



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 8/17/2016

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

Panel's Recommendations

- In children who have severe or life-threatening toxicity, all components of their drug regimen should be stopped immediately (**AIII**). Once symptoms of toxicity have resolved, antiretroviral therapy (ART) should be resumed with substitution of a different antiretroviral (ARV) drug or drugs for the offending agent(s) (**AII***).
- When modifying therapy because of toxicity or intolerance to a specific drug in children in whom virus has been suppressed, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen (**AI***).
- The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity to facilitate future medication choices if care is transferred (**AIII**).
- Dose reduction is not a recommended option in the setting of ARV toxicity, except when therapeutic drug monitoring (TDM) indicates a drug concentration above the normal therapeutic range (**AII***).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

[†] Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

Overview

Side effects from or intolerance to antiretroviral (ARV) agents are common in children and should prompt a re-evaluation of the ARV regimen. Drug-related toxicity can be acute, occurring soon after a drug has been administered; subacute, occurring within 1 to 2 days of administration; or late, occurring after prolonged drug administration. For some ARV medications, pharmacogenetic markers associated with risk of early treatment discontinuation because of toxicity have been identified, but the only such screen in clinical use is HLA B*5701 as a marker for abacavir hypersensitivity.¹ The differential diagnosis of drug toxicity includes toxicity due to HIV infection or other infections or conditions, bone marrow suppression with disseminated *Mycobacterium avium* complex (MAC) infection, and anemia due to blood loss from cytomegalovirus colitis. ARV drug-related adverse events can vary in severity from mild to severe and life threatening (see [Tables 17a–17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations](#)).

Identification of the responsible agent may allow for substitution of a similar agent that recent HIV drug-resistance testing predicts will be active against a patient's virus. Knowledge of a patient's ARV history and viral resistance profile before the current course of antiretroviral therapy (ART) is essential. Any new agent used should be assessed for likely effectiveness against a patient's virus and for possible interactions with other medications the patient will take.

Experience with ARV drugs has led to the recognition of several types of distinct adverse drug effects that may be most common with certain ARV drugs or drug classes (see [Tables 17a–17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations](#)).

Physicians, patients, and caregivers should discuss the response to medication-related toxicity, taking into

account its severity, the relative need for viral suppression, and the available ARV options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution. However, even mild adverse effects may have a negative impact on medication adherence and should be discussed before therapy is initiated, at regular provider visits, and at onset of any adverse effects. Common, self-limited adverse effects should be anticipated. For example, when initiating therapy with boosted protease inhibitors (PIs) many patients experience gastrointestinal (GI) adverse effects such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these side effects. Some patients may require antiemetics and antidiarrheal agents for symptom management. Central nervous system (CNS) adverse effects are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime to help minimize these adverse effects and be advised that these side effects should diminish or disappear within 2 to 4 weeks of initiating therapy. In addition, mild rash can be treated with drugs such as antihistamines. For some moderate toxicities, using a drug in the same class as the one causing toxicity but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required. Severe, life-threatening toxicity requires discontinuation of all ARV drugs and the initiation of appropriate supportive therapy (depending on the type of toxicity). Once the patient is stable and toxicity has resolved, another drug can be substituted for the drug associated with the toxicity.

In patients who experience an unacceptable adverse effect from ART, every attempt should be made to identify the offending agent and replace the drug with another effective agent as soon as possible.^{2,3} For example, if therapy needs to be stopped because of a severe or life-threatening side effect, all ARV drugs should be stopped at the same time. Once the offending drug or alternative cause for the adverse event has been determined, planning can begin for resumption of therapy with a new ARV regimen that does not contain the offending drug or with the original regimen, if the event is attributable to another cause. All drugs in the ARV regimen should then be started simultaneously, rather than one at a time with observation for adverse effects. Many experts recommend stopping efavirenz, **etravirine**, or nevirapine before stopping other drugs, if possible, because these drugs have significantly longer half-lives than nucleoside reverse transcriptase inhibitors (see [Discontinuation or Interruption of Therapy](#) section). However, in patients who have a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

When therapy is changed because of toxicity or intolerance in the context of virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible.⁴⁻⁸ Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is a permissible **for patients whose viral loads** are undetectable. However, substitution of a single active agent for a single drug in a **failing** multidrug regimen is generally not recommended because of concern for development of resistance (see [Approach to the Management of Antiretroviral Treatment Failure](#)).

Therapeutic drug monitoring (TDM) is not available on a routine basis to most clinicians, and the settings in which it is useful are unclear, especially in children. One such setting, however, may be in the context of the child with mild or moderate toxicity possibly attributable to a particular ARV agent (see [Role of Therapeutic Drug Monitoring in Management of Treatment Failure](#)). In this situation, it is reasonable for a clinician to use TDM (if available) to determine if the toxicity is result of a drug concentration exceeding the normal therapeutic range.^{9,10} This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then, it should be used with caution.

To summarize, management strategies for drug intolerance include:

- Symptomatic treatment of mild-to-moderate transient side effects.
- If necessary, change from one drug to another drug to which a patient's virus is sensitive (such as

changing to abacavir for zidovudine-related anemia or to nevirapine for efavirenz-related CNS symptoms).

- Change drug class, if necessary (such as from a PI to a non-nucleoside reverse transcriptase inhibitor or vice versa) and if a patient's virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.

Tables 17a–17l. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

describe specific adverse drug effects observed in children, including lactic acidosis, hepatic toxicity, renal toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, GI adverse effects, CNS adverse effects, peripheral neuropathy, hypersensitivity reactions, and skin rashes. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provide selected references regarding these toxicities in pediatric patients.

References

1. Lubomirov R, Colombo S, di Iulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: An observational cohort study. *J Infect Dis*. Jan 15 2011;203(2):246-257. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21288825>.
2. Elzi L, Marzolini C, Furrer H, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. *Arch Intern Med*. Jan 11 2010;170(1):57-65. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20065200>.
3. Davidson I, Beardsell H, Smith B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: The SWITCH study. *Antiviral Res*. May 2010;86(2):227-229. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20211651>.
4. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: The SPIRAL study. *AIDS*. Jul 17 2010;24(11):1697-1707. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20467288>.
5. McComsey G, Bhumbra N, Ma JF, Rathore M, Alvarez A, First Pediatric Switch S. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics*. Mar 2003;111(3):e275-281. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12612284>.
6. Viergever RF, ten Berg MJ, van Solinge WW, Hoepelman AI, Gisolf EH. Changes in hematological parameters after switching treatment of HIV-infected patients from zidovudine to abacavir or tenofovir DF. *HIV Clin Trials*. Mar-Apr 2009;10(2):125-128. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19487183>.
7. Valantin MA, Bittar R, de Truchis P, et al. Switching the nucleoside reverse transcriptase inhibitor backbone to tenofovir disoproxil fumarate + emtricitabine promptly improves triglycerides and low-density lipoprotein cholesterol in dyslipidaemic patients. *J Antimicrob Chemother*. Mar 2010;65(3):556-561. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20053692>.
8. Mallolas J, Podzamczar D, Milinkovic A, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. *J Acquir Immune Defic Syndr*. May 1 2009;51(1):29-36. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19390327>.
9. van Luin M, Gras L, Richter C, et al. Efavirenz dose reduction is safe in patients with high plasma concentrations and may prevent efavirenz discontinuations. *J Acquir Immune Defic Syndr*. Oct 1 2009;52(2):240-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19593159>.
10. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit*. Jun 2011;33(3):265-274. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21566505>.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (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
Global CNS depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	Onset: 1–6 days after starting LPV/r Presentation: Neonates/preterm infants: global CNS depression, cardiac toxicity, respiratory complications	Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates	Prematurity Low birth weight Age <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period.
Neuropsychiatric symptoms and other CNS manifestations	EFV	Onset: 1–2 days after initiating treatment Most symptoms subside or diminish by 2–4 weeks (but may persist in a minority of patients) Presentation: May include one or more of the following: dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, suicidal ideation, seizures (including absence seizures) CNS side effects may be more difficult to detect in children because neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders may be difficult to assess.	Variable, depending on age, symptom, assessment method Children: 24% for any EFV-related CNS manifestations in one case series with 18% requiring drug discontinuation Adults: >50% for any CNS manifestations of any severity 2% for EFV-related severe CNS manifestations	Insomnia associated with elevated EFV trough concentration ≥ 4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	Provide reassurance about the likely time-limited nature of symptoms. Consider EFV trough level if symptoms excessive or persistent. If EFV trough level >4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug discontinuation.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
	RAL	<u>Presentation:</u> Increased psychomotor activity, headaches, insomnia, depression	<u>Children:</u> Psychomotor activity reported in one child <u>Adults:</u> Headache, insomnia (<5% in adult trials)	Elevated RAL concentrations Prior history of insomnia or depression	Use with caution in the presence of drugs that increase RAL concentration	Consider drug discontinuation in case of severe insomnia.
Intracranial hemorrhage	TPV	<u>Onset:</u> 7–513 days after starting TPV	<u>Children:</u> No cases of ICH reported in children <u>Adults:</u> In premarket approval data in adults, 0.23/100 patient-years or 0.04–0.22/100 patient-years in a retrospective review of 2 large patient databases	Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.
Cerebellar ataxia	RAL	<u>Onset:</u> As early as 3 days after starting RAL <u>Presentation:</u> Tremor, dysmetria, ataxia	Two cases reported in adults during post marketing period	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (such as drug-drug interaction) identified and removed.

Key to Acronyms: ARV = antiretroviral, CNS = central nervous system, CYP = cytochrome P, EFV = efavirenz, ICH = intracranial hemorrhage, LPV/r = lopinavir/ritonavir, RAL = raltegravir, TDM = therapeutic drug monitoring, UGT = uridine diphosphate-glucurononyl transferase, TPV = tipranavir, ATV = atazanavir

References

1. Boxwell D, K. Cao, et al. . Neonatal Toxicity of Kaletra Oral Solution—LPV, Ethanol, or Propylene Glycol?- Abstract #708. 18th Conference on Retroviruses and Opportunistic Infections (CROI). Boston MA. 2011. Available at <http://www.retroconference.org/2011/PDFs/708.pdf>.
2. Schouten JT, Krambrink A, Ribaldo HJ, et al. Substitution of nevirapine because of efavirenz toxicity in AIDS clinical trials group A5095. *Clin Infect Dis*. Mar 1 2010;50(5):787-791. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20121419>.
3. Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. *J Antimicrob Chemother*. Nov 2009;64(5):910-928. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19767318>.
4. Jena A, Sachdeva RK, Sharma A, Wanchu A. Adverse drug reactions to nonnucleoside reverse transcriptase inhibitor-based antiretroviral regimen: a 24-week prospective study. *J Int Assoc Physicians AIDS Care (Chic)*. Sep-Oct 2009;8(5):318-322. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19721097>.
5. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis*. Dec 1 2005;41(11):1648-1653. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16267739>.
6. Elzi L, Marzolini C, Furrer H, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. *Arch Intern Med*. Jan 11 2010;170(1):57-65. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20065200>.
7. Haas DW, Ribaldo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS*. Dec 3 2004;18(18):2391-2400. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15622315>.
8. van Luin M, Gras L, Richter C, et al. Efavirenz dose reduction is safe in patients with high plasma concentrations and may prevent efavirenz discontinuations. *J Acquir Immune Defic Syndr*. Oct 1 2009;52(2):240-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19593159>.
9. van Luin M, Bannister WP, Mocroft A, et al. Absence of a relation between efavirenz plasma concentrations and toxicity-driven efavirenz discontinuations in the EuroSIDA study. *Antivir Ther*. 2009;14(1):75-83. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19320239>.
10. Waters L, Fisher M, Winston A, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS*. Jan 2 2011;25(1):65-71. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21099666>.
11. Nguyen A, Calmy A, Delhumeau C, et al. A randomized crossover study to compare efavirenz and etravirine treatment. *AIDS*. Jan 2 2011;25(1):57-63. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21076278>.
12. Puthanakit T, Tanpaiboon P, Aурpibul L, Cressey TR, Sirisanthana V. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther*. 2009;14(3):315-320. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19474465>.
13. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review. *AIDS reviews*. Apr-Jun 2009;11(2):103-109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19529750>.
14. Cabrera Figueroa S, Fernandez de Gatta M, Hernandez Garcia L, et al. The convergence of therapeutic drug monitoring and pharmacogenetic testing to optimize efavirenz therapy. *Ther Drug Monit*. Oct 2010;32(5):579-585. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20720517>.

15. Tepler H, Brown DD, Leavitt RY, et al. Long-term safety from the raltegravir clinical development program. *Current HIV research*. Jan 2011;9(1):40-53. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21198432>.
16. Lennox JL, Dejesus E, Berger DS, et al. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *J Acquir Immune Defic Syndr*. Sep 2010;55(1):39-48. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20404738>.
17. Eiden C, Peyriere H, Peytavin G, Reynes J. Severe insomnia related to high concentrations of raltegravir. *AIDS*. Mar 13 2011;25(5):725-727. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21368594>.
18. Gray J, Young B. Acute onset insomnia associated with the initiation of raltegravir: a report of two cases and literature review. *AIDS Patient Care STDS*. Sep 2009;23(9):689-690. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19663717>.
19. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. Jul 6 2011;306(1):70-78. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21730243>.
20. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. Sep 12 2008;22(14):1890-1892. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18753871>.
21. Reiss KA, Bailey JR, Pham PA, Gallant JE. Raltegravir-induced cerebellar ataxia. *AIDS*. Nov 13 2010;24(17):2757. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20980871>.
22. Jamshidi Y, Moreton M, McKeown DA, et al. Tribal ethnicity and CYP2B6 genetics in Ugandan and Zimbabwean populations in the UK: implications for efavirenz dosing in HIV infection. *J Antimicrob Chemother*. Dec 2010;65(12):2614-2619. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20952418>.
23. Strehlau R, Martens L, Coovadia A, et al. Absence seizures associated with efavirenz initiation. *Pediatr Infect Dis J*. Nov 2011;30(11):1001-1003. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21633320>.
24. Rakhmanina NY, van den Anker JN, Soldin SJ, van Schaik RH, Mordwinkin N, Neely MN. Can therapeutic drug monitoring improve pharmacotherapy of HIV infection in adolescents? *Ther Drug Monit*. Jun 2010;32(3):273-281. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20445485>.
25. Cattaneo D, Ripamonti D, Baldelli S, Cozzi V, Conti F, Clementi E. Exposure-related effects of atazanavir on the pharmacokinetics of raltegravir in HIV-1-infected patients. *Ther Drug Monit*. Dec 2010;32(6):782-786. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20926993>.
26. Chan-Tack KM, Struble KA, Birnkrant DB. Intracranial hemorrhage and liver-associated deaths associated with tipranavir/ritonavir: Review of cases from the FDA's Adverse Event Reporting System. *AIDS Patient Care STDS*. Nov 2008;22(11):843-850. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19025478>.
27. Justice AC, Zingmond DS, Gordon KS, et al. Drug toxicity, HIV progression, or comorbidity of aging: Does tipranavir use increase the risk of intracranial hemorrhage? *Clin Infect Dis*. Nov 1 2008;47(9):1226-1230. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18831696>.

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Dyslipidemia	<p>PIs: All PIs; lower incidence with ATV and DRV</p> <p>NRTIs: Especially d4T</p> <p>NNRTIs: RPV < EFV</p>	<p>Onset: Weeks to months after beginning therapy</p> <p>Presentation: <i>PIs:</i> ↑LDL-C, TC, and TG</p> <p><i>NNRTIs:</i> ↑LDL-C, TC, and HDL-C</p> <p><i>NRTIs:</i> ↑LDL-C, TC, and TG</p>	20%–50% of children receiving ART will have lipoprotein abnormalities.	<p>HIV infection</p> <p>High-fat, high-cholesterol diet</p> <p>Lack of exercise</p> <p>Obesity</p> <p>Hypertension</p> <p>Smoking</p> <p>Family history of dyslipidemia or premature CVD</p> <p>Metabolic syndrome</p>	<p>Prevention: Low-fat diet, exercise, no smoking</p> <p>Monitoring: <i>Adolescents and adults:</i> Obtain fasting (12-hour) TC, HDL-C, non-HDL-C, LDL-C, and TG before initiating or changing ART, then every 6 months, and thereafter, every 6–12 months.</p> <p><i>Children (aged ≥2 years) without lipid abnormalities or additional risk factors:</i> Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests.</p> <p><i>Children with lipid abnormalities and/or additional risk factors:</i> Obtain fasting (12-hour) TC, HDL-C, TG, and LDL-C before initiating or changing therapy and every 6 months thereafter (or more often if indicated).</p> <p><i>Children receiving lipid-lowering therapy with statins or fibrates:</i> Obtain fasting (12-hour) lipid profiles, LFTs, and CK before initiating lipid therapy and at 4 weeks and 8 weeks after starting lipid therapy. If minimal alterations in AST, ALT, and CK, repeat tests every 3 months. Also repeat tests 4 weeks after increasing doses of antihyperlipidemic agents.</p>	<p>Counsel lifestyle modification (low-fat diet, exercise, smoking cessation) for adequate trial period (3–6 months).</p> <p>Switch to a new ART regimen less likely to cause lipid abnormalities.^a</p> <p>Pharmacologic Management: Initiate drug therapy promptly in patients with TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin.^b Ezetimibe may be considered in addition to statins.^c</p> <p>Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children.</p> <p>No consensus as to what LDL-C should prompt treatment in children receiving ARVs.^d HIV-infected patients are considered to be at moderate risk of CVD. Assessment of additional risk factors should be done in all patients.^e</p> <p><i>High-risk patients:</i> Goal LDL-C ≤100 mg/dL.</p> <p><i>Moderate-risk patients:</i> Goal LDL-C ≤130 mg/dL.</p> <p><i>At-risk patients:</i> Goal LDL-C ≤160 mg/dL.</p>

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

^a The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

^b Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Experience with statins is limited to children >6 years of age.

^c In general, recommend using in boys aged ≥ 10 years and in girls preferably after onset of menses. Treatment with statins in children ≤ 10 years of age is limited to those with severe primary hyperlipidemia, a high-risk condition, or evident CVD, all under the care of a lipid specialist. Multiple drug interactions exist between ARVs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin (Pravachol®), atorvastatin (Lipitor®), rosuvastatin (Crestor®), fluvastatin (Lescol®), and ezetimide (Zetia®) are approved for use in children ≥ 10 years of age.

^d The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children is likely to lead to premature CVD.

^e Refer to NHLBI guidelines at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

Key to Acronyms: ALT = alanine transaminase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, ART = antiretroviral therapy, CK = creatine kinase, CVD = cardiovascular disease, d4T = stavudine, EFV = efavirenz, HDL-C = high-density lipoprotein cholesterol, non-HDL-C = non-high-density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, LFT = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PUFA = polyunsaturated fatty acid, RPV = rilpivirine, TC = total cholesterol, TG = triglycerides

References

1. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation*. Apr 10 2007;115(14):1948-1967. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17377073>.
2. Lainka E, Oezbek S, Falck M, Ndagijimana J, Niehues T. Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. *Pediatrics*. Nov 2002;110(5):e56. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12415062>.
3. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. Dec 12 2006;114(24):2710-2738. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17130340>.
4. Belay B, Belamarich PF, Tom-Revzon C. The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics*. Feb 2007;119(2):370-380. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17272627>.
5. McComsey G, Bhumbra N, Ma JF, Rathore M, Alvarez A, First Pediatric Switch S. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: Results of the First Pediatric Switch Study. *Pediatrics*. Mar 2003;111(3):e275-281. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12612284>.

6. De Truchis P, Kirstetter M, Perier A, et al. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy: a randomized prospective study. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):278-285. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17179770>.
7. Engler MM, Engler MB, Malloy MJ, Paul SM, Kulkarni KR, Mietus-Snyder ML. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *The American journal of cardiology*. Apr 1 2005;95(7):869-871. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15781019>.
8. Gerber JG, Kitch DW, Fichtenbaum CJ, et al. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: results of ACTG A5186. *J Acquir Immune Defic Syndr*. Apr 1 2008;47(4):459-466. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17971707>.
9. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antivir Ther*. 2005;10(8):917-924. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16430197>.
10. Carter RJ, Wiener J, Abrams EJ, et al. Dyslipidemia among perinatally HIV-infected children enrolled in the PACTS-HOPE cohort, 1999-2004: a longitudinal analysis. *J Acquir Immune Defic Syndr*. Apr 1 2006;41(4):453-460. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16652053>.
11. Tassiopoulos K, Williams PL, Seage GR, 3rd, et al. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. Apr 15 2008;47(5):607-614. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18209684>.
12. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. Mar 27 2009;23(6):661-672. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19279441>.
13. Chantry CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics*. Jul 2008;122(1):e129-138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18519448>.
14. Rhoads MP, Lanigan J, Smith CJ, Lyall EG. Effect of specific ART drugs on lipid changes and the need for lipid management in children with HIV. *J Acquir Immune Defic Syndr*. Aug 15 2011;57(5):404-412. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21499114>.
15. Jacobson DL, Williams P, Tassiopoulos K, Melvin A, Hazra R, Farley J. Clinical management and follow-up of hypercholesterolemia among perinatally HIV-infected children enrolled in the PACTG 219C study. *J Acquir Immune Defic Syndr*. Aug 15 2011;57(5):413-420. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21602698>.
16. O'Gorman CS, O'Neill MB, Conwell LS. Considering statins for cholesterol-reduction in children if lifestyle and diet changes do not improve their health: A review of the risks and benefits. *Vascular health and risk management*. 2011;7:1-14. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21339908>.
17. Hamilton-Craig I, Kostner K, Colquhoun D, Woodhouse S. Combination therapy of statin and ezetimibe for the treatment of familial hypercholesterolemia. *Vascular health and risk management*. 2010;6:1023-1037. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21127699>.
18. Estrada V, Portilla J. Dyslipidemia related to antiretroviral therapy. *AIDS reviews*. Jan-Mar 2011;13(1):49-56. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21412389>.
19. Feeney ER, Mallon PW. HIV and HAART-Associated Dyslipidemia. *The open cardiovascular medicine journal*. 2011;5:49-63. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21643501>.
20. Dube MP, Cadden JJ. Lipid metabolism in treated HIV Infection. *Best practice & research. Clinical endocrinology & metabolism*. Jun 2011;25(3):429-442. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21663837>.

21. Singh S, Willig JH, Mugavero MJ, et al. Comparative Effectiveness and Toxicity of Statins Among HIV-Infected Patients. *Clin Infect Dis*. Feb 1 2011;52(3):387-395. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21189273>.
22. Tomaka F, Lefebvre E, Sekar V, et al. Effects of ritonavir-boosted darunavir vs. ritonavir-boosted atazanavir on lipid and glucose parameters in HIV-negative, healthy volunteers. *HIV Med*. May 2009;10(5):318-327. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19210693>.
23. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. The Report of the Expert Panel. 2011. Available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm.
24. FDA. FDA Drug Safety Communication: Interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. 2012. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm>.

Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (such as LPV/r, RTV) but can occur with all ARVs	<u>Onset:</u> Early <u>Presentation:</u> Nausea, emesis—may be associated with anorexia and/or abdominal pain	Varies with ARV agent. 10%–30% in some series.	Unknown	Instruct patient to take PIs with food. Generally improves with time; monitor for weight loss, ARV adherence.	Reassure patient/ caretaker that nausea and vomiting will likely decrease over time. Provide supportive care including instruction on dietary modification. Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases.
Diarrhea	PIs (NFV, LPV/r, FPV/r), buffered ddl	<u>Onset:</u> Early <u>Presentation:</u> Generally soft, more frequent stools	Varies with ARV agent. 10%–30% in some series.	Unknown	Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea. Although data in children on treatment for ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate, bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful.
Pancreatitis	ddl (especially with concurrent d4T or TDF); reported, albeit rarely, with most ARVs	<u>Onset:</u> Any time, usually after months on therapy <u>Presentation:</u> Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<1%–2% in recent series. Frequency was higher in the past with higher dosing of ddl.	Concomitant treatment with other medications associated with pancreatitis (such as TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia	Avoid use of ddl in patients with history of pancreatitis.	Discontinue offending agent. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.

Key to Acronyms: ARV = antiretroviral, d4T = stavudine, ddl = didanosine, FPV/r = fosamprenavir/ritonavir, LPV = lopinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, TDF = tenofovir disoproxil fumarate, TG = triglyceride, TMP-SMX = trimethoprim sulfamethoxazole, ZDV = zidovudine

References

1. 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>.
2. Butler KM, Venzon D, Henry N, et al. Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics.* Apr 1993;91(4):747-751. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7681940>.
3. Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. *Clin Infect Dis.* Jun 2000;30(6):908-914. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10854364>.
4. Pryce C, Pierre RB, Steel-Duncan J, et al. Safety of antiretroviral drug therapy in Jamaican children with HIV/AIDS. *The West Indian medical journal.* Jun 2008;57(3):238-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19583122>.
5. Kumarasamy N, Venkatesh KK, Devaleenol B, Poongulali S, Mothi SN, Solomon S. Safety, tolerability and effectiveness of generic HAART in HIV-infected children in South India. *J Trop Pediatrics.* Jun 2009;55(3):155-159. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18829638>.
6. Nachman SA, Chernoff M, Gona P, et al. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med.* Feb 2009;163(2):164-171. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19188649>.
7. Carr A, Amin J. Efficacy and tolerability of initial antiretroviral therapy: a systematic review. *AIDS.* Jan 28 2009;23(3):343-353; discussion 355-346. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19114855>.
8. Hoffmann CJ, Fielding KL, Charalambous S, et al. Antiretroviral therapy using zidovudine, lamivudine, and efavirenz in South Africa: tolerability and clinical events. *AIDS.* Jan 2 2008;22(1):67-74. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18090393>.
9. Malan N, Su J, Mancini M, et al. Gastrointestinal tolerability and quality of life in antiretroviral-naive HIV-1-infected patients: data from the CASTLE study. *AIDS Care.* Jun 2010;22(6):677-686. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20467943>.
10. Manfredi R, Calza L. HIV infection and the pancreas: risk factors and potential management guidelines. *Int J STD AIDS.* Feb 2008;19(2):99-105. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18334062>.
11. Croxtall JD, Perry CM. Lopinavir/Ritonavir: A review of its use in the management of HIV-1 infection. *Drugs.* Oct 1 2010;70(14):1885-1915. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20836579>.
12. Turner MJ, Angel JB, Woodend K, Giguere P. The efficacy of calcium carbonate in the treatment of protease inhibitor-induced persistent diarrhea in HIV-infected patients. *HIV Clin Trials.* Jan-Feb 2004;5(1):19-24. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15002083>.
13. Heiser CR, Ernst JA, Barrett JT, French N, Schutz M, Dube MP. Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhea. *J Int Assoc Physicians AIDS Care (Chic).* Oct-Dec 2004;3(4):121-129. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15768732>.
14. Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr.* Mar 1 2012;59(3):274-280. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22126740>.
15. Wegzyn CM, Fredrick LM, Stubbs RO, Woodward WC, Norton M. Diarrhea Associated with Lopinavir/Ritonavir-Based Therapy: Results of a Meta-Analysis of 1469 HIV-1-Infected Participants. *J Int Assoc Physicians AIDS Care (Chic).* Jul-Aug 2012;11(4):252-259. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22544446>.

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (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
Anemia ^a	Principally ZDV	<p><u>Onset:</u> Variable, weeks to months</p> <p><u>Presentation:</u> Most commonly asymptomatic or mild fatigue, pallor, tachypnea; rarely, congestive heart failure</p>	<p><u>HIV-exposed newborns:</u> Severe anemia uncommon, but may be seen coincident with physiologic Hgb nadir</p> <p><u>HIV-infected children on ARVs:</u> 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV</p>	<p><u>HIV-exposed newborns:</u> Premature birth</p> <p><i>In utero</i> exposure to ARVs</p> <p>Advanced maternal HIV</p> <p>Neonatal blood loss</p> <p>Concurrent ZDV + 3TC neonatal prophylaxis</p> <p><u>HIV-infected children on ARVs:</u> Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency)</p> <p>Myelosuppressive drugs (e.g., TMP-SMX, rifabutin)</p> <p>Iron deficiency</p> <p>Advanced or poorly controlled HIV disease</p>	<p><u>HIV-exposed newborns:</u> Monitor CBC at birth.</p> <p>Consider repeat CBC at 4 weeks for neonates who are at higher risk (such as those born prematurely or known to have low birth Hgb).</p> <p><u>HIV-infected children on ARVs:</u> Avoid ZDV in children with moderate to severe anemia when alternative agents are available.</p> <p>Monitor CBC 3–4 times per year as part of routine care.</p>	<p><u>HIV-exposed newborns:</u> Rarely require intervention unless Hgb is <7.0 g/dL or anemia is associated with symptoms.</p> <p>Consider discontinuing ZDV if 4 weeks or more of 6-week ZDV prophylaxis regimen are already completed (see Perinatal Guidelines^b).</p> <p><u>HIV-infected children on ARVs:</u> Discontinue non-ARV marrow-toxic drugs, if feasible.</p> <p>Treat coexisting iron deficiency, OIs, malignancies.</p> <p>For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin.</p>

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Neutropenia ^a	Principally ZDV	Onset: Variable Presentation: Most commonly asymptomatic	HIV-exposed newborns: Rare HIV-infected children on ARVs: 9.9%–26.8% of children on ARVs, depending upon the ARV regimen Highest rates with ZDV-containing regimens	HIV-exposed newborns: <i>In utero</i> exposure to ARVs Concurrent ZDV + 3TC neonatal prophylaxis HIV-infected children on ARVs: Advanced or poorly controlled HIV infection Myelosuppressive drugs (such as TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	HIV-infected children on ARVs: Monitor CBC 3–4 times per year as part of routine care.	HIV-exposed newborns: No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/μL, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see Perinatal Guidelines^b). HIV-infected children on ARVs: Discontinue non-ARV marrow-toxic drugs if feasible. Treat coexisting OIs, malignancies. For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of G-CSF.

^a HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

^b *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

Key to Acronyms: 3TC = lamivudine, ANC = absolute neutrophil count, ARV = antiretroviral, CBC = complete blood count, G6PD = glucose-6-phosphate dehydrogenase, G-CSF = granulocyte colony-stimulating factor, Hgb = hemoglobin, NRTI = nucleoside reverse transcriptase inhibitor, OIs = opportunistic infections, TMP-SMX = trimethoprim-sulfamethoxazole, ZDV = zidovudine

References

1. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. Jun 12 1997;336(24):1704-1712. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9182213>.
2. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. Dec 16 1999;341(25):1874-1881. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10601506>.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. Nov 3 1994;331(18):1173-1180. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7935654>.
4. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. Apr 1 2002;34(7):991-1001. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
5. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr*. Oct 1998;133(4):500-508. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9787687>.
6. Najean Y, Rain JD. The mechanism of thrombocytopenia in patients with HIV infection. *The Journal of laboratory and clinical medicine*. Mar 1994;123(3):415-420. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8133154>.
7. Caselli D, Maccabruni A, Zuccotti GV, et al. Recombinant erythropoietin for treatment of anaemia in HIV-infected children. *AIDS*. Jul 1996;10(8):929-931. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8828757>.
8. Allen UD, Kirby MA, Goeree R. Cost-effectiveness of recombinant human erythropoietin versus transfusions in the treatment of zidovudine-related anemia in HIV-infected children. *Pediatric AIDS and HIV infection*. Feb 1997;8(1):4-11. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11361510>.
9. Mueller BU, Jacobsen F, Butler KM, Husson RN, Lewis LL, Pizzo PA. Combination treatment with azidothymidine and granulocyte colony-stimulating factor in children with human immunodeficiency virus infection. *J Pediatr*. Nov 1992;121(5 Pt 1):797-802. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1279153>.
10. Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. *Blood*. May 1 1991;77(9):1884-1893. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1850307>.
11. Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood*. Apr 15 1997;89(8):2689-2700. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9108386>.
12. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J*. Apr 2010;29(4):376-379. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19949355>.
13. Dryden-Peterson S, Shapiro RL, Hughes MD, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr*. Apr 15 2011;56(5):428-436. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21266910>.
14. Mocroft A, Lifson AR, Touloumi G, et al. Haemoglobin and anaemia in the SMART study. *Antivir Ther*. 2011;16(3):329-337. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21555815>.

**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)	<p><u>Onset:</u> <i>NNRTI and PI therapy:</i> Within 12 weeks of initiation.</p> <p><i>NRTI therapy:</i> Within months to years of initiation.</p> <p><i>Any ARV combination regimen:</i> Early due to IRIS.</p> <p><u>Presentation:</u> Asymptomatic elevation of AST, ALT.</p> <p>May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice.</p> <p>AST, ALT elevations while on NVP, ABC, or RAL may be associated with skin rash or a hypersensitivity reaction.</p> <p>HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, and TDF.</p> <p>NRTIs, especially ZDV, ddI, and d4T, may be associated with lactic acidosis and hepatic steatosis.</p>	<p>Uncommon in children.</p> <p>Frequency varies with different agents and drug combinations.</p>	<p>HIV infection</p> <p>HBV or HCV coinfection</p> <p>Elevated baseline ALT, AST</p> <p>Other hepatotoxic medications</p> <p>Alcohol use</p> <p>Underlying liver disease</p> <p>Pregnancy</p> <p><u>For NVP-associated hepatic events in adults:</u> Female with pre-NVP CD4 count >250 cells/mm³ Male with pre-NVP CD4 count >400 cells/mm³</p> <p>Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.^a</p> <p>Higher drug concentrations for PIs, particularly TPV</p>	<p><u>Prevention:</u> Avoid concomitant use of hepatotoxic medications.</p> <p>If hepatic enzymes are elevated >5–10 times ULN, most clinicians would avoid NVP.</p> <p><u>Monitoring:</u> <i>For ARVs other than NVP:</i> 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).</p> <p><i>For NVP:</i> Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.</p>	<p>If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP hypersensitivity).</p> <p>In asymptomatic patients with ALT or AST >5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy and monitor patient closely.</p> <p>In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent.</p> <p>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).</p> <p>Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.</p>

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

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

Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Insulin resistance, asymptomatic hyperglycemia, DM ^a	Thymidine analogue NRTIs (d4T, ddI, ZDV) Some PIs (IDV, LPV/r; perhaps less often ATV, ATV/r, DRV/r, TPV/r)	<u>Onset:</u> Weeks to months after beginning therapy; median of 60 days (adult data) <u>Presentation:</u> <i>Most commonly:</i> Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay <i>Also possible:</i> Frank DM (polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	<u>Impaired fasting glucose:</u> <i>ARV-treated adults:</i> 3%–25% <i>ARV-treated children:</i> 0%–7% <u>Impaired glucose tolerance:</u> <i>ARV-treated adults:</i> 16%–35% <i>ARV-treated children:</i> 3%–4% <u>DM:</u> <i>ARV-treated adults:</i> 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults) <i>ARV-treated children:</i> Very rare in HIV-infected children	<u>Risk factors for Type 2 DM:</u> Lipodystrophy Metabolic syndrome Family history of DM High BMI Obesity	<u>Prevention:</u> Lifestyle modification (see Management). Although uncertain, avoiding use of d4T, IDV may reduce risk. <u>Monitoring:</u> Monitor for polydipsia, polyuria, polyphagia, change in body habitus, acanthosis nigricans. <i>Obtain RPG levels at:</i> Initiation of ARV therapy; 3–6 months after therapy initiation; and once a year thereafter. For RPG ≥140 mg/dL, obtain FPG performed after 8-hour fast and consider referral to endocrinologist.	Counsel on lifestyle modification (low-fat diet, exercise, no smoking). Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen. <i>For either RPG ≥200 mg/dL plus symptoms of DM or FPG ≥126 mg/dL:</i> Patient meets diagnostic criteria for DM; consult endocrinologist. <i>FPG 100–125 mg/dL:</i> Impaired FPG is suggestive of insulin resistance; consult endocrinologist. <i>FPG <100 mg/dL:</i> Normal FPG but does not exclude insulin resistance; recheck FPG in 6–12 months.

^a Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired FPG* as an FPG of 100–125 mg/dL; *impaired glucose tolerance* as an elevated 2-hour PG of 140–199 mg/dL in a standard OGTT; and *diabetes mellitus* as either an FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, HgbA1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

Key to Acronyms: ARV = antiretroviral, ATV = atazanavir, **ATV/r = atazanavir/ritonavir**, d4T = stavudine, ddI = didanosine, DM = diabetes mellitus, **DRV/r = darunavir/ritonavir**, FPG = fasting plasma glucose, IDV = indinavir, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, OGTT = oral glucose tolerance test, PG = plasma glucose, PI = protease inhibitor, RPG = random plasma glucose, **TPV/r = tipranavir/ritonavir**, ZDV = zidovudine

References

Clinical features of hyperglycemia, insulin resistance, and diabetes mellitus

1. Amaya RA, Kozinetz CA, McMeans A, Schwarzwald H, Kline MW. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. May 2002;21(5):405-410. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12150177>.
2. Arpadi SM, Cuff PA, Horlick M, Wang J, Kotler DP. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ -lymphocyte count and CD4+ -lymphocyte percentage at baseline and use of protease inhibitors and stavudine. *J Acquir Immune Defic Syndr*. May 1 2001;27(1):30-34. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11404517>.
3. Beregszaszi M, Dollfus C, Levine M, et al. Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. *J Acquir Immune Defic Syndr*. Oct 1 2005;40(2):161-168. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16186733>.
4. Bitnun A, Sochett E, Babyn P, et al. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naive HIV-infected children. *AIDS*. Jun 13 2003;17(9):1319-1327. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12799553>.
5. Bitnun A, Sochett E, Dick PT, et al. Insulin sensitivity and beta-cell function in protease inhibitor-treated and -naive human immunodeficiency virus-infected children. *The Journal of clinical endocrinology and metabolism*. Jan 2005;90(1):168-174. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15483082>.
6. Bockhorst JL, Ksseiry I, Toye M, et al. Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. *Pediatr Infect Dis J*. May 2003;22(5):463-465. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12797313>.
7. Hadigan C. Insulin resistance among HIV-infected patients: unraveling the mechanism. *Clin Infect Dis*. Nov 1 2005;41(9):1341-1342. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16206113>.
8. Leonard EG, McComsey GA. Antiretroviral therapy in HIV-infected children: the metabolic cost of improved survival. *Infectious disease clinics of North America*. Sep 2005;19(3):713-729. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16102657>.
9. McComsey GA, Leonard E. Metabolic complications of HIV therapy in children. *AIDS*. Sep 3 2004;18(13):1753-1768. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15316336>.
10. Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr*. Jan 1 2000;23(1):35-43. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10708054>.
11. Morse CG, Kovacs JA. Metabolic and skeletal complications of HIV infection: the price of success. *JAMA*. Aug 16 2006;296(7):844-854. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16905789>.
12. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. May 23 2005;165(10):1179-1184. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15911733>.
13. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr*. Mar 1 2003;32(3):298-302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12626890>.
14. Abdel-Khalek I, Moallem HJ, Fikrig S, Castells S. New onset diabetes mellitus in an HIV-positive adolescent. *AIDS Patient Care STDS*. Mar 1998;12(3):167-169. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11361930>.

15. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. Mar 27 2009;23(6):661-672. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19279441>.
16. Chantray CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics*. Jul 2008;122(1):e129-138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18519448>.
17. Blumer RM, van Vonderen MG, Sutinen J, et al. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. *AIDS*. Jan 11 2008;22(2):227-236. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18097225>.
18. Lee GA, Rao M, Mulligan K, et al. Effects of ritonavir and amprenavir on insulin sensitivity in healthy volunteers. *AIDS*. Oct 18 2007;21(16):2183-2190. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18090045>.
19. Tien PC, Schneider MF, Cole SR, et al. Antiretroviral therapy exposure and insulin resistance in the Women's Interagency HIV study. *J Acquir Immune Defic Syndr*. Dec 1 2008;49(4):369-376. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19186350>.
20. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes care*. Jun 2008;31(6):1224-1229. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18268071>.
21. Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr*. Apr 15 2009;50(5):499-505. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19223782>.
22. Geffner ME, Patel K, Miller TL, et al. Factors associated with insulin resistance among children and adolescents perinatally infected with HIV-1 in the pediatric HIV/AIDS cohort study. *Hormone Research In Paediatrics*. 2011;76(6):386-391. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22042056>.

Management of hyperglycemia, insulin resistance, and diabetes mellitus

23. American Diabetes A. Standards of medical care in diabetes—2012. *Diabetes Care*. Jan 2012;35 Suppl 1:S11-63. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22187469>.
24. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes care*. Jan 2009;32(1):193-203. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18945920>.
25. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes care*. Mar 2007;30(3):753-759. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17327355>.
26. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr*. Nov 1 2002;31(3):257-275. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12439201>.
27. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. Sep 1 2006;43(5):645-653. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16886161>.
28. Feeney ER, Mallon PW. Insulin resistance in treated HIV infection. *Best Pract Res Cl En*. Jun 2011;25(3):443-458. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21663838>.
29. Paik IJ, Kotler DP. The prevalence and pathogenesis of diabetes mellitus in treated HIV-infection. *Best Pract Res Cl En*. Jun 2011;25(3):469-478. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21663840>.

Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (alone and in combination)	<p><u>Onset:</u> 1–20 months after starting therapy (median onset 4 months in 1 case series).</p> <p><u>Presentation:</u> Usually insidious onset of a combination of signs and symptoms: generalized fatigue, weakness, and myalgias; vague abdominal pain, weight loss, unexplained nausea or vomiting; dyspnea; peripheral neuropathy.</p> <p>Patients may present with acute multi-organ failure (such as fulminant hepatic, pancreatic, and respiratory failure).</p>	<p><u>Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L):</u> <i>Adults:</i> 15%–35% of adults receiving NRTI therapy for longer than 6 months <i>Children:</i> 29%–32%</p> <p><u>Symptomatic severe hyperlactatemia (>5.0 mmol/L):</u> <i>Adults:</i> 0.2%–5.7%</p> <p><u>Symptomatic lactic acidosis/hepatic steatosis:</u> Rare in all age groups (1.3–11 episodes per 1,000 person-years), but associated with a high fatality rate (33%–58%)</p>	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (such as d4T, TDF, RBV, or tetracycline) <p>Coadministration of TDF with metformin</p> <ul style="list-style-type: none"> • Overdose of propylene glycol • CD4 T lymphocyte count <350 cells/mm³ • Acquired riboflavin or thiamine deficiency • Possibly, pregnancy <p><u>Pre-term infants:</u></p> <ul style="list-style-type: none"> • Use of propylene glycol (e.g., as an diluent for LPV/r) 	<p><u>Prevention:</u> Avoid d4T and ddI in combination.</p> <p>Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.</p> <p><u>Monitoring:</u> <i>Asymptomatic:</i> Measurement of serum lactate is not recommended.</p> <p><i>Clinical signs or symptoms consistent with lactic acidosis:</i> Obtain blood lactate level;^a additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.</p>	<p><u>Lactate 2.1–5.0 mmol/L (confirmed with second test):</u> Consider replacing ddI and d4T with other ARVs.</p> <p>As alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.</p> <p><u>Lactate >5.0 mmol/L (confirmed with second test)^b or >10.0 mmol/L (any one test):</u> Discontinue all ARVs. Provide supportive therapy (intravenous fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues).</p> <p><u>Anecdotal (unproven) supportive therapies:</u> bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C).</p> <p>Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and monthly monitoring of lactate for at least 3 months.</p>

^a Blood for lactate determination should be collected without prolonged tourniquet application or fist clenching into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

^b Management can be initiated before the results of the confirmatory test.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARVs = antiretrovirals, BMI = body mass index, d4T = stavudine, ddI = didanosine, FTC = emtricitabine, HCV = hepatitis C virus, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, RBV = ribavirin, TDF = tenofovir disoproxil fumarate, THAM = tris-hydroxymethyl-aminomethane

References

General Reviews

1. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis*. Mar 15 2002;34(6):838-846. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11850865>.
2. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother*. Mar 2002;46(3):716-723. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11850253>.
3. Carr A. Lactic acidemia in infection with human immunodeficiency virus. *Clin Infect Dis*. Apr 1 2003;36(Suppl 2):S96-S100. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12652378>.
4. Fichtenbaum CJ. Metabolic abnormalities associated with HIV infection and antiretroviral therapy. *Curr Infect Dis Rep*. Jan 2009;11(1):84-92. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19094829>.
5. Desai N, Mathur M, Weedon J. Lactate levels in children with HIV/AIDS on highly active antiretroviral therapy. *AIDS*. Jul 4 2003;17(10):1565-1568. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12824798>.
6. Foster C, Lyall H. HIV and mitochondrial toxicity in children. *J Antimicrob Chemother*. Jan 2008;61(1):8-12. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17999978>.
7. Noguera A, Fortuny C, Sanchez E, et al. Hyperlactatemia in human immunodeficiency virus-infected children receiving antiretroviral treatment. *Pediatr Infect Dis J*. Sep 2003;22(9):778-782. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14506367>.
8. Arenas-Pinto A, Grant A, Bhaskaran K, et al. Risk factors for fatality in HIV-infected patients with dideoxynucleoside-induced severe hyperlactataemia or lactic acidosis. *Antivir Ther*. 2011;16(2):219-226. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21447871>.

Risk Factors

9. Datta D, Moyle G, Mandalia S, Gazzard B. Matched case-control study to evaluate risk factors for hyperlactataemia in HIV patients on antiretroviral therapy. *HIV Med*. Oct 2003;4(4):311-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14525541>.
10. Fielder J, Rambiki K. Occurrence of stavudine-induced lactic acidosis in 3 members of an African family. *J Int Assoc Physicians AIDS Care (Chic)*. Jul-Aug 2010;9(4):236-239. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20798404>.

11. Imhof A, Ledergerber B, Gunthard HF, Haupts S, Weber R, Swiss HIVCS. Risk factors for and outcome of hyperlactatemia in HIV-infected persons: is there a need for routine lactate monitoring? *Clin Infect Dis*. Sep 1 2005;41(5):721-728. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16080096>.
12. Lactic Acidosis International Study G. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. *AIDS*. Nov 30 2007;21(18):2455-2464. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18025882>.
13. Manosuthi W, Prasithsirikul W, Chumpathat N, et al. Risk factors for mortality in symptomatic hyperlactatemia among HIV-infected patients receiving antiretroviral therapy in a resource-limited setting. *Int J Infect Dis*. Nov 2008;12(6):582-586. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18337140>.
14. Osler M, Stead D, Rebe K, Meintjes G, Boulle A. Risk factors for and clinical characteristics of severe hyperlactataemia in patients receiving antiretroviral therapy: a case-control study. *HIV Med*. Feb 2010;11(2):121-129. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19702629>.
15. Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivannis P. Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection. *Journal of renal care*. Mar 2011;37(1):25-29. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21288314>.
16. Boxwell DC, K.; et al. Neonatal Toxicity of Kaletra Oral Solution—LPV, Ethanol, or Propylene Glycol? Abstract #708. Paper presented at. 18th Conference on Retroviruses and Opportunistic Infections (CROI). Boston MA. 2011.
17. Feeney ER, Chazallon C, O'Brien N, et al. Hyperlactataemia in HIV-infected subjects initiating antiretroviral therapy in a large randomized study (a substudy of the INITIO trial). *HIV Med*. Nov 2011;12(10):602-609. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21599820>.
18. Leung L, Wilson D, Manini AF. Fatal toxicity from symptomatic hyperlactataemia: a retrospective cohort study of factors implicated with long-term nucleoside reverse transcriptase inhibitor use in a South African hospital. *Drug safety: an international journal of medical toxicology and drug experience*. Jun 1 2011;34(6):521-527. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21488705>.
19. Maskew M, Westreich D, Fox MP, Maotoe T, Sanne IM. Effectiveness and safety of 30 mg versus 40 mg stavudine regimens: A cohort study among HIV-infected adults initiating HAART in South Africa. *J Int AIDS Soc*. 2012;15(1):13. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22410312>.
20. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS One*. 2011;6(4):e18736. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21494566>.
21. Menezes CN, Maskew M, Sanne I, Crowther NJ, Raal FJ. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. *BMC Infect Dis*. 2011;11:244. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21923929>.
22. Phan V, Thai S, Choun K, Lynen L, van Griensven J. Incidence of treatment-limiting toxicity with stavudine-based antiretroviral therapy in Cambodia: A retrospective cohort study. *PLoS One*. 2012;7(1):e30647. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22303447>.

Monitoring and Management

23. Brinkman K. Management of hyperlactatemia: No need for routine lactate measurements. *AIDS*. 2001;15(6):795-797. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11371695.
24. Carter RW, Singh J, Archambault C, Arrieta A. Severe lactic acidosis in association with reverse transcriptase inhibitors with potential response to L-carnitine in a pediatric HIV-positive patient. *AIDS Patient Care STDS*. Mar 2004;18(3):131-134. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15104873>.
25. Claessens YE, Cariou A, Monchi M, et al. Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with L-carnitine. *Critical care medicine*. Apr 2003;31(4):1042-1047. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12682470>.

26. Delgado J, Harris M, Tesiorowski A, Montaner JS. Symptomatic elevations of lactic acid and their response to treatment manipulation in human immunodeficiency virus-infected persons: a case series. *Clin Infect Dis*. 2001;33(12):2072-2074. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11712096.
27. Loneragan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. *AIDS*. Nov 21 2003;17(17):2495-2499. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14600521>.
28. Marfo K, Garala M, Kvetan V, Gasperino J. Use of Tris-hydroxymethyl aminomethane in severe lactic acidosis due to highly active antiretroviral therapy: a case report. *Journal of clinical pharmacy and therapeutics*. Feb 2009;34(1):119-123. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19125910>.
29. McComsey G, Loneragan JT. Mitochondrial dysfunction: patient monitoring and toxicity management. *J Acquir Immune Defic Syndr*. Sep 1 2004;37 Suppl 1:S30-35. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15319667>.
30. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr*. Nov 1 2002;31(3):257-275. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12439201>.
31. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. Sep 1 2006;43(5):645-653. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16886161>.

Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Lipodystrophy (fat redistribution)—general information	See below for specific associations.	<u>Onset:</u> Trunk and limb fat initially increases within a few months of start of ART; peripheral fat wasting may not begin to appear for 12 to 24 months.	<u>Adults:</u> 2%–84% <u>Children:</u> 1%–33%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART	See below	See below
Central lipohypertrophy	Can occur in the absence of ART, but most associated with PIs and EFV; EFV also associated with gynecomastia and breast hypertrophy	<u>Presentation:</u> Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Up to 25%	Obesity before initiation of therapy Sedentary lifestyle	<u>Prevention:</u> Calorically appropriate, low-fat diet and exercise. <u>Monitoring:</u> Measure BMI.	Calorically appropriate, low-fat diet and exercise, especially strength training. Smoking cessation (if applicable) to decrease future CVD risk. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: recombinant human growth hormone, growth hormone-releasing hormone, metformin, thiazolidinediones, anabolic steroids, or liposuction.
Facial/peripheral lipoatrophy	Most associated with thymidine analogue NRTI (d4T > ZDV)	<u>Presentation:</u> Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Risk low (up to 15%) in patients not treated with d4T or ZDV	d4T and ZDV Obesity before ART	<u>Prevention:</u> Avoid use of d4T and ZDV. <u>Monitoring:</u> Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Switch from d4T or ZDV to other NRTIs if possible without loss of virologic control. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: injections of poly-L-lactic acid, recombinant human leptin, autologous fat transplantation, or thiazolidinediones.

Key to Acronyms: ARV = antiretroviral, BMI = body mass index, ART = antiretroviral therapy. CVD = cardiovascular disease, d4T = stavudine, DXA = dual energy x-ray absorptiometry, EFV = efavirenz, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, ZDV = zidovudine

References

See the archived version of *Supplement III, February 23, 2009 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, (<http://www.aidsinfo.nih.gov>) for a more complete discussion and reference list.

General Reviews

1. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr*. Oct 2004;145(4):439-444. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15480363>.
2. Lee JM, Davis MM, Woolford SJ, Gurney JG. Waist circumference percentile thresholds for identifying adolescents with insulin resistance in clinical practice. *Pediatric diabetes*. Aug 2009;10(5):336-342. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19175894>.
3. Carr A. Treatment strategies for HIV lipodystrophy. *Curr Opin HIV AIDS*. Jul 2007;2(4):332-338. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19372908>.
4. Phillips DR, Hay P. Current perspectives on the management and prevention of antiretroviral-associated lipodystrophy. *J Antimicrob Chemother*. Nov 2008;62(5):866-871. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18703527>.
5. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. Sep 1 2006;43(5):645-653. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16886161>.
6. Moyle G, Moutschen M, Martinez E, et al. Epidemiology, assessment, and management of excess abdominal fat in persons with HIV infection. *AIDS reviews*. Jan-Mar 2010;12(1):3-14. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20216906>.
7. Dzwonek A, Clapson M, Withey S, Bates A, Novelli V. Severe gynecomastia in an African boy with perinatally acquired human immunodeficiency virus infection receiving highly active antiretroviral therapy. *Pediatr Infect Dis J*. Feb 2006;25(2):183-184. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16462304>.

Associated ARVs/Etiology

8. Chang E, Sekhar R, Patel S, Balasubramanyam A. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. *Clin Infect Dis*. Jun 1 2007;44(11):1509-1517. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17479951>.
9. Dube MP, Komarow L, Mulligan K, et al. Long-term body fat outcomes in antiretroviral-naive participants randomized to nelfinavir or efavirenz or both plus dual nucleosides. Dual X-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. *J Acquir Immune Defic Syndr*. Aug 15 2007;45(5):508-514. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17589373>.
10. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. Jun 1 2009;23(9):1109-1118. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19417580>.
11. Hulgán T, Tebas P, Canter JA, et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipodystrophy during antiretroviral therapy. *J Infect Dis*. Mar 15 2008;197(6):858-866. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18419350>.
12. McComsey GA, Libutti DE, O'Riordan M, et al. Mitochondrial RNA and DNA alterations in HIV lipodystrophy are linked to antiretroviral therapy and not to HIV infection. *Antivir Ther*. 2008;13(5):715-722. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18771055>.

13. Tien PC, Benson C, Zolopa AR, Sidney S, Osmond D, Grunfeld C. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. *American journal of epidemiology*. May 1 2006;163(9):860-869. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16524955>.
14. 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>.
15. Mulligan K, Parker RA, Komarow L, et al. Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. *J Acquir Immune Defic Syndr*. Apr 15 2006;41(5):590-597. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16652032>.
16. Scherzer R, Shen W, Bacchetti P, et al. Comparison of dual-energy X-ray absorptiometry and magnetic resonance imaging-measured adipose tissue depots in HIV-infected and control subjects. *The American journal of clinical nutrition*. Oct 2008;88(4):1088-1096. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18842798>.
17. Benn P, Sauret-Jackson V, Cartledge J, et al. Improvements in cheek volume in lipoatrophic individuals switching away from thymidine nucleoside reverse transcriptase inhibitors. *HIV Med*. Jul 2009;10(6):351-355. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19490181>.

Management

18. Wohl DA, Brown TT. Management of morphologic changes associated with antiretroviral use in HIV-infected patients. *J Acquir Immune Defic Syndr*. Sep 1 2008;49 Suppl 2:S93-S100. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18725818>.
19. Carey DL, Baker D, Rogers GD, et al. A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipoatrophy. *J Acquir Immune Defic Syndr*. Dec 15 2007;46(5):581-589. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18193500>.
20. Cavalcanti RB, Raboud J, Shen S, Kain KC, Cheung A, Walmsley S. A randomized, placebo-controlled trial of rosiglitazone for HIV-related lipoatrophy. *J Infect Dis*. Jun 15 2007;195(12):1754-1761. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17492590>.
21. Falutz J, Allas S, Blot K, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med*. Dec 6 2007;357(23):2359-2370. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18057338>.
22. Gerschenson M, Kim C, Berzins B, et al. Mitochondrial function, morphology and metabolic parameters improve after switching from stavudine to a tenofovir-containing regimen. *J Antimicrob Chemother*. Jun 2009;63(6):1244-1250. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19321503>.
23. Hadigan C. Peroxisome proliferator-activated receptor gamma agonists and the treatment of HIV-associated lipoatrophy: unraveling the molecular mechanism of their shortcomings. *J Infect Dis*. Dec 15 2008;198(12):1729-1731. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18954262>.
24. Lindegaard B, Hansen T, Hvid T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. *The Journal of clinical endocrinology and metabolism*. Oct 2008;93(10):3860-3869. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18628529>.
25. Lo J, You SM, Canavan B, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA*. Aug 6 2008;300(5):509-519. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18677023>.
26. Mulligan K, Khatami H, Schwarz JM, et al. The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipoatrophy and hypoleptinemia. *The Journal of clinical endocrinology and metabolism*. Apr 2009;94(4):1137-1144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19174500>.

27. Tebas P, Zhang J, Hafner R, et al. Peripheral and visceral fat changes following a treatment switch to a non-thymidine analogue or a nucleoside-sparing regimen in HIV-infected subjects with peripheral lipoatrophy: results of ACTG A5110. *J Antimicrob Chemother.* May 2009;63(5):998-1005. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19299471>.
28. Tebas P, Zhang J, Yarasheski K, et al. Switching to a protease inhibitor-containing, nucleoside-sparing regimen (lopinavir/ritonavir plus efavirenz) increases limb fat but raises serum lipid levels: results of a prospective randomized trial (AIDS clinical trial group 5125s). *J Acquir Immune Defic Syndr.* Jun 1 2007;45(2):193-200. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17527093>.
29. Dollfus C, Blanche S, Trocme N, Funck-Brentano I, Bonnet F, Levan P. Correction of facial lipoatrophy using autologous fat transplants in HIV-infected adolescents. *HIV Med.* May 2009;10(5):263-268. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19178590>.
30. Cofrancesco J, Jr., Freedland E, McComsey G. Treatment options for HIV-associated central fat accumulation. *AIDS Patient Care STDS.* Jan 2009;23(1):5-18. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19055407>.
31. Degris E, Delpierre C, Sommet A, et al. Longitudinal study of body composition of 101 HIV men with lipodystrophy: dual-energy X-ray criteria for lipodystrophy evolution. *Journal of clinical densitometry: the official journal of the International Society for Clinical Densitometry.* Apr-Jun 2010;13(2):237-244. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20347366>.
32. Falutz J, Mamputu JC, Potvin D, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *The Journal of clinical endocrinology and metabolism.* Sep 2010;95(9):4291-4304. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20554713>.
33. Ferrer E, del Rio L, Martinez E, et al. Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. *AIDS Res Hum Retroviruses.* Oct 2011;27(10):1061-1065. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21166602>.
34. Negro E, Miro O, Rodriguez-Santiago B, et al. Improvement of mitochondrial toxicity in patients receiving a nucleoside reverse-transcriptase inhibitor-sparing strategy: results from the Multicenter Study with Nevirapine and Kaletra (MULTINEKA). *Clin Infect Dis.* Sep 15 2009;49(6):892-900. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19663689>.
35. Raboud JM, Diong C, Carr A, et al. A meta-analysis of six placebo-controlled trials of thiazolidinedione therapy for HIV lipoatrophy. *HIV Clin Trials.* Jan-Feb 2010;11(1):39-50. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20400410>.
36. Sheth SH, Larson RJ. The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials. *BMC Infect Dis.* 2010;10:183. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20573187>.
37. Tungsiripat M, Bejjani DE, Rizk N, et al. Rosiglitazone improves lipoatrophy in patients receiving thymidine-sparing regimens. *AIDS.* Jun 1 2010;24(9):1291-1298. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20453626>.
38. Spoulou V, Kanaka-Gantenbein C, Bathrellou I, et al. Monitoring of lipodystrophic and metabolic abnormalities in HIV-1 infected children on antiretroviral therapy. *Hormones.* Apr-Jun 2011;10(2):149-155. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21724540>.
39. Minami R, Yamamoto M, Takahama S, Ando H, Miyamura T, Suematsu E. Comparison of the influence of four classes of HIV antiretrovirals on adipogenic differentiation: the minimal effect of raltegravir and atazanavir. *Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy.* Apr 2011;17(2):183-188. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20706762>.

Table 17i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Urolithiasis/nephrolithiasis	IDV, ATV	<u>Onset:</u> Weeks to months after starting therapy <u>Clinical findings:</u> Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	IDV-related nephrolithiasis is more common in adults (4%–43%) than in children (0%–20%). ATV nephrolithiasis rare	In adults, high serum IDV concentrations and elevated urine pH (>5.7) associated with persistent pyuria. Unknown in children.	<u>Prevention:</u> Maintain adequate hydration. <u>Monitoring:</u> Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV agent.
Renal dysfunction	TDF	<u>Onset:</u> Variable; in adults, weeks to months after initiation of therapy. Hypophosphatemia appears at a median of 18 months. <u>Presentation:</u> Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria	<u>Adults:</u> ~2% with increased serum creatinine; ~0.5% with severe renal complications <u>Children:</u> ~4% with hypophosphatemia or proximal tubulopathy; 25% to 78% with severe proteinuria (may be confounded by advanced HIV infection in children studied, and concomitant use of ddl)	Risk may be increased in children aged >6 years, black race, Hispanic/Latino ethnicity, and by advanced HIV infection, concurrent use of ddl or PIs (especially LPV/r), and pre-existing renal dysfunction).	<u>Urinalysis, measurement of serum creatinine, calcium, and phosphorus and determination of spot urine protein/creatinine ratios at least every 6–12 months.</u>	If TDF is the likely cause, consider using alternative medication.
	IDV	Renal cortical atrophy, acute renal failure	Rare	Unknown	Unknown	If IDV is likely cause, consider using alternative medication.

Key to Acronyms: ARV = antiretroviral, ATV = atazanavir, ddl = didanosine, IDV = indinavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate

References

1. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J*. Jul 2009;28(7):619-625. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19561425>.
2. Brennan A, Evans D, Fox M, et al. Renal Insufficiency, Nephrotoxicity, and Mortality among HIV-infected Adults on TDF in a South African Cohort: A Marginal Structural Models Analysis. Abstract 840. 18th Conference on Retroviruses and Opportunistic Infections (CROI); February 27-March 3, 2011; Boston, MA. Available at <http://www.retroconference.org/2011/Abstracts/41417.htm>.
3. Judd A, Boyd KL, Stohr W, et al. Effect of tenofovir disoproxil fumarate on risk of renal abnormality in HIV-1-infected children on antiretroviral therapy: A nested case-control study. *AIDS*. Feb 20 2010;24(4):525-534. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20139752>.
4. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*. Mar 1998;101(3 Pt 1):335-343. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9480994>.
5. Nachman SA, Chernoff M, Gona P, et al. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med*. Feb 2009;163(2):164-171. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19188649>.
6. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J*. Mar 2009;28(3):204-209. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19209091>.
7. Soler-Palacin P, Melendo S, Noguera-Julian A, et al. Prospective study of renal function in HIV-infected pediatric patients receiving tenofovir-containing HAART regimens. *AIDS*. Jan 14 2011;25(2):171-176. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21076275>.
8. van Rossum AM, Dieleman JP, Fraaij PL, et al. Indinavir-associated asymptomatic nephrolithiasis and renal cortex atrophy in two HIV-1 infected children. *AIDS*. Sep 7 2001;15(13):1745-1747. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11546957>.
9. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics*. Aug 2002;110(2 Pt 1):e19. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12165618>.
10. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. May 2011;57(5):773-780. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21435764>.
11. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney international*. Dec 2010;78(11):1171-1177. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20811330>.
12. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis*. Sep 1 2010;51(5):496-505. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20673002>.
13. Vigano A, Bedogni G, Manfredini V, et al. Long-term renal safety of tenofovir disoproxil fumarate in vertically HIV-infected children, adolescents, and young adults: A 60-month follow-up study. *Clin Drug Investig*. 2011;31(6):407-415. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21528939>.
14. Fraaij PL, Verweel G, van Rossum AM, Hartwig NG, Burger DM, de Groot R. Indinavir/low-dose ritonavir containing HAART in HIV-1 infected children has potent antiretroviral activity, but is associated with side effects and frequent discontinuation of treatment. *Infection*. Jun 2007;35(3):186-189. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17565462>.

Table 17j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia, Osteoporosis, Osteonecrosis (page 1 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
Osteopenia and osteoporosis	cART, especially following initiation of cART, regardless of regimen. <u>Specific agents of possible concern:</u> TDF, d4T, and PIs	<u>Onset:</u> Any age; greatest risk in months after initiation of associated ARV. <u>Presentation:</u> Most commonly asymptomatic; fracture (rare). Osteoporosis diagnosis in children requires clinical evidence of bone fragility (e.g., fracture with minimal trauma) and cannot rely solely on measured low BMD.	<u>Low BMD:</u> 20% of children treated with cART had BMD z score < -1.5.	Longer duration of HIV infection Greater severity of HIV disease Growth delay, pubertal delay Low BMI Lipodystrophy Non-black race Smoking Corticosteroid use Medroxyprogesterone use	<u>Prevention:</u> Ensure sufficient calcium and vitamin D intake. Encourage weight-bearing exercise. Minimize modifiable risk factors (smoking, low BMI, steroid use). <u>Monitoring:</u> Assess nutritional intake (calcium, vitamin D, and total calories). Obtain serum 25-OH-vitamin D. ^a Obtain DXA. ^b	Ensure sufficient calcium and vitamin D intake. Encourage weight-bearing exercise. Reduce modifiable risk factors (smoking, low BMI, use of steroids, medroxyprogesterone). Role of bisphosphonates not established in children. Consider change in ARV regimen.
Osteonecrosis	No specific ARV identified; may be related to HIV infection itself.	<u>Onset:</u> Any age <u>Presentation:</u> Limp; hip or other periarticular pain Asymptomatic reported in adults	<u>Prevalence:</u> 0.2% in children <u>Incidence:</u> 0.03% per year in children	<u>Children:</u> Unknown <u>Adults:</u> Steroid use Alcohol abuse Hemoglobinopathies Hyperlipidemia Pancreatitis Osteopenia Osteoporosis Hypercoagulable states	<u>Prevention:</u> Minimize steroid and alcohol use. <u>Monitoring:</u> Consider diagnostic evaluation in patients with unexplained limp, hip or other periarticular pain.	<u>Confirm diagnosis:</u> Obtain plain radiographs and MRI; bone scan or CT if negative x-ray/MRI but clinical suspicion high. <u>Treatment:</u> <i>Early stages:</i> Decrease weight bearing on affected joint and use analgesic. Limited evidence for use of bisphosphonates. <i>Later stages:</i> Consider surgical intervention.

Table 17j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia, Osteoporosis, Osteonecrosis (page 2 of 2) (Last updated November 1, 2012; last reviewed November 1, 2012)

^a Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth because, in this population, the prevalence of vitamin D insufficiency is high.

^b Until more data are available about the long-term effects of tenofovir on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for **prepubertal** children **and children** in early puberty who are initiating treatment with tenofovir. DXA should also be obtained in children with indications not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ARVs = antiretrovirals, BMD = bone mineral density, BMI = body mass index, cART = combination antiretroviral therapy, CT = computed tomography, d4T = stavudine, DXA = dual energy x-ray absorptiometry, MRI = magnetic resonance imaging, PIs = protease inhibitors, TDF = tenofovir disoproxil fumarate

References

Osteopenia and Osteoporosis

1. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. Oct 15 2010;51(8):937-946. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20839968>.
2. Mora S, Sala N, Bricalli D, et al. Bone mineral loss through increased bone turnover in HIV-infected children treated with highly active antiretroviral therapy. *AIDS*. 2001;15(14):1823-1829. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11579244.
3. Mora S, Zamproni I, Beccio S, Bianchi R, Giacomet V, Vigano A. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocr Metab* Jan 2004;89(1):24-28. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14715822>.
4. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*. Dec 2005;116(6):e846-854. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16291735>.
5. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. Sep 2006;118(3):e711-718. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16923923>.
6. Purdy JB, Gafni RI, Reynolds JC, Zeichner S, Hazra R. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr*. Apr 2008;152(4):582-584. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18346519>.
7. Jacobson DL, Lindsey JC, Gordon CM, et al. Total body and spinal bone mineral density across Tanner stage in perinatally HIV-infected and uninfected children and youth in PACTG 1045. *AIDS*. Mar 13 2010;24(5):687-696. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20168204>.
8. Jacobson DL, Spiegelman D, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastr Nutr*. Sep 2005;41(3):339-346. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16131991>.
9. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocr Metab*. Jun 2007;92(6):2087-2099. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17311856>.

10. Bachrach LK, Sills IN, Section on E. Clinical report-bone densitometry in children and adolescents. *Pediatrics*. Jan 2011;127(1):189-194. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21187316>.

Osteonecrosis

11. Gaughan DM, Mofenson LM, Hughes MD, et al. Osteonecrosis of the hip (Legg-Calve-Perthes disease) in human immunodeficiency virus-infected children. *Pediatrics*. May 2002;109(5):E74-74. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11986480>.
12. Glesby MJ. Bone disorders in human immunodeficiency virus infection. *Clin Infect Dis*. 2003;37 Suppl 2(Suppl 2):S91-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12942380>.
13. Morse CG, Mican JM, Jones EC, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. *Clin Infect Dis*. Mar 1 2007;44(5):739-748. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17278070>.
14. Allison GT, Bostrom MP, Glesby MJ. Osteonecrosis in HIV disease: epidemiology, etiologies, and clinical management. *AIDS*. Jan 3 2003;17(1):1-9. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12478064>.

Table 17k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency ^a	Risk Factors	Prevention/Monitoring	Management
ARV toxic neuropathy ^b	d4T, ddl	<p>Onset: Variable, weeks to months following NRTI initiation</p> <p>Presentation: Decreased sensation Aching, burning, painful numbness Hyperalgesia (lowered pain threshold) Allodynia (non-noxious stimuli cause pain) Decreased or absent ankle reflexes Distribution: bilateral soles of feet, ascending to legs and fingertips</p>	<p>HIV-infected children: 1.13% prevalence (baseline 2001); 0.23 per 100 person-years (2001–2006)</p> <p>0.07%–0.26% incidence in two large African cohorts (aged 1 month–18 years, median follow-up 1.8–3.2 years)</p> <p>HIV-infected adults: 17%–57% taking d4T</p>	<p>HIV-infected adults: Pre-existing neuropathy (diabetes, alcohol abuse, vitamin B₁₂ deficiency)</p> <p>Elevated triglyceride levels</p> <p>Older age</p> <p>Poor nutrition</p> <p>More advanced HIV disease</p> <p>Mitochondrial DNA haplogroup</p>	<p>Limit use of d4T and ddl, if possible.</p> <p>As part of routine care, monitor for symptoms and signs of peripheral neuropathy.</p>	<p>Discontinue offending agent.</p> <p>Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful. Data are insufficient to allow the Panel to safely recommend use of any of the following modalities in children: tricyclic antidepressants, gabapentin, pregabalin, mexilitine, or lamotrigine.</p>

^a Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

^b HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

Key to Acronyms: ARV = antiretroviral, d4T = stavudine, ddl = didanosine, NRTI = nucleoside reverse transcriptase inhibitor

References

- Nachman SA, Chernoff M, Gona P, et al. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med.* Feb 2009;163(2):164-171. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19188649>.
- 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>.

3. Keswani SC, Pardo CA, Cherry CL, Hoke A, McArthur JC. HIV-associated sensory neuropathies. *AIDS*. Nov 8 2002;16(16):2105-2117. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12409731>.
4. Ances BM, Vaida F, Rosario D, et al. Role of metabolic syndrome components in HIV-associated sensory neuropathy. *AIDS*. Nov 13 2009;23(17):2317-2322. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19823068>.
5. Banerjee S, McCutchan JA, Ances BM, et al. Hypertriglyceridemia in combination antiretroviral-treated HIV-positive individuals: potential impact on HIV sensory polyneuropathy. *AIDS*. Jan 14 2011;25(2):F1-6. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21150557>.
6. Canter JA, Robbins GK, Selph D, et al. African mitochondrial DNA subhaplogroups and peripheral neuropathy during antiretroviral therapy. *J Infect Dis*. Jun 1 2010;201(11):1703-1707. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20402593>.
7. McCormack PL. Capsaicin dermal patch: in non-diabetic peripheral neuropathic pain. *Drugs*. Oct 1 2010;70(14):1831-1842. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20836576>.
8. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. *PLoS One*. 2010;5(12):e14433. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21203440>.
9. Menezes CN, Maskew M, Sanne I, Crowther NJ, Raal FJ. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. *BMC Infect Dis*. 2011;11:244. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21923929>.
10. Wadley AL, Cherry CL, Price P, Kamerman PR. HIV neuropathy risk factors and symptom characterization in stavudine-exposed South Africans. *Journal of Pain and Symptom Management*. Apr 2011;41(4):700-706. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21145196>.
11. Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr*. Mar 1 2012;59(3):274-280. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22126740>.

Table 17I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 1 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash.	<p>Onset: First few days to weeks after starting therapy</p> <p>Presentation: Most rashes are mild-to-moderate, diffuse maculopapular eruptions.</p> <p>Some rashes are a manifestation of systemic hypersensitivity (see also HSR).</p>	<p>Common (>10% adults and/or children): NVP, EFV, ETR, FPV, ATV, FTC</p> <p>Less common (5%–10%): ABC, DRV, TPV, TDF</p> <p>Unusual (2%–4%): LPV/r, RAL, MVC, RPV</p>	<ul style="list-style-type: none"> Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, TPV). Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP. 	<ul style="list-style-type: none"> When starting NVP or restarting after interruptions >14 days: Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.^a Avoid use of corticosteroids during NVP dose escalation. Assess patient for concomitant medications and illnesses that cause rash, rash severity, mucosal involvement, and presence of systemic signs and symptoms (see also HSR). 	<p><i>Mild-to-moderate maculopapular rash without systemic or mucosal involvement:</i></p> <p>Prescribe antihistamine as needed; ARV medication can be continued.^a</p> <p><i>Severe rash (accompanied by blisters, fever, involvement of the mucous membranes, conjunctivitis, edema, arthralgias):</i></p> <ul style="list-style-type: none"> Discontinue all ARVs and other possible causative agents such as cotrimoxazole. Do not restart the offending medication. (See SJS/EM/TEN.) In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs. <p>If rash develops with NVP treatment, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity).</p>
	ENF	<p>Onset: First few days to weeks after starting therapy</p> <p>Presentation: Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.</p>	Adults and children: >90%	Unknown	<ul style="list-style-type: none"> During routine visits, assess patient for local reactions. Rotate injection sites. Massage area after injection. 	<ul style="list-style-type: none"> Continue the agent as tolerated by the patient. Adjust injection technique. Rotate injection sites.

Table 17I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 2 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
SJS/EM major/TEN	Many ARVs, especially NNRTIs (see frequency column)	<p>Onset: First few days to weeks after initiating therapy</p> <p>Presentation: Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bulla formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia.</p>	<p>Infrequent: NVP (0.3%), EFV (0.1%), ETR (<0.1%)</p> <p>Case reports: FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL</p>	<p>Adults:</p> <ul style="list-style-type: none"> • Female gender • Race/ethnicity (black, Asian, Hispanic) 	<ul style="list-style-type: none"> • <i>When starting NVP or restarting after interruptions >14 days:</i> Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.^a • Counsel families to report symptoms as soon as they appear. 	<ul style="list-style-type: none"> • Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used but use of each is controversial. • Do not reintroduce the offending medication. • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs.
Systemic HSR (with or without skin involvement and excluding SJS)	ABC	<p>Onset: <i>With first use:</i> within first 6 weeks <i>With reintroduction:</i> within hours</p> <p>Presentation: Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis.</p>	2.3%–9% (varies by racial/ethnic group)	<ul style="list-style-type: none"> • HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701 negative); also HLA-DR7, HLA-DQ3. • Whites are at much greater risk of HSR than blacks or Asians. 	<ul style="list-style-type: none"> • Screen for HLA- B*5701. ABC should not be prescribed if HLA-B*5701 is positive. The medical record should clearly indicate that the patient is ABC allergic. • Counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions. 	<ul style="list-style-type: none"> • Discontinue ARVs and investigate for other causes of the symptoms, such as an intercurrent viral illness. • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.

Table 17I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 3 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Systemic HSR (with or without skin involvement and excluding SJS)	NVP	<p><u>Onset:</u> Most frequent in the first few weeks of therapy but can occur through 18 weeks.</p> <p><u>Presentation:</u> Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy.</p> <p>DRESS syndrome has also been described.</p>	4% (2.5%–11%)	<p><u>Adults:</u></p> <ul style="list-style-type: none"> • Treatment-naïve with higher CD4 count (>250 cells/mm³ in women; >400 cells/mm³ in men). • Female gender (Risk is 3-fold higher in females compared with males.) <p><u>Children:</u> NVP hepatotoxicity and hypersensitivity are less common in prepubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 <15%.</p>	<ul style="list-style-type: none"> • 2-week lead-in period for start or restart for interruptions >14 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.^a • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • Obtain AST and ALT in patients with rash. Obtain AST and ALT at baseline, before dose escalation, 2 weeks post dose escalation, and thereafter at 3-month intervals. • Avoid NVP use in women with CD4 counts >250 cells/mm³ and in men with CD4 counts >400 cells/mm³ unless benefits outweigh risks. • Do not use NVP in postexposure prophylaxis. 	<ul style="list-style-type: none"> • Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor patient closely. • Do not reintroduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

Table 17I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (page 4 of 4) (Last updated November 1, 2012; last reviewed November 1, 2012)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Systemic HSR (with or without skin involvement and excluding SJS)	ENF, ETR	<p><u>Onset:</u> Any time during therapy.</p> <p><u>Presentation:</u> Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.</p>	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue ARVs. Rechallenge is not recommended.
	RAL	DRESS syndrome	Case report	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARVs. Rechallenge with RAL is not recommended.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.	Discontinue all ARVs. Rechallenge with MVC is not recommended.

^a The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of subtherapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. NVP should be stopped if the rash is severe or is worsening or progressing.

Key to Acronyms: ABC = abacavir, ALT = alanine transaminase, ARVs = antiretrovirals, AST = aspartate aminotransferase, ATV = atazanavir, ddl = didanosine, DRESS = drug rash with eosinophilia and systemic symptoms, DRV = darunavir, EFV = efavirenz, EM = erythema multiforme, ENF = enfuvirtide, ETR = etravirine, FPV = fosamprenavir, FTC = emtricitabine, HSR = hypersensitivity reaction, IDV = indinavir, IV = intravenous, IVIG = intravenous immune globulin, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, SJS = Stevens Johnson syndrome, TDF = tenofovir disoproxil fumarate, TEN = toxic epidermal necrolysis, TPV = tipranavir, ZDV = zidovudine

References

1. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. Abstract 776. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston, MA. Available at: <http://www.retroconference.org/2005/cd/PDFs/776.pdf>.

2. Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Castera E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J Antimicrob Chemother*. Nov 2008;62(5):879-888. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18653488>.
3. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet*. Oct 21 2000;356(9239):1423-1430. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11052597>.
4. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. *J Allergy Clin Immunol*. Apr 2008;121(4):826-832 e825. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18190954>.
5. Kea C, Puthanakit T, Apornpong 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. Abstract MOPE240. Paper presented at: 6th International AIDS Society Conference on HIV Pathogenesis and Treatment and Prevention; July, 2011; Rome, Italy. Available at <http://pag.ias2011.org/abstracts.aspx?aid=3248>.
6. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359(9308):727-732. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11888582.
7. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. Feb 7 2008;358(6):568-579. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18256392>.
8. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clinical pharmacokinetics*. Oct 2000;39(4):281-293. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11069214>.
9. 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>.
10. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology*. 2003;206(4):353-356. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12771485>.
11. Trottier B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. *J Acquir Immune Defic Syndr*. Dec 1 2005;40(4):413-421. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16280695>.
12. Vitezica ZG, Milpied B, Lonjou C, et al. HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS*. Feb 19 2008;22(4):540-541. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18301070>.
13. Yuan J, Guo S, Hall D, et al. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. *AIDS*. Jun 19 2011;25(10):1271-1280. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21505298>.