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>
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<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
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<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  Neonates/Premature Infants:  • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)</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 ≥14 days).</td>
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<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.</td>
<td>Variable, depending on age, symptoms, and assessment method  <strong>Children:</strong>  • 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.  <strong>Adults:</strong>  • 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.  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>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days. 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>
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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) | 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. |
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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>
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<tr>
<td>Presentation</td>
<td></td>
<td>Neuropsychiatric Symptoms: • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/ completed suicide</td>
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<tr>
<td>Other CNS Manifestations (Generally Mild):</td>
<td></td>
<td>• Insomnia • Dizziness • Headache</td>
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<tr>
<td>Children:</td>
<td>CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.</td>
<td></td>
<td>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)</td>
<td>Use with caution in the presence of psychiatric illness, especially depression. Consider morning dosing of DTG.</td>
<td>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.</td>
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<td>Adults:</td>
<td>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.</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


