# Table 17e. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Hepatic Events

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| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Hepatitis** | Most ARV drugs have been associated with hepatitis, but a strong association exists between hepatitis and the use of NVP and EFV.<br><br>NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs.<br><br>NRTIs, especially ZDV, have been associated with lactic acidosis and hepatic steatosis. | **Onset**<br>• Acute toxic hepatitis occurs most commonly within the first few months of therapy, but it can occur later.<br>• Steatosis presents after months or years of therapy.<br>• Patients with HBV coinfection can experience a hepatitis flare with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. A flare also can occur with the emergence of resistance to 3TC or FTC (especially if the patient is receiving only one anti-HBV agent). Note that TDF and TAF have high barriers to resistance when used to treat HBV. | Uncommon | HBV or HCV coinfection<br><br>Underlying liver disease<br><br>Use of other hepatotoxic medications and supplements (e.g., St. John's wort [*Hypericum perforatum*], chaparral [*Larrea tridentata*], germander [*Teucrium chamaedrys*])<br><br>Alcohol use<br><br>Pregnancy<br><br>Obesity<br><br>Higher drug concentrations of PIs | **Prevention**<br>• Avoid concomitant use of hepatotoxic medications.<br>• In patients with elevated levels of hepatic enzymes (>5 times to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP.<br><br>**Monitoring**<br>*For ARV Drugs Other than NVP*<br>• Obtain AST and ALT levels at baseline and at least every 3–4 months thereafter[b]; monitor at-risk patients more frequently (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT levels). | Evaluate the patient for other infectious and noninfectious causes of hepatitis and monitor the patient closely.<br><br>**Asymptomatic Hepatitis**<br>• Potentially offending ARV drugs should be discontinued if ALT or AST level is >5 times ULN.<br><br>**Symptomatic Hepatitis**<br>• Discontinue all ARV drugs and other potentially hepatotoxic drugs.<br>• If a patient experiences hepatitis that is attributed to NVP, **NVP should be discontinued permanently.**<br>• Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV. |

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| | | • Hepatitis can be a manifestation of IRIS if it occurs early in therapy, especially in patients with HBV or HCV coinfection.<br>**Presentation**<br>• Asymptomatic elevation of AST and ALT levels<br>• Symptomatic hepatitis with nausea, fatigue, and jaundice<br>• Hepatitis may present in the context of HSR with rash, lactic acidosis, and hepatic steatosis. | | **For NVP-Associated Hepatic Events in Adults**<br>• Female sex with pre-NVP CD4 count >250 cells/mm$^3$<br>• Male sex with pre-NVP CD4 count >400 cells/mm$^3$<br>• Population-specific HLA types[a] | *For NVP*<br>• Obtain AST and ALT levels at baseline, at 2 weeks, and at 4 weeks, and then every 3 months. | |
| **Indirect Hyperbilirubinemia** | ATV | **Onset**<br>• Within the first months of therapy<br>**Presentation**<br>• Can be asymptomatic or associated with jaundice<br>• Levels of direct bilirubin can be normal or slightly elevated when levels of indirect bilirubin are very high.<br>• Normal AST and ALT | In long-term follow-up, 9% of children who were receiving ATV had at least one total bilirubin level >5 times ULN, and 1.4% of children experienced jaundice. | None established | **Monitoring**<br>• No ongoing monitoring is needed.<br>• After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels can improve over time. | Isolated indirect hyperbilirubinemia is not an indication to stop ATV.<br>Psychological impact of jaundice should be evaluated, and alternative agents should be considered.<br>Jaundice can result in nonadherence, particularly in adolescents; this side effect should be discussed with patients. |

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[a] For example, HLA-DRB1*0101 in White people, HLA-DRB1*0102 in South African people, and HLA-B35 in Thai people and White people.

[b] Less frequent monitoring can be considered in children whose clinical status has been stable for >2 years to 3 years (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

**Key:** 3TC = lamivudine; ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; DTG = dolutegravir; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; ZDV = zidovudine

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