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

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Panel’s Recommendations

- In children who have severe or life-threatening toxicity, all components of their drug regimen should be stopped immediately (All). 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) (All*).

- 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 (All*).

- 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 (All).

- 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 (All*).

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

Rating of Evidence: I = One or more randomized trials in children\(^1\) 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\(^1\) 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\(^1\) 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\(^1\) from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

\(^1\) Studies that include children or children and adolescents but not studies limited to postpubertal adolescents
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. 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. 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. 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


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<th>Adverse Effects</th>
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<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
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<tr>
<td>Global CNS depression</td>
<td>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</td>
<td>Onset: 1–6 days after starting LPV/r&lt;br&gt;Presentation: Neonates/preterm infants: global CNS depression, cardiac toxicity, respiratory complications</td>
<td>Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates</td>
<td>Prematurity&lt;br&gt;Low birth weight&lt;br&gt;Age &lt;14 days (whether premature or term)</td>
<td>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.</td>
<td>Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period.</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms and other CNS manifestations</td>
<td>EFV</td>
<td>Onset: 1–2 days after initiating treatment&lt;br&gt;Most symptoms subside or diminish by 2–4 weeks (but may persist in a minority of patients)&lt;br&gt;Presentation: May include one or more of the following: dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, suicidal ideation, seizures (including absence seizures)</td>
<td>Variable, depending on age, symptom, assessment method&lt;br&gt;Children: 24% for any EFV-related CNS manifestations in one case series with 18% requiring drug discontinuation&lt;br&gt;Adults: &gt;50% for any CNS manifestations of any severity&lt;br&gt;2% for EFV-related severe CNS manifestations</td>
<td>Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL&lt;br&gt;Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype)&lt;br&gt;Prior history of psychiatric illness or use of psychoactive drugs</td>
<td>Administer EFV on an empty stomach, preferably at bedtime.&lt;br&gt;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).</td>
<td>Provide reassurance about the likely time-limited nature of symptoms.&lt;br&gt;Consider EFV trough level if symptoms excessive or persistent. If EFV trough level &gt;4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug discontinuation.</td>
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### 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)*

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</table>
| Increased psychomotor activity, headaches, insomnia, depression | RAL | Presentation: Increased psychomotor activity, headaches, insomnia, depression | Children: Psychomotor activity reported in one child  
Adults: 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 | Onset: 7–513 days after starting TPV | Children: No cases of ICH reported in children  
Adults: 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 | Onset: As early as 3 days after starting RAL  
Presentation: 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


<table>
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<tr>
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<tr>
<td>Dyslipidemia</td>
<td>PIs: All PIs; lower incidence with ATV and DRV</td>
<td>Onset: Weeks to months after beginning therapy</td>
<td>20%–50% of children receiving ART will have lipoprotein abnormalities.</td>
<td>HIV infection, High-fat, high-cholesterol diet, Lack of exercise, Obesity, Hypertension, Smoking, Family history of dyslipidemia or premature CVD, Metabolic syndrome</td>
<td>Prevention: Low-fat diet, exercise, no smoking  Monitoring: Adolescents and adults: 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. Children (aged ≤2 years) without lipid abnormalities or additional risk factors: Obtain non-fasting screening lipid profiles before initiating or changing therapy and every 6 months thereafter (or more often if indicated). Children with lipid abnormalities and/or additional risk factors: 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). Children receiving lipid-lowering therapy with statins or fibrates: 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.</td>
<td>Counsel lifestyle modification (low-fat diet, exercise, smoking cessation) for adequate trial period (3–6 months). Switch to a new ART regimen less likely to cause lipid abnormalities. Pharmacologic Management: Initiate drug therapy promptly in patients with TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin. Ezetimibe may be considered in addition to statins. 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. No consensus as to what LDL-C should prompt treatment in children receiving ARVs. HIV-infected patients are considered to be at moderate risk of CVD. Assessment of additional risk factors should be done in all patients. High-risk patients: Goal LDL-C ≤100 mg/dL. Moderate-risk patients: Goal LDL-C ≤130 mg/dL. At-risk patients: Goal LDL-C ≤160 mg/dL.</td>
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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.

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.

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.

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.


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


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<tbody>
<tr>
<td>Nausea/ Vomiting</td>
<td>Principally ZDV and PIs (such as LPV/r, RTV) but can occur with all ARVs</td>
<td>Onset: Early Presentation: Nausea, emesis—may be associated with anorexia and/or abdominal pain</td>
<td>Varies with ARV agent. 10%–30% in some series.</td>
<td>Unknown</td>
<td>Instruct patient to take PIs with food. Generally improves with time; monitor for weight loss, ARV adherence.</td>
<td>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.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>PIs (NFV, LPV/r, FPV/r), buffered ddl</td>
<td>Onset: Early Presentation: Generally soft, more frequent stools</td>
<td>Varies with ARV agent. 10%–30% in some series.</td>
<td>Unknown</td>
<td>Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.</td>
<td>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.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ddl (especially with concurrent d4T or TDF); reported, albeit rarely, with most ARVs</td>
<td>Onset: Any time, usually after months on therapy Presentation: Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)</td>
<td>&lt;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</td>
<td>Avoid use of ddl in patients with history of pancreatitis.</td>
<td>Discontinue offending agent. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.</td>
<td></td>
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</tbody>
</table>

**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


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

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</thead>
<tbody>
<tr>
<td>Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Principally ZDV</td>
<td>Onset: Variable</td>
<td>HIV-exposed newborns: Rare</td>
<td>HIV-exposed newborns: In utero exposure to ARVs</td>
<td>HIV-infected children on ARVs: Concurrent ZDV + 3TC neonatal prophylaxis</td>
<td>HIV-exposed newborns: No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC &lt;500 cells/μL, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see Perinatal Guidelines&lt;sup&gt;b&lt;/sup&gt;).&lt;br&gt;&lt;br&gt;HIV-infected children on ARVs: Discontinue non-ARV marrow-toxic drugs if feasible.&lt;br&gt;&lt;br&gt;Treat coexisting OIs, malignancies.&lt;br&gt;&lt;br&gt;For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of G-CSF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation: Most commonly asymptomatic</td>
<td>HIV-infected children on ARVs: 9.9%–26.8% of children on ARVs, depending upon the ARV regimen</td>
<td>HIV-infected children on ARVs: Advanced or poorly controlled HIV infection</td>
<td>HIV-infected children on ARVs: Monitor CBC 3–4 times per year as part of routine care.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Highest rates with ZDV-containing regimens</td>
<td>Myelosuppressive drugs (such as TMP-SMX, ganciclovir, hydroxyurea, rifabutin)</td>
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<sup>a</sup> HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

<sup>b</sup> 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


**Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events**

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

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

* 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


### 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*

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

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**Key to Acronyms:**
- ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, d4T = stavudine, ddl = 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

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*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.*
References

Clinical features of hyperglycemia, insulin resistance, and diabetes mellitus


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### Management of hyperglycemia, insulin resistance, and diabetes mellitus


**Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis**

_Last updated November 1, 2012; last reviewed November 1, 2012_

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention / Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>NRTIs, in particular, d4T and ddI (alone and in combination)</td>
<td>Onset: 1–20 months after starting therapy (median onset 4 months in 1 case series). Presentation: 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.</td>
<td>Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L); Adults: 15%–35% of adults receiving NRTI therapy for longer than 6 months; Children: 29%–32%; Symptomatic severe hyperlactatemia (&gt;5.0 mmol/L); Adults: 0.2%–5.7%; Symptomatic lactic acidosis/hepatic steatosis: Rare in all age groups (1.3–11 episodes per 1,000 person-years), but associated with a high fatality rate (33%–58%)</td>
<td>Adults: • 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)  • Coadministration of TDF with metformin  • Overdose of propylene glycol  • CD4 T lymphocyte count &lt;350 cells/mm³  • Acquired riboflavin or thiamine deficiency  • Possibly, pregnancy  Pre-term infants:  • Use of propylene glycol (e.g., as an diluent for LPV/r)</td>
<td>Prevention: Avoid d4T and ddI in combination.  Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.  Monitoring: Asymptomatic: Measurement of serum lactate is not recommended.  Clinical signs or symptoms consistent with lactic acidosis: Obtain blood lactate level; additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.  Anecdotal (unproven) supportive therapies: bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C).  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.</td>
<td>Lactate 2.1–5.0 mmol/L (confirmed with second test): Consider replacing ddI and d4T with other ARVs.  As alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.  Lactate &gt;5.0 mmol/L (confirmed with second test) or &gt;10.0 mmol/L (any one test): 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).  Anecdotal (unproven) supportive therapies: bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C).  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.</td>
</tr>
</tbody>
</table>
**References**

**General Reviews**


**Risk Factors**


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*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, ddl = 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.


Monitoring and Management


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

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention / Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipodystrophy (fat redistribution)—general information</td>
<td>See below for specific associations.</td>
<td>Onset: 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.</td>
<td>Adults: 2%–84%</td>
<td>Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART</td>
<td>See below</td>
<td>See below</td>
</tr>
<tr>
<td>Central lipohypertrophy</td>
<td>Can occur in the absence of ART, but most associated with PIs and EFV; EFV also associated with gynaecomastia and breast hypertrophy</td>
<td>Presentation: Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynaecomastia in males or breast hypertrophy in females. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).</td>
<td>Up to 25%</td>
<td>Obesity before initiation of therapy Sedentary lifestyle</td>
<td>Prevention: Calorically appropriate, low-fat diet and exercise. Monitoring: Measure BMI.</td>
<td>Calorically appropriate, low-fat diet and exercise, especially strength training. Smoking cessation (if applicable) to decrease future CVD risk.</td>
</tr>
<tr>
<td>Facial/peripheral lipoatrophy</td>
<td>Most associated with thymidine analogue NRTI (d4T &gt; ZDV)</td>
<td>Presentation: 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.</td>
<td>Risk low (up to 15%) in patients not treated with d4T or ZDV d4T and ZDV Obesity before ART</td>
<td>Prevention: Avoid use of d4T and ZDV. Monitoring: Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

**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

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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](http://www.aidsinfo.nih.gov) for a more complete discussion and reference list.

**General Reviews**


**Associated ARVs/Etiology**


**Management**


<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention / Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Urolithiasis/ nephrolithiasis         | IDV, ATV        | Onset: Weeks to months after starting therapy  
Clinical findings: Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine  
ATV nephrolithiasis rare | 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.  
Monitoring: Obtain urinalysis at least every 6–12 months. | Provide adequate hydration and pain control; consider using alternative ARV agent. |

Renal dysfunction

| TDF | Variable; in adults, weeks to months after initiation of therapy, Hypophosphatemia appears at a median of 18 months.  
Presentation: Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria  
25% to 78% with severe proteinuria (may be confounded by advanced HIV infection in children studied, and concomitant use of ddI) | Risk may be increased in children aged >6 years, black race, Hispanic/Latino ethnicity, and by advanced HIV infection, concurrent use of ddI or PIs (especially LPV/r), and pre-existing renal dysfunction. | Urinalysis, measurement of serum creatinine, calcium, and phosphorus and determination of spot urine protein/creatinine ratios at least every 6–12 months. | 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, ddI = didanosine, IDV = indinavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate
References


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## 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)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention / Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteonecrosis</td>
<td>No specific ARV identified; may be related to HIV infection itself.</td>
<td>Onset: Any age Presentation: Limp; hip or other periarticular pain Asymptomatic reported in adults</td>
<td>Prevalence: 0.2% in children Incidence: 0.03% per year in children</td>
<td>Children: Unknown Adults: Steroid use Alcohol abuse Hemoglobinopathies Hyperlipidemia Pancreatitis Osteopenia Osteoporosis Hypercoagulable states</td>
<td>Prevention: Minimize steroid and alcohol use. Monitoring: Consider diagnostic evaluation in patients with unexplained limp, hip or other periarticular pain.</td>
<td>Confirm diagnosis: Obtain plain radiographs and MRI; bone scan or CT if negative x-ray/MRI but clinical suspicion high. Treatment: Early stages: Decrease weight bearing on affected joint and use analgesic. Limited evidence for use of bisphosphonates. Later stages: Consider surgical intervention.</td>
</tr>
</tbody>
</table>
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


**Osteonecrosis**


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

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| ARV toxic neuropathy<sup>b</sup> | d4T, ddI | Onset: Variable, weeks to months following NRTI initiation  
Presentation: Decreased sensation  
Aching, burning, painful numbness  
Hyperalgesia (lowered pain threshold)  
Alloodynia (non-noxious stimuli cause pain)  
Decreased or absent ankle reflexes  
Distribution: bilateral soles of feet, ascending to legs and fingertips | HIV-infected children: 1.13% prevalence (baseline 2001); 0.23 per 100 person-years (2001–2006)  
HIV-infected adults: Pre-existing neuropathy (diabetes, alcohol abuse, vitamin B12 deficiency)  
Elevated triglyceride levels  
Older age  
Poor nutrition  
More advanced HIV disease  
Mitochondrial DNA haplogroup | Limit use of d4T and ddI, if possible.  
As part of routine care, monitor for symptoms and signs of peripheral neuropathy. | Discontinue offending agent.  
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. |

<sup>a</sup> Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

<sup>b</sup> HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

**Key to Acronym s:** ARV = antiretroviral, d4T = stavudine, ddI = didanosine, NRTI = nucleoside reverse transcriptase inhibitor

**References**


### Table 17l. 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)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Rash           | Any ARV can cause rash. | Onset: First few days to weeks after starting therapy  
Presentation: Most rashes are mild-to-moderate, diffuse maculopapular eruptions.  
Some rashes are a manifestation of systemic hypersensitivity (see also HSR). | Common (>10% adults and/or children): NVP, EFV, ETR, FPV, ATV, FTC  
Less common (5%–10%): ABC, DRV, TPV, TDF  
Unusual (2%–4%): LPV/r, RAL, MVC, RPV | • 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.  
• 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.  
• 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). | • During routine visits, assess patient for local reactions.  
• Rotate injection sites.  
• Massage area after injection.  
• Continue the agent as tolerated by the patient.  
• Adjust injection technique.  
• Rotate injection sites. | Mild-to-moderate maculopapular rash without systemic or mucosal involvement:  
Prescribe antihistamine as needed; ARV medication can be continued.  
Severe rash (accompanied by blisters, fever, involvement of the mucous membranes, conjunctivitis, edema, arthralgias):  
• 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.  
If rash develops with NVP treatment, measure hepatic transaminases. If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity). |

ENF  
Onset: First few days to weeks after starting therapy  
Presentation: Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.  
Adults and children: >90%  
Unknown | • During routine visits, assess patient for local reactions.  
• Rotate injection sites.  
• Massage area after injection. | • Continue the agent as tolerated by the patient.  
• Adjust injection technique.  
• Rotate injection sites. |
### Table 17l. 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)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
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<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS/EM major/TEN</td>
<td>Many ARVs, especially NNRTIs (see frequency column)</td>
<td>Onset: First few days to weeks after initiating therapy</td>
<td>Infrequent: NVP (0.3%), EFV (0.1%), ETR (&lt;0.1%)</td>
<td>Adults: • Female gender • Race/ethnicity (black, Asian, Hispanic)</td>
<td>When starting NVP or restarting after interruptions &gt;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. • Counsel families to report symptoms as soon as they appear.</td>
<td>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.</td>
</tr>
<tr>
<td>Systemic HSR (with or without skin involvement and excluding SJS)</td>
<td>ABC</td>
<td>Onset: With first use: within first 6 weeks With reintroduction: within hours 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.</td>
<td>2.3%–9% (varies by racial/ethnic group)</td>
<td>HLA-B<em>5701 (HSR very uncommon in people who are HLA-B</em>5701 negative); also HLA-DR7, HLA-DQ3. • Whites are at much greater risk of HSR than blacks or Asians. Screen for HLA- B<em>5701. ABC should not be prescribed if HLA-B</em>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.</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 171. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash, SJS/EM/TEN, HSR (Last updated November 1, 2012; last reviewed November 1, 2012)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
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</tr>
</thead>
</table>
| Systemic HSR (with or without skin involvement and excluding SJS) | NVP | **Onset:** Most frequent in the first few weeks of therapy but can occur through 18 weeks. **Presentation:** 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. DRESS syndrome has also been described. | 4% (2.5%–11%) | Adults:  
• 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.)  

Children:  
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%. | • 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.  
• 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. | • 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 171. 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)

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

* 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, ddI = 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**


