Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Hepatic toxicity (elevated AST, ALT, clinical hepatitis)	All ARVs (NVP, TPV of particular concern)	Onset: *NNRTI and PI therapy:* Within 12 weeks of initiation. *NRTI therapy:* Within months to years of initiation. *Any ARV combination regimen:* Early due to IRIS. Presentation: Asymptomatic elevation of AST, ALT. May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice. AST, ALT elevations while on NVP, ABC, or RAL may be associated with skin rash or a hypersensitivity reaction. HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, and TDF. NRTIs, especially ZDV, ddI, and d4T, may be associated with lactic acidosis and hepatic steatosis.	Uncommon in children. Frequency varies with different agents and drug combinations.	HIV infection HBV or HCV coinfection Elevated baseline ALT, AST Other hepatotoxic medications Alcohol use Underlying liver disease Pregnancy For NVP-associated hepatic events in adults: Female with pre-NVP CD4 count >250 cells/mm^3 Male with pre-NVP CD4 count >400 cells/mm^3 Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.[a] Higher drug concentrations for PIs, particularly TPV	Prevention: Avoid concomitant use of hepatotoxic medications. If hepatic enzymes are elevated >5–10 times ULN, most clinicians would avoid NVP. Monitoring: *For ARVs other than NVP:* Obtain AST, ALT at baseline and thereafter at least every 3–4 months or more frequently in at-risk patients (such as HBV- or HCV-coinfected or elevated baseline AST, ALT). *For NVP:* Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.	If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP hypersensitivity). In asymptomatic patients with ALT or AST >5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy and monitor patient closely. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent. When clinical hepatitis is associated with lactic acidosis, avoid restart of the most likely agent, and ZDV, d4T, and ddI in particular (see also lactic acidosis). Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Indirect hyperbilirubinemia	IDV, ATV	Onset: Early in therapy Presentation: Jaundice; Asymptomatic elevation of indirect bilirubin levels with normal direct bilirubin, AST, and ALT.	HIV-infected children receiving ATV: 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.	Not associated with HBV or HCV	Monitoring: No specific monitoring.	Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).
Non-cirrhotic portal hypertension	ARVs, especially ddI, d4T and combination of ddI and d4T	Onset: Late in therapy Presentation: GI bleeding, esophageal varices, hypersplenism. Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism). Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis	Rare: Probably less than 1%	Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T	Monitoring: No specific monitoring.	Manage complications of GI bleeding and esophageal varices.

[a] HLA-DRB1*0101 in Caucasians, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and Caucasians

Key to Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine transaminase, ALP = alkaline phosphatase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, CMV = cytomegalovirus, d4T = stavudine, ddI = didanosine, EBV = Epstein-Barr virus, FTC = emtricitabine, HAV = hepatitis A virus, HBV = hepatitis B virus, HCV = hepatitis C virus, IDV = indinavir, IRIS = immune reconstitution inflammatory syndrome, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, TDF = tenofovir, TPV = tipranavir, ULN = upper limit of normal, ZDV = zidovudine

References

1. Aceti A, Pasquazzi C, Zechini B, De Bac C, LIVERHAART Group. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection. *J Acquir Immune Defic Syndr*. Jan 1 2002;29(1):41-48. Available at http://www.ncbi.nlm.nih.gov/pubmed/11782588.
2. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5):538-539. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15021321.
3. Buck WC, Kabue MM, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children. *J Int AIDS* Soc. 2010;13:31. Available at http://www.ncbi.nlm.nih.gov/pubmed/20691049.
4. Busti AJ, Hall RG, Margolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. *Pharmacotherapy*. Dec 2004;24(12):1732-1747. Available at http://www.ncbi.nlm.nih.gov/pubmed/15585441.
5. Cotte L, Benet T, Billioud C, et al. The role of nucleoside and nucleotide analogues in nodular regenerative hyperplasia in HIV-infected patients: A case control study. *J Hepatol*. Mar 2011;54(3):489-496. Available at http://www.ncbi.nlm.nih.gov/pubmed/21056493.
6. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis*. 2004;38(Suppl 2):S80-89. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14986279.
7. Gray D, Nuttall J, Lombard C, et al. Low rates of hepatotoxicity in HIV-infected children on anti-retroviral therapy with and without isoniazid prophylaxis. *Journal of tropical pediatrics*. Jun 2010;56(3):159-165. Available at http://www.ncbi.nlm.nih.gov/pubmed/19710246.
8. Kea C, Puthanakit T, et al. Incidence and risk factors for nevirapine related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 17-20, 2011, 2011; Rome, Italy. Available at http://pag.ias2011.org/abstracts.aspx?aid=3248.
9. Kovari H, Ledergerber B, Battegay M, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis b or c virus co-infection. *Clin Infect Dis*. Feb 15 2010;50(4):502-511. Available at http://www.ncbi.nlm.nih.gov/pubmed/20085465.
10. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis*. Aug 15 2009;49(4):626-635. Available at http://www.ncbi.nlm.nih.gov/pubmed/19589079.
11. Levy V, Grant RM. Antiretroviral therapy for hepatitis B virus-HIV-coinfected patients: promises and pitfalls. *Clin Infect Dis*. Oct 1 2006;43(7):904-910. Available at http://www.ncbi.nlm.nih.gov/pubmed/16941375.
12. McKoy JM, Bennett CL, Scheetz MH, et al. Hepatotoxicity associated with long- versus short-course HIV-prophylactic nevirapine use: a systematic review and meta-analysis from the Research on Adverse Drug events And Reports (RADAR) project. *Drug safety: an international journal of medical toxicology and drug experience*. 2009;32(2):147-158. Available at http://www.ncbi.nlm.nih.gov/pubmed/19236121.
13. Nunez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. *Hepatology*. Sep 2010;52(3):1143-1155. Available at http://www.ncbi.nlm.nih.gov/pubmed/20812358.
14. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS*. Nov 27 2009;23(18):2425-2430. Available at http://www.ncbi.nlm.nih.gov/pubmed/19617813.

15. Phillips E, Bartlett J, Sanne I, et al. Associations between HLA to DRB1*0102, HLA to B*5801 and hepatotoxicity in patients who initiated NVP-containing regimens: South Africa, Abstract 949. Conference on Retroviruses and Opportunistic Infections; 2011, 2011; Boston, MA. Available at http://www.retroconference.org/2011/Abstracts/41833.htm.

16. Puoti M, Torti C, Ripamonti D, et al. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. *J Acquir Immune Defic Syndr*. Mar 1 2003;32(3):259-267. Available at http://www.ncbi.nlm.nih.gov/pubmed/12626885.

17. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr*. Sep 2003;34 Suppl 1(Suppl 1):S21-33. Available at http://www.ncbi.nlm.nih.gov/pubmed/14562855.

18. Van Dyke RB, Wang L, Williams PL, Pediatric ACTGCT. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. Dec 1 2008;198(11):1599-1608. Available at http://www.ncbi.nlm.nih.gov/pubmed/19000014.

19. Vispo E, Morello J, Rodriguez-Novoa S, Soriano V. Noncirrhotic portal hypertension in HIV infection. *Curr Opin Infect Dis*. Feb 2011;24(1):12-18. Available at http://www.ncbi.nlm.nih.gov/pubmed/21157331.

20. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. Jul 1 2002;186(1):23-31. Available at http://www.ncbi.nlm.nih.gov/pubmed/12089658.