoking</p> <p>Family history of dyslipidemia or premature CVD</p> <p>Metabolic syndrome</p> <p>Fat maldistribution</p>	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>Low-fat diet</li> <li>Exercise</li> <li>Smoking-prevention counseling</li> </ul> <p><u>Monitoring<sup>a</sup></u></p> <p><i>Adolescents and Adults:</i></p> <ul style="list-style-type: none"> <li>Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (&gt;2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy.</li> </ul> <p><i>Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:</i></p> <ul style="list-style-type: none"> <li>Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests.</li> </ul> <p><i>Children with Lipid Abnormalities and/or Additional Risk Factors:</i></p> <ul style="list-style-type: none"> <li>Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated).</li> </ul> <p><i>Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:</i></p> <ul style="list-style-type: none"> <li>Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3</li> </ul>	<p>Assessment of additional CVD risk factors should be done in all patients. HIV-infected patients are considered to be at moderate risk of CVD.<sup>b</sup></p> <p>Counsel on lifestyle modification, dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars particularly in case of ↑TG, elimination of trans fat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician.</p> <p>If receiving d4T, it should be discontinued. If receiving PI-based ART, consider switching to a new PI-sparing ART regimen or PI-based regimen containing boosted ATV or DRV, which are less likely to cause lipid abnormalities.</p> <p>Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails.</p> <p>Some experts suggest treatment in children receiving ARV drugs at cut points recommended by NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL-C ≥190 mg/dL, regardless of additional risk factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.<sup>b</sup></p> <p>The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL.</p>

**Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia**

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
			weeks 24 and 36 were 26 mg/dl and 36 mg/dl, respectively for fasting TC, and 10 mg/dl and 17 mg/dl, respectively for direct LDL-C.		<p>months after starting lipid therapy.</p> <ul style="list-style-type: none"> <li>• If minimal alterations in AST, ALT, and CK, monitor every 3–4 months in the first year and every 6 months thereafter (or as clinically indicated).</li> <li>• Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.</li> </ul>	<p><u>Initiate Drug Therapy Promptly in Patients with Fasting TG <math>\geq 500</math> mg/dL:</u></p> <p>Statins such as pravastatin, atorvastatin, or rosuvastatin.<sup>c</sup> Ezetimibe can be considered in addition to statins.<sup>d</sup> Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.<sup>c</sup> Risks must be weighed against potential benefits.</p> <p>Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with <math>\uparrow</math>TG but are not approved for use in children. The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.</p>

<sup>a</sup> Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides from non-fasting blood samples and follow up abnormal values with a test done in the fasted state.

<sup>b</sup> Refer to NHLBI guidelines at [http://www.nhlbi.nih.gov/guidelines/cvd\\_ped/summary.htm#chap9](http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9).

<sup>c</sup> The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

<sup>d</sup> Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosuvastatin (Crestor®), fluvastatin, and ezetimibe (Zetia®) are approved for use in children aged  $\geq 10$  years. For additional information, see the PI, NNRTI, NRTI, and INSTI Drug Interactions Tables in the [Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#).

**Key to Acronyms:** ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; FLP = fasting lipid

profile; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TC = total cholesterol; TG = triglyceride lopinavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TC = total cholesterol; TG = triglyceride

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