### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  
(Last updated April 27, 2017; last reviewed April 27, 2017)  (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>
</table>
| **Global CNS Depression** | LPV/r oral solution (contains both ethanol and propylene glycol as excipients) | Onset:  
• 1–6 days after starting LPV/r | Unknown, rare case reports | 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** | EFV | 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. | 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-carriage 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. |
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<tbody>
<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td>• Cerebellar dysfunction (tremor, dysmetria, ataxia)</td>
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**Note:** Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.

| | RPV | Presentation | Neuropsychiatric Symptoms: | • Depressive disorders  
| | | | • Suicidal ideation  
| | | | • Abnormal dreams/nightmares  
| | | Other CNS Manifestations: | • Headache  
| | | | • Dizziness  
| | | | • Insomnia  
| | | • Somnolence |  |

**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.

**Prior history of neuropsychiatric illness**

**Monitor carefully for depressive disorders and other CNS symptoms.**

**Consider drug substitution in case of severe symptoms.**

| | RAL | Presentation: | Increased psychomotor activity  
| | | | Headaches  
| | | | Insomnia  
| | | | Depression  
| | | • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)  
| | | | • Rare case reports of cerebellar dysfunction in adults  

**Children:**
- Increased psychomotor activity reported in one child.

**Adults:**
- Headache  
- Insomnia (<5% in adult trials)

**Elevated RAL concentrations**

**Co-treatment with TDF or 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 co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.**
### Table 15a. 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>
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<td>• 7–30 days after initiating drug</td>
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<td></td>
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<td>Presentation</td>
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<td>Neuropsychiatric Symptoms:</td>
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<tr>
<td></td>
<td></td>
<td>• Depression or exacerbation of preexisting depression</td>
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<tr>
<td></td>
<td></td>
<td>• Anxiety</td>
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<tr>
<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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<tr>
<td></td>
<td></td>
<td>• Insomnia</td>
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<td></td>
<td></td>
<td>• Dizziness</td>
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<td></td>
<td></td>
<td>• Headache</td>
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<tr>
<td>Intracranial Hemorrhage</td>
<td>TPV</td>
<td>Onset:</td>
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<td></td>
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<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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</table>

**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


