Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### Hepatitis

**Onset/Clinical Manifestations**
- Acute toxic hepatitis most commonly occurs within the first few months of therapy, but it can occur later.
- Hepatitis may be a manifestation of IRIS if it occurs early in therapy, especially in patients with HBV or HCV coinfection.
- 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 the patient is receiving only one anti-HBV agent). Note that HBV has a high genetic barrier for resistance to TDF and TAF.

**Presentation**
- Asymptomatic elevation of AST and ALT levels
- Symptomatic hepatitis with nausea, fatigue, and jaundice
- Hepatitis may present in the context of HSR with rash, lactic acidosis, and hepatic steatosis.

**Estimated Frequency**
- Uncommon

**Risk Factors**
- 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
- Higher drug concentrations of PIs

**Prevention/Monitoring**
- Evaluate the patient for other infectious and non-infectious causes of hepatitis and monitor the patient closely.
- Asymptomatic Hepatitis:
  - Potentially offending ARV drugs should be discontinued if ALT or AST level is >5 times ULN.
- Symptomatic Hepatitis:
  - Discontinue all ARV drugs and other potentially hepatotoxic drugs.
  - If a patient experiences hepatitis that is attributed to NVP, NVP should be permanently discontinued.
  - Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

**Management**
- Female sex with pre-NVP CD4 count >250 cells/mm³
- Male sex with pre-NVP CD4 count >400 cells/mm³
- Population-specific HLA types

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

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| Indirect Hyperbilirubinemia          | ATV             | **Onset:** • Within the first months of therapy  
 **Presentation:** • May be asymptomatic or associated with jaundice  
 • Levels of 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 one total bilirubin level >5 times ULN and 1.4% of children 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; levels may improve over time. | Isolated indirect hyperbilirubinemia is not an indication for cessation of the potentially offending ARV drug.  
 Psychological impact of jaundice should be evaluated, and alternative agents should be considered.  
 Jaundice may result in nonadherence, particularly in adolescents; this side effect should be discussed. |
| Non-Cirrhotic Portal Hypertension    | d4T, ddI        | **Onset:** • Generally after years of therapy; may occur years after stopping therapy.  
 **Presentation:** • GI bleeding, esophageal varices, and hypersplenism  
 • Mild elevations in AST and ALT levels, moderate increases in ALP levels, and pancytopenia  
 **Liver Biopsy Findings:** • Most commonly seen findings include nodular regenerative hyperplasia and hepatoportal sclerosis. | Rare               | Prolonged exposure to ddI and the combination of d4T and ddI. | Monitoring: • No specific monitoring | Manage complications of GI bleeding and esophageal varices.  
 The Panel **no longer recommends** the use of these agents.  
 Rare Prolonged exposure to ddI and the combination of d4T and ddI. |
References

General Reviews


Hepatic Events and NRTIs


Hepatic Events and NNRTIs


Hepatic Events and NRTIs plus NNRTIs

Hepatic Events and PIs including Indirect Hyperbilirubinemia


HIV and Hepatitis B/C Coinfections


Nodular Regenerative Hyperplasia and Noncirrhotic Portal Hypertension

