



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

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**Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events**

(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
<p><b>Hepatic Toxicity</b> Elevated AST, ALT, clinical hepatitis</p>	<p>All ARVs may be associated with hepatitis. NVP and TPV are of particular concern.</p> <p>NVP, EFV, ABC, RAL, and MVC have been associated with hypersensitivity reactions.</p> <p>NRTIs (especially ZDV, ddI, and d4T) are associated with lactic acidosis and hepatic steatosis.</p>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>Hepatitis generally occurs within the first few months of therapy, but can occur later.</li> <li>Steatosis presents after months to years of therapy.</li> <li>HBV-coinfected patients may develop severe hepatic flare with the initiation, withdrawal, or development of resistance to 3TC, FTC, or TDF (especially in patients receiving only one anti-HBV agent).</li> <li>Hepatitis may also represent IRIS early in therapy, especially in HBV- and HCV-infected patients.</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>Asymptomatic elevation of AST and ALT</li> <li>Symptomatic hepatitis with nausea, fatigue, and jaundice</li> <li>Hepatitis may be component of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis.</li> </ul>	<p>Uncommon in children</p> <p>Frequency varies with different agents and drug combinations.</p>	<p>HBV or HCV coinfection</p> <p>Elevated baseline ALT and AST</p> <p>Other hepatotoxic medications (including herbal preparations such as St. John's wort [<i>Hypericum perforatum</i>], Chaparral [<i>Larrea tridentate</i>], Germander [<i>Teucrium chamaedrys</i>])</p> <p>Alcohol use</p> <p>Underlying liver disease</p> <p>Pregnancy</p> <p><u>For NVP-Associated Hepatic Events in Adults:</u></p> <ul style="list-style-type: none"> <li>Female with pre-NVP CD4 count &gt;250 cells/mm<sup>3</sup></li> <li>Male with pre-NVP CD4 count &gt;400 cells/mm<sup>3</sup></li> </ul> <p>Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.<sup>a</sup> Higher drug concentrations for PIs, particularly TPV.</p>	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>Avoid concomitant use of hepatotoxic medications.</li> <li>If hepatic enzymes are elevated &gt;5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP.</li> </ul> <p><u>Monitoring:</u></p> <p><i>For ARVs Other Than NVP:</i></p> <ul style="list-style-type: none"> <li>Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., HBV- or HCV-coinfected or elevated baseline AST and ALT).</li> </ul> <p><i>For NVP:</i></p> <ul style="list-style-type: none"> <li>Obtain AST and ALT at baseline, at 2 and 4 weeks, then every 3 months.</li> </ul>	<p>Asymptomatic patients with elevated ALT or AST should be evaluated for other causes and monitored closely</p> <p>(including repeating AST, ALT and checking total bilirubin). If ALT or AST is more than 5–10 times ULN and felt to be possibly or probably associated with ARVs, the potentially offending ARVs should be discontinued.</p> <p>In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restarting the offending agent.</p> <p>If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP Hypersensitivity).</p> <p>When clinical hepatitis is associated with lactic acidosis, avoid restarting the most likely agent, including ZDV, d4T, and ddI in particular (see also Lactic Acidosis).</p> <p>Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.</p>

**Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events**

(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
<b>Indirect Hyperbilirubinemia</b>	IDV, ATV (with either RTV or COBI)	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• First months of therapy</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Jaundice; otherwise asymptomatic elevation of indirect bilirubin levels with normal AST, and ALT.</li> </ul> <p>Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.</p>	<p><u>HIV-Infected Children Receiving ATV:</u></p> <ul style="list-style-type: none"> <li>• In long-term follow-up, 9% had at least 1 total bilirubin level &gt; 5 x ULN and 1.4% experienced jaundice</li> </ul>	N/A	<p><u>Monitoring:</u></p> <ul style="list-style-type: none"> <li>• No specific monitoring.</li> </ul>	<p>Not necessary to discontinue the offending agent except for cosmetic reasons.</p> <p>After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time.</p>
<b>Non-Cirrhotic Portal Hypertension</b>	ddl, d4t	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Generally after years of therapy</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• GI bleeding, esophageal varices, hypersplenism</li> <li>• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism)</li> <li>• Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis.</li> </ul>	<p><u>Rare:</u></p> <ul style="list-style-type: none"> <li>• Probably less than 1%</li> </ul>	Prolonged exposure to ARV therapy, especially ddl and the combination of ddl and d4T	<p><u>Monitoring:</u></p> <ul style="list-style-type: none"> <li>• No specific monitoring</li> </ul>	<p>Manage complications of GI bleeding and esophageal varices.</p> <p>Discontinue/replace d4T or ddl, if patient is receiving either.</p>

<sup>a</sup> For example, HLA-DRB1\*0101 in whites, HLA-DRB1\*0102 in South Africans, and HLA-B35 in Thai and whites.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; COBI = cobicistat; d4T = stavudine; ddl = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

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