Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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<td>Global CNS Depression</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 &lt;br&gt;Presentation: <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.</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>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td>Onset: &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> <strong>Neuropsychiatric Symptoms:</strong> &lt;br&gt;Abnormal dreams &lt;br&gt;Psychosis &lt;br&gt;Suicidal ideation or attempted/completed suicide &lt;br&gt;<strong>Other CNS Manifestations:</strong> &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)</td>
<td>Variable, depending on age, symptoms, and assessment method &lt;br&gt;<strong>Children:</strong> &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;<strong>Adults:</strong> &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)</td>
<td>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. &lt;br&gt;Avoid concomitant use of psychoactive drugs.</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) | Adults:  
• Increased psychomotor activity was reported in one child.  
Children:  
• Increased psychomotor activity was reported in one child. | 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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| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | DTG | Onset:  
- 7 days–30 days after starting DTG |  |  | 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. |

Presentation  
Neuropsychiatric Symptoms:  
- Depression or exacerbation of preexisting depression  
- Anxiety  
- Suicidal ideation or attempted/ completed suicide  
Other CNS Manifestations (Generally Mild):  
- Insomnia  
- Dizziness  
- Headache  

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)  

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


