Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/18/2020

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>
<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: • 1 day–6 days after starting LPV/r Presentation</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>
<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 ≥14 days).</td>
</tr>
<tr>
<td><strong>Neuropsychiatric Symptoms and Other CNS Manifestations</strong></td>
<td>EFV</td>
<td>Onset: • 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. 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) • 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. Variable, depending on age, symptoms, and assessment method Children: • 24% for any EFV-related CNS manifestations in one case series, with 18% of participants requiring drug discontinuation. • 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. • Cases of cerebellar dysfunction have been reported in children 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. • 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) 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) Prior history of psychiatric illness or use of psychoactive drugs</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>
<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>
<td></td>
</tr>
</tbody>
</table>
### 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)

<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 | 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)

<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 | DTG | Onset:  
- 7 days–30 days after starting DTG | Children:  
- CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.  
- 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


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

K-10


