Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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**Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity** *(Last updated April 27, 2017; last reviewed April 27, 2017)*

<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>
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</table>
| Global CNS Depression  
  Depression  
  Neonates/Premature Infants:  
  Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)  
  Onset:  
  • 1–6 days after starting LPV/r  
  Presentation  
  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 ≥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 (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days). |
| Neuropsychiatric Symptoms and Other CNS Manifestations  
  Onset:  
  • 1–2 days after initiating treatment for many symptoms  
  • Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% experienced persistent symptoms at 12 months and in another, half of discontinuations occurred after 12 months.  
  Presentation (May Include One or More of the Following)  
  Neuropsychiatric Symptoms:  
  • Abnormal dreams  
  • Psychosis  
  • Suicidal ideation or attempted/completed suicide  
  Other CNS Manifestations:  
  • Dizziness  
  • Somnolence  
  • Insomnia or poor sleep quality  
  • Impaired concentration  
  • Seizures (including absence seizures)  
  Variable, depending on age, symptom, assessment method  
  Children:  
  • 24% for any EFV-related CNS manifestations in 1 case series with 18% requiring drug discontinuation  
  • 9% incidence of new-onset seizures reported in 1 study in children aged <36 months. In 2 of the children the seizures had alternative causes.  
  • Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels.  
  Adults:  
  • 30% incidence for any CNS manifestations of any severity.  
  • 6% incidence for EFV-related severe CNS manifestations including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.  
  Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL  
  Presence of CYP450 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 TT genotype or co-circus of CYP2B6 516 G/T and 983 T/C variants)  
  Prior history of psychiatric illness or use of psychoactive drugs  
  Administer EFV on an empty stomach, preferably at bedtime.  
  Prescreen for and avoid use in the presence of psychiatric illness including depression or suicidal thoughts or with concomitant use of psychoactive drugs.  
  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).  
  Obtain EFV trough concentration if symptoms excessive or persistent. If EFV trough concentration ≥4 mcg/mL, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).  
  In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time. | EFV |
Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 3)

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</thead>
<tbody>
<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td>• Cerebellar dysfunction (tremor, dysmetria, ataxia)</td>
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<td>Note: Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.</td>
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<td>RPV</td>
<td>Presentation&lt;br&gt;Neuropsychiatric Symptoms: • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares Other CNS Manifestations: • Headache • Dizziness • Insomnia • Somnolence</td>
<td>In Adults: • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (mostly Grade 1). Depressive disorders of all severity grades were reported in 9% of patients, and were severe requiring RPV discontinuation in 1% of patients. In Children: • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years to 17 years. Severe depressive disorders were reported in 5.6% of patients, including a suicide attempt in 1 subject. • Somnolence reported in 5/36 (14%) children.</td>
<td>Prior history of neuropsychiatric illness</td>
<td>Monitor carefully for depressive disorders and other CNS symptoms.</td>
<td>Consider drug substitution in case of severe symptoms.</td>
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<td>RAL</td>
<td>Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)</td>
<td>Children: • Increased psychomotor activity reported in one child. Adults: • Headache • Insomnia (&lt;5% in adult trials) • Rare case reports of cerebellar dysfunction in adults</td>
<td>Elevated RAL concentrations Co-treatment with TDF or PPI or inhibitors of UGT1A1 Prior history of insomnia or depression</td>
<td>Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.</td>
<td>Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.</td>
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</tbody>
</table>
### Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (page 3 of 3)

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<td>DTG</td>
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<td>Onset:</td>
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<td></td>
<td></td>
<td>• 7–30 days after initiating drug</td>
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<td></td>
<td>Presentation</td>
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<td></td>
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<td>Neuropsychiatric Symptoms:</td>
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<td></td>
<td></td>
<td>• Depression or exacerbation of preexisting depression</td>
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<td></td>
<td></td>
<td>• Anxiety</td>
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<td></td>
<td></td>
<td>• Suicidal ideation attempt, behavior, or completion</td>
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<td>Other CNS Manifestations (Generally Mild):</td>
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<td></td>
<td></td>
<td>• Insomnia</td>
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<td></td>
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<td>• Dizziness</td>
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<td></td>
<td></td>
<td>• Headache</td>
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<td>Intracranial Hemorrhage</td>
<td>TPV</td>
<td>Onset:</td>
<td>• 7–513 days after starting TPV</td>
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<td>Children:</td>
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<td>• No cases of ICH reported in children.</td>
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<td>Adults:</td>
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<td>• In premarket approval data in adults, 0.23/100 py or 0.04–0.22/100 py in a retrospective review of 2 large patient databases.</td>
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<td>Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported.</td>
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**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; PPI = proton pump inhibitor; py = patient years; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucurononyl transferase

**References**


