### 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 1 of 3)

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<tr>
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| **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  
  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.  
  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). | 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.  
  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-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).  
  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. | 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). |
### 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><strong>Neuropsychiatric Symptoms and Other CNS Manifestations</strong></td>
<td>EFV</td>
<td>• Cerebellar dysfunction (tremor, dysmetria, ataxia)</td>
<td>In Adults:</td>
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<td></td>
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<td><strong>Note:</strong> 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></td>
<td>RPV</td>
<td>Presentation <strong>Neuropsychiatric Symptoms:</strong></td>
<td></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></td>
<td></td>
<td>• Depressive disorders</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>
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<td></td>
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<td>• Suicidal ideation</td>
<td>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.</td>
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<td></td>
<td></td>
<td>• Abnormal dreams/nightmares</td>
<td>• Somnolence reported in 5/36 (14%) children.</td>
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<td><strong>Other CNS Manifestations:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Headache</td>
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<td></td>
<td></td>
<td>• Dizziness</td>
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<td></td>
<td></td>
<td>• Insomnia</td>
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<tr>
<td></td>
<td></td>
<td>• Somnolence</td>
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<td>RAL</td>
<td>Presentation:</td>
<td>Elevated RAL concentrations</td>
<td>Prescreen for psychiatric symptoms.</td>
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<td>Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.</td>
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<td>• Increased psychomotor activity</td>
<td>Co-treatment with TDF or PPI or inhibitors of UGT1A1</td>
<td>Monitor carefully for CNS symptoms.</td>
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<td></td>
<td>• Headaches</td>
<td>Prior history of insomnia or depression</td>
<td>Use with caution in the presence of drugs that increase RAL concentration.</td>
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<td></td>
<td></td>
<td>• Insomnia</td>
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<td>• Depression</td>
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<td></td>
<td></td>
<td>• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)</td>
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<td><strong>Rare case reports of cerebellar dysfunction in adults</strong></td>
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<td></td>
<td></td>
<td>• In adults</td>
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| DTG             |                 | Onset: 7–30 days after initiating drug  
Presentation  
Neuropsychiatric Symptoms:  
• Depression or exacerbation of preexisting depression  
• Anxiety  
• Suicidal ideation attempt, behavior, or completion  
Other CNS Manifestations (Generally Mild):  
• Insomnia  
• Dizziness  
• Headache | Adults:  
• Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common, reported in up to 10% of patients. Less than 1% of patients experienced more severe symptoms. | Pre-existing depression or other psychiatric illness | Use with caution in the presence of psychiatric illness, especially depression. | For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.  
Discontinuation resulted in resolution of neuropsychiatric symptom 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. |

| 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 py or 0.04–0.22/100 py 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, or recent neurosurgery. | Discontinue TPV if ICH is suspected or confirmed. |

**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**


