Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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 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>Onset:</td>
<td>Unknown; rare case reports have been published</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>
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<td></td>
<td></td>
<td>1 day–6 days after starting LPV/r</td>
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<td>Low birth weight</td>
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<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 of ≥14 days).</td>
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<tr>
<td></td>
<td></td>
<td>Presentation</td>
<td></td>
<td>Aged &lt;14 days (whether birth was premature or term)</td>
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<tr>
<td></td>
<td></td>
<td>Neonates/Premature Infants:</td>
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<tr>
<td></td>
<td></td>
<td>Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)</td>
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<tr>
<td><strong>Neuropsychiatric Symptoms and Other CNS Manifestations</strong></td>
<td>EFV</td>
<td>Onset:</td>
<td>For many symptoms, onset is 1 day–2 days after starting EFV. Many symptoms subside or diminish by 2 weeks–4 weeks, but symptoms may persist in a significant proportion of patients.</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>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.</td>
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<td></td>
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<td>Presentation</td>
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<td></td>
<td>Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).</td>
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<td>(May Include One or More of the Following)</td>
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<tr>
<td></td>
<td></td>
<td>Neuropsychiatric Symptoms:</td>
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<tr>
<td></td>
<td></td>
<td>Abnormal dreams</td>
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<td></td>
<td></td>
<td>Psychosis</td>
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<td></td>
<td></td>
<td>Suicidal ideation or attempted/ completed suicide</td>
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<td></td>
<td></td>
<td>Other CNS Manifestations:</td>
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<tr>
<td></td>
<td></td>
<td>Dizziness</td>
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<td></td>
<td></td>
<td>Somnolence</td>
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<tr>
<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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<tr>
<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>

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection K-6**

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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  *(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>
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<td></td>
<td></td>
<td>Presentation</td>
<td>Neuropsychiatric Symptoms: • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/completed suicide</td>
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<tr>
<td></td>
<td></td>
<td>Other CNS Manifestations (Generally Mild): • Insomnia • Dizziness • Headache</td>
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</tr>
</tbody>
</table>

Children: • CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.

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. 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.

Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.

Pre-existing depression or other psychiatric illness

Higher frequency of neuropsychiatric symptoms reported when coadministered with ABC; however, evidence is conflicting.

UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)

Use with caution in the presence of psychiatric illness, especially depression. Consider morning dosing of DTG.

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.

**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


