Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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| Hepatitis      | Most ARV drugs have been associated with hepatitis, but there is a strong association between hepatitis, NVP, and EFV. NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs. NRTIs have been associated with lactic acidosis and hepatic steatosis, especially ZDV. | Onset:  
• Acute toxic hepatitis most commonly occurs within the first few months of therapy, but it can occur later.  
• Steatosis presents after months to years of therapy.  
• Patients with HBV co-infection 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.  
• Hepatitis may be a manifestation of IRIS if it occurs early in therapy, especially in patients with HBV or HCV co-infection.  
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. | Uncommon | HBV or HCV co-infection  
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  
For NVP-Associated Hepatic Events in Adults:  
• Female sex with pre-NVP CD4 count >250 cells/mm³  
• Male sex with pre-NVP CD4 count >400 cells/mm³  
• Population-specific HLA types | Prevention:  
• Avoid concomitant use of hepatotoxic medications.  
• In patients with elevated levels of hepatic enzymes (>5 times to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP.  
Monitoring  
For ARV Drugs Other Than NVP:  
• Obtain AST and ALT levels at baseline and at least every 3 months–4 months thereafter; monitor at-risk patients more frequently (e.g., those with HBV or HCV co-infection or elevated baseline AST and ALT levels).  
For NVP:  
• Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months. | 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. |
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<td>Indirect Hyperbilirubinemia</td>
<td>ATV</td>
<td>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.</td>
<td>In long-term follow-up, 9% of children receiving ATV had at least one total bilirubin level &gt;5 times ULN and 1.4% of children experienced jaundice.</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; levels may improve over time.</td>
<td>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.</td>
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<tr>
<td>Non-Cirrhotic Portal Hypertension</td>
<td>d4T, ddI</td>
<td>The Panel no longer recommends the use of these agents. 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.</td>
<td>Rare</td>
<td>Prolonged exposure to ddI and the combination of d4T and ddI.</td>
<td>Monitoring: No specific monitoring</td>
<td>Manage complications of GI bleeding and esophageal varices.</td>
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Note: ULN = upper limit of normal; a = For example, HLA-DRB1*0101 in white people, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai people and white people.

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; DTG = dolutegravir; 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; HSR = hypersensitivity reaction; 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; ULN = upper limit of normal; ZDV = zidovudine

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References

General Reviews


Hepatic Events and NRTIs


Hepatic Events and NNRTIs


Hepatic Events and NRTIs plus NNRTIs


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Hepatic Events and PIs including Indirect Hyperbilirubinemia


HIV and Hepatitis B/C Coinfections


Nodular Regenerative Hyperplasia and Noncirrhotic Portal Hypertension

