### 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>
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<tr>
<td>Global CNS Depression</td>
<td>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</td>
<td><strong>Onset:</strong>&lt;br&gt;• 1 day–6 days after starting LPV/r</td>
<td><strong>Presentation</strong>&lt;br&gt;<em>Neonates/Premature Infants:</em>&lt;br&gt;• Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)</td>
<td>Unknown; rare case reports have been published</td>
<td>Prematurity&lt;br&gt;Low birth weight&lt;br&gt;Aged &lt;14 days (whether birth was premature or term)</td>
<td>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days. 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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<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td><strong>Onset:</strong>&lt;br&gt;• For many symptoms, onset is 1 day–2 days after starting EFV.&lt;br&gt;• Many symptoms subside or diminish by 2 weeks–4 weeks, but symptoms may persist in a significant proportion of patients.&lt;br&gt;<strong>Presentation (May Include One or More of the Following)</strong>&lt;br&gt;<em>Neuropsychiatric Symptoms:</em>&lt;br&gt;• Abnormal dreams&lt;br&gt;• Psychosis&lt;br&gt;• Suicidal ideation or attempted/ completed suicide&lt;br&gt;<em>Other CNS Manifestations:</em>&lt;br&gt;• Dizziness&lt;br&gt;• Somnolence&lt;br&gt;• Insomnia or poor sleep quality&lt;br&gt;• Impaired concentration&lt;br&gt;• Seizures (including absence seizures)&lt;br&gt;• Cerebellar dysfunction (tremor, dysmetria, ataxia)&lt;br&gt;<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>Variable, depending on age, symptoms, and assessment method&lt;br&gt;<em>Children:</em>&lt;br&gt;• 24% for any EFV-related CNS manifestations in one case series, with 18% of participants requiring drug discontinuation.&lt;br&gt;• Five 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.&lt;br&gt;• Cases of cerebellar dysfunction have been reported in children with very high EFV plasma levels.&lt;br&gt;<em>Adults:</em>&lt;br&gt;• 30% incidence for any CNS manifestations of any severity.&lt;br&gt;• 6% incidence for EFV-related, severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.&lt;br&gt;• One case series reported 20 women with ataxia that resolved upon EFV discontinuation, but frequency was not reported.</td>
<td>Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL)&lt;br&gt;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)&lt;br&gt;Prior history of psychiatric illness or use of psychoactive drugs</td>
<td>Administer EFV on an empty stomach, preferably at bedtime.&lt;br&gt;Prescreen for psychiatric illness; avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs. Consider using TDM in children with mild or moderate EFV-associated toxicities 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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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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| 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

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<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>DTG</td>
<td>Onset: 7 days–30 days after starting DTG</td>
<td>Children: CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.</td>
<td>Pre-existing depression or other psychiatric illness</td>
<td>Use with caution in the presence of psychiatric illness, especially depression.</td>
<td>For persistent or severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.</td>
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<td>Presentation</td>
<td>Adults: Exact frequency of neuropsychiatric symptoms is uncertain; there are case reports for four adult patients. Headache, insomnia, and dizziness are common and usually mild, with a rate of 6.1% reported for insomnia in adults.</td>
<td>Higher frequency of neuropsychiatric symptoms reported when coadministered with ABC; however, evidence is conflicting.</td>
<td>Consider morning dosing of DTG.</td>
<td>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</td>
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<td>Neuropsychiatric Symptoms: Depression or exacerbation of preexisting depression</td>
<td>More severe symptoms that require drug discontinuation, including suicidality, are less common, occurring in ≤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>UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)</td>
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<td>Anxiety</td>
<td>Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.</td>
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<td>Suicidal ideation or attempted/completed suicide</td>
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<td></td>
<td>Other CNS Manifestations (Generally Mild): Insomnia, Dizziness, 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


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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