Table 15e. 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. • Hepatitis can be a manifestation of IRIS if it occurs early in	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	**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	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.** • Consider viral causes of hepatitis:

		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.		• Male sex with pre-NVP CD4 count >400 cells/mm^3 • Population-specific HLA types[a]	AST and ALT levels). *For NVP* • Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.	HAV, HBV, HCV, EBV, and CMV.
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

References

1. Anadol E, Lust K, Boesecke C, et al. Exposure to previous cART is associated with significant liver fibrosis and cirrhosis in human immunodeficiency virus-infected patients. *PLoS One*. 2018;13(1):e0191118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29346443.

2. Aurpibul L, Bunupuradah T, Sophan S, et al. Prevalence and incidence of liver dysfunction and assessment of biomarkers of liver disease in HIV-infected Asian children. *Pediatr Infect Dis J*. 2015;34(6):e153-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25970117.

3. Bienczak A, Denti P, Cook A, et al. Determinants of virological outcome and adverse events in African children treated with paediatric nevirapine fixed-dose-combination tablets. *AIDS*. 2017;31(7):905-915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28060017.

4. Cai J, Osikowicz M, Sebastiani G. Clinical significance of elevated liver transaminases in HIV-infected patients. *AIDS*. 2019;33(8):1267-1282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31008799.

5. Cotton MF, Liberty A, Torres-Escobar I, et al. Safety and efficacy of atazanavir powder and ritonavir in HIV-1-infected infants and children from 3 months to <11 years of age: the PRINCE-2 study. *Pediatr Infect Dis J*. 2018;37(6):e149-e156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29206747.

6. Crutchley RD, Guduru RC, Cheng AM. Evaluating the role of atazanavir/cobicistat and darunavir/cobicistat fixed-dose combinations for the treatment of HIV-1 infection. *HIV AIDS (Auckl)*. 2016;8:47-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27022304.

7. European P, Paediatric HIVCCSGiE. Safety of darunavir and atazanavir in HIV-infected children in Europe and Thailand. *Antivir Ther*. 2016;21(4):353-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26561496.

8. European Paediatric HC-iSGitEP, Paediatric HIVCCiE. Coinfection with HIV and hepatitis C virus in 229 children and young adults living in Europe. *AIDS*. 2017;31(1):127-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27898593.

9. Gervasoni C, Cattaneo D, Filice C, Galli M, Gruppo Italiano Studio Nimi. Drug-induced liver steatosis in patients with HIV infection. *Pharmacol Res*. 2019;145:104267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31077811.

10. Gowda C, Newcomb CW, Liu Q, et al. Risk of acute liver injury with antiretroviral therapy by viral hepatitis status. *Open Forum Infect Dis*. 2017;4(2):ofx012. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28470014.

11. Huntington S, Thorne C, Newell ML, et al. Pregnancy is associated with elevation of liver enzymes in HIV-positive women on antiretroviral therapy. *AIDS*. 2015;29(7):801-809. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25710412.

12. Kaspar MB, Sterling RK. Mechanisms of liver disease in patients infected with HIV. *BMJ Open Gastroenterol*. 2017;4(1):e000166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29119002.

13. Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drugs and risk of chronic alanine aminotransferase elevation in human immunodeficiency virus (HIV)-monoinfected persons: the data collection on adverse events of anti-HIV Drugs study. *Open Forum Infect Dis*. 2016;3(1):ofw009. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26925429.

14. Leger P, Chirwa S, Nwogu JN, et al. Race/ethnicity difference in the pharmacogenetics of bilirubin-related atazanavir discontinuation. *Pharmacogenet Genomics*. 2018;28(1):1-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29117017.

15. Melvin AJ, Warshaw M, Compagnucci A, et al. Hepatic, renal, hematologic, and inflammatory markers in HIV-infected children on long-term suppressive antiretroviral therapy. *J Pediatric Infect Dis Soc*. 2017;6(3):e109-e115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28903520.

16. Naidoo K, Hassan-Moosa R, Mlotshwa P, et al. High rates of drug-induced liver injury in people living with HIV Coinfected with tuberculosis (TB) irrespective of antiretroviral therapy timing during antituberculosis treatment: results from the starting antiretroviral therapy at three points in TB trial. *Clin Infect Dis*. 2020;70(12):2675-2682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31622456.

17. Navarro VJ, Khan I, Bjornsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65(1):363-373. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27677775.

18. Neukam K, Mira JA, Collado A, et al. Liver toxicity of current antiretroviral regimens in HIV-infected patients with chronic viral hepatitis in a real-life setting: the HEPAVIR SEG-HEP cohort. *PLoS One*. 2016;11(2):e0148104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26848975.

19. Otto AO, Rivera CG, Zeuli JD, Temesgen Z. Hepatotoxicity of contemporary antiretroviral drugs: a review and evaluation of published clinical data. *Cells*. 2021;10(5). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34065305.

20. Phillips E, Bartlett JA, Sanne I, et al. Associations between HLA-DRB1*0102, HLA-B*5801, and hepatotoxicity during initiation of nevirapine-containing regimens in South Africa. *J Acquir Immune Defic Syndr*. 2013;62(2):e55-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23328091.

21. Phung BC, Sogni P, Launay O. Hepatitis B and human immunodeficiency virus co-infection. *World J Gastroenterol*. 2014;20(46):17360-17367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25516647.

22. Pillaye JN, Marakalala MJ, Khumalo N, Spearman W, Ndlovu H. Mechanistic insights into antiretroviral drug-induced liver injury. *Pharmacol Res Perspect*. 2020;8(4):e00598. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32643320.

23. Pokorska-Spiewak M, Stanska-Perka A, Popielska J, et al. Prevalence and predictors of liver disease in HIV-infected children and adolescents. *Sci Rep*. 2017;7(1):12309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28951598.

24. Rutstein RM, Samson P, Fenton T, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the pediatric AIDS clinical trials group protocol 1020A. *Pediatr Infect Dis J*. 2015;34:162-167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25232777.

25. Scott JA, Chew KW. Treatment optimization for HIV/HCV co-infected patients. *Ther Adv Infect Dis*. 2017;4(1):18-36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28357062.

26. Sevinsky H, Zaru L, Wang R, et al. Pharmacokinetics and pharmacodynamics of atazanavir in HIV-1-infected children treated with atazanavir powder and ritonavir: combined analysis of the PRINCE-1 and -2 studies. *Pediatr Infect Dis J*. 2018;37(6):e157-e165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29206748.

27. Sohrab SS, Suhail M, Ali A, Qadri I, Harakeh S, Azhar EI. Consequence of HIV and HCV co-infection on host immune response, persistence and current treatment options. *Virusdisease*. 2018;29(1):19-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29607354.

28. Sonderup MW, Maughan D, Gogela N, et al. Identification of a novel and severe pattern of efavirenz drug-induced liver injury in South Africa. *AIDS*. 2016;30(9):1483-1485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26959511.

29. Sonderup MW, Wainwright HC. Human Immunodeficiency virus infection, antiretroviral therapy, and liver pathology. *Gastroenterol Clin North Am*. 2017;46(2):327-343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28506368.

30. Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naive and -experienced infants and children aged ≥3 months to <6 years. *J Int AIDS Soc*. 2015;18:19467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26066346.

31. Sudjaritruk T, Bunupuradah T, Aurpibul L, et al. Nonalcoholic fatty liver disease and hepatic fibrosis among perinatally HIV-monoinfected Asian adolescents receiving antiretroviral therapy. *PLoS One*. 2019;14(12):e0226375. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31856189.

32. Tadesse BT, Foster BA, Kabeta A, et al. Hepatic and renal toxicity and associated factors among HIV-infected children on antiretroviral therapy: a prospective cohort study. *HIV Med*. 2019;20(2):147-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30474906.

33. The European Pregnancy and Paediatric HIV Cohort Collaboration, (EPPICC) Study Group in EuroCoord. Safety of zidovudine/lamivudine scored tablets in children with HIV infection in Europe and Thailand. *Eur J Clin Pharmacol*. 2017;73(4):463-468. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28028587.

34. The National Institute of Diabetes and Digestive and Kidney Diseases. Clinical and research information on drug-induced liver Injury. 2019.

35. Wu PY, Cheng CY, Liu CE, et al. Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naive HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. *PLoS One*. 2017;12(2):e0171596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28222098.