### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  
**(Last updated April 16, 2019; last reviewed April 16, 2019)** (page 1 of 3)

<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><strong>Global CNS Depression</strong></td>
<td>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</td>
<td><strong>Onset:</strong></td>
<td><strong>Unknown; rare case reports have been published</strong></td>
<td>Prematurity</td>
<td>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days.</td>
<td>Discontinue LPV/r; symptoms should resolve in 1 day–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).</td>
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<td></td>
<td><strong>Presentation</strong></td>
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<td><strong>Neonates/Premature Infants:</strong></td>
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<td></td>
<td></td>
<td>• Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)</td>
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<td></td>
<td></td>
<td><strong>Neuropsychiatric Symptoms and Other CNS Manifestations</strong></td>
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<td>EFV</td>
<td><strong>Onset:</strong></td>
<td>Variable, depending on age, symptoms, and assessment method</td>
<td>Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL)</td>
<td>Administer EFV on an empty stomach, preferably at bedtime.</td>
<td>If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration &gt;4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if a suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).</td>
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<td><strong>Children:</strong></td>
<td>• 24% for any EFV-related CNS manifestations in one case series, with 18% of participants requiring drug discontinuation.</td>
<td>CYP2B6 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 TT genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants)</td>
<td>Prior history of psychiatric illness or use of psychoactive drugs.</td>
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<td>• 5 of 45 participants (11%) experienced new-onset seizures in one study in children aged &lt;36 months. Two of these participants had alternative causes for seizures.</td>
<td>• 6% incidence for EFV-related, severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.</td>
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<td>Consider using TDM in children with mild or moderate EFV-associated toxicities</td>
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<td>• Cases of cerebellar dysfunction have been reported in children with very high EFV plasma levels.</td>
<td>• One case series reported 20 women with ataxia that resolved upon EFV discontinuation, but frequency was not reported.</td>
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<td><strong>Adults:</strong></td>
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<td></td>
<td>• Dizziness</td>
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<td>• Somnolence</td>
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<td></td>
<td></td>
<td>• Insomnia or poor sleep quality</td>
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<td></td>
<td></td>
<td>• Impaired concentration</td>
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<td></td>
<td></td>
<td>• Seizures (including absence seizures)</td>
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<td></td>
<td></td>
<td>• Cerebellar dysfunction (tremor, dysmetria, ataxia)</td>
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<td><strong>Note:</strong> CNS side effects such as impaired concentration, abnormal dreams, or sleep disturbances may be more difficult to assess in children.</td>
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Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  (Last updated April 16, 2019; last reviewed April 16, 2019)  (page 2 of 3)

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</table>
| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | RPV | Onset:  
Most symptoms occur in the first 4 weeks–8 weeks of treatment  
**Presentation**  
**Neuropsychiatric Symptoms:**  
Depressive disorders  
Suicidal ideation  
Abnormal dreams/nightmares  
**Other CNS Manifestations:**  
Headache  
Dizziness  
Insomnia  
Somnolence | 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. One percent of patients discontinued RPV due to severe depressive disorders.  
**Children:**  
Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt.  
Somnolence was reported in five of 36 children (14%). | Prior history of neuropsychiatric illness | Monitor carefully for depressive disorders and other CNS symptoms. | Consider drug substitution in cases of severe symptoms. |
| | RAL | Onset:  
As early as 3 days–4 days after starting RAL  
**Presentation:**  
Increased psychomotor activity  
Headaches  
Insomnia  
Depression  
Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia) | Children:  
Increased psychomotor activity was reported in one child.  
**Adults:**  
Headache  
Insomnia (<5% in adult trials)  
Rare case reports of cerebellar dysfunction in adults  
**Elevated RAL concentrations**  
Co-treatment with TDF, a PPI, or inhibitors of UGT1A1  
Prior history of insomnia or depression | Prescreen for psychiatric symptoms.  
Monitor carefully for CNS symptoms.  
Use with caution in the presence of drugs that increase RAL concentration. | Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms. |
### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  *(Last updated April 16, 2019; last reviewed April 16, 2019)*  (page 3 of 3)

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<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</td>
<td>DTG</td>
<td>Onset: 7 days–30 days after starting DTG</td>
<td>Neuropsychiatric Symptoms: Depression or exacerbation of preexisting depression</td>
<td>Pre-existing depression or other psychiatric illness</td>
<td>Use with caution in the presence of psychiatric illness; consider discontinuation of DTG if suitable alternative exists.</td>
<td>For persistent or severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</td>
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<td>Presentation</td>
<td>Anxiety</td>
<td>Higher frequency of neuropsychiatric symptoms reported when coadministered with ABC; however, evidence is conflicting.</td>
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<td>Neuropsychiatric Symptoms:</td>
<td>Suicidal ideation or attempted/completed suicide</td>
<td>UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)</td>
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<td>Other CNS Manifestations (Generally Mild):</td>
<td>Insomnia</td>
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<td>Dizziness</td>
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<td></td>
<td>Headache</td>
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**Key to Acronyms:**  
- ABC = abacavir  
- ARV = antiretroviral  
- CNS = central nervous system  
- CYP = cytochrome P  
- DTG = dolutegravir  
- EEG = electroencephalogram  
- EFV = efavirenz  
- INSTI = integrase strand transfer inhibitor  
- LPV/r = lopinavir/ritonavir  
- PPI = proton pump inhibitor  
- RAL = raltegravir  
- RPV = rilpivirine  
- TDF = tenofovir disoproxil fumarate  
- TDM = therapeutic drug monitoring  
- UGT = uridine diphosphate-glucuronosyltransferase
References


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