Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### Table 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

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<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Most ARVs have been associated with hepatitis, but there is a strong association with NVP, EFV, and TPV. NVP, EFV, ABC, RAL, and MVC have been associated with hepatitis in context of HSRs. NRTIs have been associated with lactic acidosis and hepatic steatosis, especially ZDV, d4T, and ddI (co-administering d4T and ddI poses the highest risk). d4T or ddI are no longer recommended for use in an ARV regimen.</td>
<td>Onset:  • An acute toxic hepatitis most commonly occurs within the first few months of therapy (but can occur later).  • Steatosis presents after months to years of therapy.  • Patients with HBV coinfection may develop flare of hepatitis with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if receiving only 1 anti-HBV agent). Note that HBV has a high genetic barrier for resistance to TDF and TAF.  • Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-coinfection. Presentation:  • Asymptomatic elevation of AST and ALT  • Symptomatic hepatitis with nausea, fatigue, and jaundice  • Hepatitis may present in context of HSR with rash, lactic acidosis, and hepatic steatosis.</td>
<td>Uncommon</td>
<td>HBV or HCV coinfection  Underlying liver disease  Use of other hepatotoxic medications and supplements (e.g., St. John’s wort [Hypericum perforatum], chaparral [Larrea tridentata], germander [Teucrium chamaedrys])  Alcohol use  Pregnancy  Obesity  For NVP-Associated Hepatic Events in Adults:  • Female with pre-NVP CD4 count &gt;250 cells/mm³  • Male with pre-NVP CD4 count &gt;400 cells/mm³  • Population-specific HLA types⁴  • Higher drug concentrations for PIs, particularly TPV</td>
<td><strong>Prevention:</strong>  • Avoid concomitant use of hepatotoxic medications.  • Do not use d4T or ddI (individually or together); co-administration is contraindicated (no exceptions).  • In patients with elevated hepatic enzymes (&gt;5 to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP.  <strong>Monitoring</strong>  <strong>For ARVs Other Than NVP:</strong>  • Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT).  <strong>For NVP:</strong>  • Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months.</td>
<td>Evaluate for other infectious and non-infectious causes and monitor closely.  <strong>Asymptomatic:</strong>  • Potentially offending ARVs should be discontinued if ALT or AST is &gt;5 times ULN.  <strong>Symptomatic:</strong>  • Discontinue all ARVs and other potentially hepatotoxic drugs.  • If a patient experiences hepatitis attributed to NVP, it should be permanently discontinued.  • Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.</td>
</tr>
</tbody>
</table>
### 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; ddI = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FDA = Food and Drug Administration; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

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<tr>
<td>Indirect Hyperbilirubinemia</td>
<td>ATV (with either RTV or COBI), IDV</td>
<td>Onset:</td>
<td>In long-term follow-up, 9% of children receiving ATV had at least 1 total bilirubin level &gt;5 times ULN and 1.4% experienced jaundice.</td>
<td>N/A</td>
<td>Prevention: IDV is not FDA-approved or recommended for use in the pediatric population.</td>
<td>Isolated indirect hyperbilirubinemia is not indication for cessation of a potentially offending ARV. Psychological impact of jaundice should be evaluated, and alternative agents considered.</td>
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<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
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<td>Monitoring: No ongoing monitoring needed.</td>
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<tr>
<td></td>
<td></td>
<td>• First months of therapy</td>
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<td></td>
<td>After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.</td>
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<td></td>
<td></td>
<td>• May be asymptomatic or associated with jaundice</td>
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<td></td>
<td></td>
<td>• Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.</td>
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<tr>
<td></td>
<td></td>
<td>• Normal AST and ALT</td>
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<tr>
<td>Non-Cirrhotic Portal Hypertension</td>
<td>d4T, ddI</td>
<td>Onset:</td>
<td>Prolonged exposure to ARV therapy, especially ddI and the combination of d4T and ddI.</td>
<td>Rare</td>
<td>Prevention: Do not use d4T, or ddI (individually or together); co-administration is contraindicated (no exceptions).</td>
<td>Discontinue potentially offending agents. Manage complications of GI bleeding and esophageal varices.</td>
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<tr>
<td></td>
<td>d4T or ddI are no longer recommended for use in an ARV regimen.</td>
<td>Presentation:</td>
<td></td>
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<td>Monitoring: No specific monitoring</td>
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<td></td>
<td></td>
<td>• Generally after years of therapy</td>
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<td></td>
<td></td>
<td>• GI bleeding, esophageal varices, hypersplenism</td>
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<td></td>
<td></td>
<td>• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (due to hypersplenism)</td>
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<tr>
<td>Liver Biopsy</td>
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<td>Variety of Findings, Most Commonly:</td>
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<tr>
<td></td>
<td></td>
<td>• Nodular regenerative hyperplasia</td>
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<td></td>
<td></td>
<td>• Hepatoportal sclerosis</td>
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</tbody>
</table>

* For example, HLA-DRB1*0101 in whites, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and whites.

Less frequent monitoring can be considered in children whose clinical status is stable for more than 2–3 years (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).
References

General Reviews

Hepatic Events and NRTIs

Hepatic Events and NNRTIs

Hepatic Events and NRTIs plus NNRTIs

Hepatic Events and PIs including Indirect Hyperbilirubinemia
13.  Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naive and


HIV and Hepatitis B/C Coinfections


Nodular Regenerative Hyperplasia and Noncirrhotic Portal Hypertension


