Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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

(Last updated April 27, 2017; last reviewed April 27, 2017)  
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<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</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 d4T) have been associated with lactic acidosis and hepatic steatosis | 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 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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| Indirect Hyperbilirubinemia          | IDV, ATV (with either RTV or COBI) | Onset:  
• First months of therapy  
Presentation:  
• May be associated with jaundice or asymptomatic  
• 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 > 5x ULN and 1.4% experienced jaundice. | N/A | 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. | • Isolated indirect hyperbilirubinemia is not indication for cessation of potentially offending ARV  
• Psychological impact of jaundice should be evaluated and alternative agents considered |
| Non-Cirrhotic Portal Hypertension    | ddl, d4T        | Onset:  
• Generally after years of therapy  
Presentation:  
• GI bleeding, esophageal varices, hypersplenism  
• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism)  
• Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatopetalral sclerosis. | Rare | Prolonged exposure to ARV therapy, especially ddl and the combination of ddl and d4T | Monitoring:  
• No specific monitoring | • Discontinue potentially offending agents.  
• Manage complications of GI bleeding and esophageal varices. |

* 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
References


