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

(Last updated May 22, 2018; last reviewed May 22, 2018)

<table>
<thead>
<tr>
<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>
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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 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. | 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. | Uncommon | HBV or HCV coinfection  
Underlying liver disease  
Use of other hepatotoxic medications and supplements (e.g., St. John's wort [Hypericum perforatum], chaparral [Larrea tridentate], germander [Teucrium chamaedrys])  
Alcohol use  
Pregnancy  
Obesity  
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.  
• Do not use d4T or ddI (individually or together); co-administration is contraindicated (no exceptions).  
• In patients with elevated hepatic enzymes (>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., those with 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 >5 times 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 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

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

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| **Indirect Hyperbilirubinemia** | ATV (with either RTV or COBI), IDV | Onset:  
- First months of therapy  
Presentation:  
- May be asymptomatic or associated with jaundice  
- Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.  
- Normal AST and ALT | In long-term follow-up, 9% of children receiving ATV had at least 1 total bilirubin level >5 times ULN and 1.4% experienced jaundice. | N/A | Prevention:  
- IDV is not FDA-approved or recommended for use in the pediatric population.  
Monitoring:  
- No ongoing monitoring needed.  
After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time. | Isolated indirect hyperbilirubinemia is not indication for cessation of a potentially offending ARV.  
Psychological impact of jaundice should be evaluated, and alternative agents considered. |

| Non-Cirrhotic Portal Hypertension | d4T, ddI  
**d4T or ddI are no longer recommended for use in an ARV regimen.** | Onset:  
- Generally after years of therapy  
Presentation:  
- GI bleeding, esophageal varices, hypersplenism  
- Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (due to hypersplenism)  
Liver Biopsy  
**Variety of Findings, Most Commonly:**  
- Nodular regenerative hyperplasia  
- Hepatoporal sclerosis | Rare | Prolonged exposure to ARV therapy, especially ddI and the combination of d4T and ddI. | Prevention:  
- Do not use d4T, or ddI (individually or together); co-administration is contraindicated (no exceptions).  
Monitoring:  
- No specific monitoring | Discontinue potentially offending agents.  
Manage complications of GI bleeding and esophageal varices. |

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

*b* 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).

**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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General Reviews


Hepatic Events and NRTIs


Hepatic Events and NNRTIs


Hepatic Events and NRTIs plus NNRTIs


Hepatic Events and PIs including Indirect Hyperbilirubinemia


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K-26

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