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. NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs. NRTIs, especially ZDV, have been associated with lactic acidosis and hepatic steatosis.	Onset • Acute toxic hepatitis occurs most commonly within the first few months of therapy, but it can occur later. • Steatosis presents after months or years of therapy. • 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 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/mm^3 • Male sex with pre-NVP CD4 count >400 cells/mm^3	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 3–4 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. 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 discontinued permanently.

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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. 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.		• Population-specific HLA types[a]	*For NVP* • Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.	• Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

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Indirect Hyperbilirubinemia	ATV	Onset • Within the first months of therapy Presentation • Can be asymptomatic or associated with jaundice. • Levels of direct bilirubin can 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 who were receiving ATV had at least one total bilirubin level >5 times ULN, and 1.4% of children experienced jaundice.	None established	Monitoring • No ongoing monitoring needed. • 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. Psychological impact of jaundice should be evaluated, and alternative agents should be considered. Jaundice can result in nonadherence, particularly in adolescents; this side effect should be discussed with patients.

[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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