Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 10/19/2018

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at https://aidsinfo.nih.gov/e-news.
### 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>
<tbody>
<tr>
<td>Global CNS Depression</td>
<td>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</td>
<td>Onset: • 1–6 days after starting LPV/r</td>
<td>Unknown, rare case reports</td>
<td>Prematurity</td>
<td>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.</td>
<td>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).</td>
</tr>
<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td>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.</td>
<td>Variable, depending on age, symptom, and assessment method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation (May Include 1 or More of the Following)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Symptoms:</td>
<td></td>
<td>• Abnormal dreams</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Suicidal ideation or attempted/ completed suicide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CNS Manifestations:</td>
<td></td>
<td>• Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Somnolence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insomnia or poor sleep quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Impaired concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Seizures (including absence seizures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children:</td>
<td></td>
<td>• 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 &lt;36 months, 2 of whom had alternative causes for seizures.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults:</td>
<td></td>
<td>• 30% incidence for any CNS manifestations of any severity.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 6% incidence for EFV-related severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior history of psychiatric illness or use of psychoactive drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administer EFV on an empty stomach, preferably at bedtime.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prescreen for and avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDM can be considered in the context of a child with mild or moderate EFV-associated toxicity.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 10/19/2018
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>
</table>
| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | EFV, continued | • Cerebellar dysfunction (tremor, dysmetria, ataxia)  
**Note:** CNS side effects such as impaired concentration, abnormal dreams, or sleep disturbances may be more difficult to assess in children. | • 1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported. | | | |
| | RPV | **Onset:**  
• Most symptoms occur in the first 4–8 weeks of treatment  
**Presentation**  
**Neuropsychiatric Symptoms:**  
• Depressive disorders  
• Suicidal ideation  
• Abnormal dreams/nightmares  
**Other CNS Manifestations:**  
• Headache  
• Dizziness  
• Insomnia  
• Somnolence | | | Monitor carefully for depressive disorders and other CNS symptoms. | Consider drug substitution in cases of severe symptoms. |
| | RAL | **Onset:**  
• As early as 3–4 days after starting RAL  
**Presentation:**  
• Increased psychomotor activity  
• Headaches  
• Insomnia  
• Depression  
• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia) | | | | |

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 10/19/2018
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)

<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>DTG</td>
<td>Onset: • 7–30 days after starting DTG Presentation Neuropsychiatric Symptoms: • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/completed suicide Other CNS Manifestations (Generally Mild): • Insomnia • Dizziness • Headache</td>
<td>Children: • CNS symptoms were uncommonly reported in early clinical experience in children and adolescents. Adults: • 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 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>
</tbody>
</table>

| Intracranial Hemorrhage (ICH) | 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 reported for most patients in case series. | 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: 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
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


