### Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  *(Last updated May 22, 2018; last reviewed May 22, 2018)*

<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  
Presentation  
Neonates/Premature Infants:  
• Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) | Unknown, rare case reports | Prematurity  
Low birth weight  
Aged <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:  
• For many symptoms, onset is 1–2 days after starting EFV  
• Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% of participants experienced persistent symptoms at 12 months and in another report, half of discontinuations occurred after 12 months.  
Presentation (May Include 1 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, and assessment method  
Children:  
• 24% for any EFV-related CNS manifestations in 1 case series, with 18% of participants requiring drug discontinuation.  
• 11% (5/45 participants) incidence of new-onset seizures reported in 1 study in children aged <36 months, 2 of whom had alternative causes for seizures.  
• 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 | Insomnia associated with elevated EFV trough concentration >4 mcg/mL  
Prescreen for and avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs.  
TDM can be considered in the context of a child with mild or moderate EFV-associated toxicity. | If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration >4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if suitable alternative exists.  
Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input). |
Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity *(Last updated May 22, 2018; last reviewed May 22, 2018)* (page 2 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>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</td>
<td>EFV, continued</td>
<td>• Cerebellar dysfunction (tremor, dysmetria, ataxia)</td>
<td>• 1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<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>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV</td>
<td></td>
<td><strong>Onset:</strong> • Most symptoms occur in the first 4–8 weeks of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Presentation</strong> Neuropsychiatric Symptoms: • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares Other CNS Manifestations: • Headache • Dizziness • Insomnia • Somnolence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults:</td>
<td></td>
<td>• 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.</td>
<td></td>
<td>Monitor carefully for depressive disorders and other CNS symptoms.</td>
<td>Consider drug substitution in cases of severe symptoms.</td>
<td></td>
</tr>
<tr>
<td>Children:</td>
<td></td>
<td>• Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including 1 suicide attempt. • Somnolence reported in 14% (5/36) of children.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td><strong>Onset:</strong> • As early as 3–4 days after starting RAL</td>
<td>Elevated RAL concentrations Co-treatment with TDF or PPI or inhibitors of UGT1A1</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></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Presentation:</strong> • Increased psychomotor activity reported in 1 child.</td>
<td>Prior history of insomnia or depression</td>
<td></td>
<td>Consider drug substitution (RAL or co-administered drug) in cases of severe insomnia or other neuropsychiatric symptoms.</td>
<td></td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Associated ARVs</td>
<td>Onset/Clinical Manifestations</td>
<td>Estimated Frequency</td>
<td>Risk Factors</td>
<td>Prevention/ Monitoring</td>
<td>Management</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>------------------------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</strong></td>
<td>DTG</td>
<td>Onset: 7–30 days after starting DTG&lt;br&gt;Presentation <em>Neuropsychiatric Symptoms:</em>&lt;br&gt;- Depression or exacerbation of preexisting depression&lt;br&gt;- Anxiety&lt;br&gt;- Suicidal ideation or attempted/completed suicide&lt;br&gt;Other CNS Manifestations (Generally Mild):&lt;br&gt;- Insomnia&lt;br&gt;- Dizziness&lt;br&gt;- Headache</td>
<td>Children:&lt;br&gt;- CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.&lt;br&gt;Adults:&lt;br&gt;- Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common and usually mild. More severe symptoms that require drug discontinuation are less common, occurring in &lt;1% patients in Phase 3 trials, but these severe symptoms are reported with increasing frequency (4% to 10%) in recent post-marketing reports.</td>
<td>Pre-existing depression or other psychiatric illness&lt;br&gt;Higher frequency of neuropsychiatric symptoms reported when co-administered with ABC</td>
<td>Use with caution in the presence of psychiatric illness, especially depression.</td>
<td>For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. Discontinuation resulted in resolution of neuropsychiatric symptoms in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation). For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</td>
</tr>
<tr>
<td><strong>Intracranial Hemorrhage (ICH)</strong></td>
<td>TPV</td>
<td>Onset: 7–513 days after starting TPV</td>
<td>Children:&lt;br&gt;- No cases of ICH reported in children.&lt;br&gt;Adults:&lt;br&gt;- 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>
<td>Unknown; prior history of bleeding disorder or risk factors for bleeding reported for most patients in case series.</td>
<td>Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.</td>
<td>Discontinue TPV if ICH is suspected or confirmed.</td>
</tr>
</tbody>
</table>

Key to Acronyms: **ABC** = abacavir; **ARV** = antiretroviral; **CNS** = central nervous system; **CYP** = cytochrome P; **DTG** = dolutegravir; **EEG** = electroencephalogram; **EFV** = efavirenz; **ICH** = intracranial hemorrhage; **LPV/r** = lopinavir/ritonavir; **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

---

Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  *(Last updated May 22, 2018; last reviewed May 22, 2018)*  (page 3 of 3)
References


17. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted


