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>
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<tr>
<td><strong>Global CNS Depression</strong></td>
<td><strong>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</strong></td>
<td>Onset:</td>
<td>Unknown; rare case reports have been published</td>
<td>Prematurity Low birth weight 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.</td>
<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><strong>Neuropsychiatric Symptoms and Other CNS Manifestations</strong></td>
<td><strong>EFV</strong></td>
<td>Onset:</td>
<td>Variable, depending on age, symptoms, and assessment method</td>
<td>Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL) 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)</td>
<td>Administer EFV on an empty stomach, preferably at bedtime. 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.</td>
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<td>For many symptoms, onset is 1 day–2 days after starting EFV.</td>
<td>Children:</td>
<td>Adults:</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. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).</td>
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<td>Many symptoms subside or diminish by 2 weeks–4 weeks, but symptoms may persist in a significant proportion of patients.</td>
<td>• 24% for any EFV-related CNS manifestations in one case series, with 18% of participants requiring drug discontinuation.</td>
<td>• 30% incidence for any CNS manifestations of any severity.</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 | 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 | Monitor carefully for CNS symptoms. | Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms. |
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<td>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</td>
<td>DTG</td>
<td>Onset: 7 days–30 days after starting DTG</td>
<td>Pre-existing depression or other psychiatric illness&lt;br&gt;Higher frequency of neuropsychiatric symptoms reported when coadministered with ABC; however, evidence is conflicting&lt;br&gt;UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)</td>
<td>Use with caution in the presence of psychiatric illness, especially depression.&lt;br&gt;Consider morning dosing of DTG.</td>
<td>For persistent or severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.&lt;br&gt;For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</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


