### Table 13e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated April 27, 2017; last reviewed April 27, 2017)  (page 1 of 2)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
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| Hepatitis       | 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 all been associated with hepatitis in context of hypersensitivity reactions. NRTIs (especially ZDV, ddI, and dd4T) have been associated with lactic acidosis and hepatic steatosis. | Onset:  
• An acute toxic hepatitis occurs most commonly 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 of, withdrawal of, or development of resistance to 3TC, FTC, or TDF (especially if receiving only 1 anti-HBV agent).  
• 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 hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis. | Uncommon | HBV or HCV coinfection  
Other underlying liver disease  
Use of other hepatotoxic medications (e.g., St. John's wort [Hypericum perforatum], Chaparral [Larrea tridentate], Germander [Teucrium chamaedrys])  
Alcohol use  
Pregnancy  
For NVP-Associated Hepatic Events in Adults:  
• Female with pre-NVP CD4 count >250 cells/mm³  
• Male with pre-NVP CD4 count >400 cells/mm³  
• Population- specific HLA types  
• Higher drug concentrations for PIs, particularly TPV. | Prevention:  
• Avoid concomitant use of hepatotoxic medications.  
If hepatic enzymes are elevated >5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP.  
Monitoring:  
For ARVs Other Than NVP:  
• 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-coinfection or elevated baseline AST and ALT).  
For NVP:  
• Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months. | • Evaluate for other infectious and non-infectious causes and monitor closely.  
Asymptomatic:  
• Potentially offending ARVs should be discontinued if ALT or AST is > 5x ULN  
Symptomatic:  
• 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. |
### Table 13e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events
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<tr>
<td>Indirect Hyperbilirubinemia</td>
<td>IDV, ATV (with either RTV or COBI)</td>
<td>Onset:</td>
<td></td>
<td>N/A</td>
<td>Monitoring: No ongoing monitoring needed. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time.</td>
<td>Isolated indirect hyperbilirubinemia is not indication for cessation of potentially offending ARV</td>
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<td></td>
<td></td>
<td>• First months of therapy</td>
<td></td>
<td></td>
<td>• Psychological impact of jaundice should be evaluated and alternative agents considered</td>
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<tr>
<td></td>
<td></td>
<td>• May be associated with jaundice or asymptomatic</td>
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<td></td>
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<td>• Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.</td>
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<td></td>
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<td>• Normal AST and ALT.</td>
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<td>In long-term follow-up, 9% of children receiving ATV had at least 1 total bilirubin level &gt; 5x ULN and 1.4% experienced jaundice.</td>
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<tr>
<td>Non-Cirrhotic Portal Hypertension</td>
<td>ddl, d4T</td>
<td>Onset:</td>
<td>Rare</td>
<td>Prolonged exposure to ARV therapy, especially ddl and the combination of ddl and d4T</td>
<td>Monitoring: No specific monitoring</td>
<td>Discontinue potentially offending agents. \ Manage complications of GI bleeding and esophageal varices.</td>
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<td></td>
<td></td>
<td>• Generally after years of therapy</td>
<td></td>
<td></td>
<td>• Isolated indirect hyperbilirubinemia is not indication for cessation of potentially offending ARV</td>
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<tr>
<td></td>
<td></td>
<td>• GI bleeding, esophageal varices, hypersplenism</td>
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<td>• Psychological impact of jaundice should be evaluated and alternative agents considered</td>
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<td></td>
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<td>• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism)</td>
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<td>• Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoporal sclerosis.</td>
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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
- ddI = 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
- IDI = 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
References


