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)

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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>
<th>Prevention/ Monitoring</th>
<th>Management</th>
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</table>
| **Global CNS Depression**           | **LPV/r oral solution (contains both ethanol and propylene glycol as excipients)** | **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) | **Unknown; rare case reports have been published** | Prematurity  
Low birth weight  
Aged <14 days (whether birth was premature or term) | Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days. | 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). |
| **Neuropsychiatric Symptoms**       | **EFV**                                                     | **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:**  
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) | 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 <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. | | 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. | If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration >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). |
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<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</td>
<td>RPV</td>
<td>Onset: • Most symptoms occur in the first 4 weeks–8 weeks of treatment</td>
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<td>Presentation Neuropsychiatric Symptoms: • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares Other CNS Manifestations: • Headache • Dizziness • Insomnia • Somnolence</td>
<td>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%).</td>
<td>Prior history of neuropsychiatric illness Monitor carefully for depressive disorders and other CNS symptoms.</td>
<td>Consider drug substitution in cases of severe symptoms.</td>
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<td>RAL</td>
<td>Onset: • As early as 3 days–4 days after starting RAL</td>
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<td>Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)</td>
<td>Adults: • Increased psychomotor activity was reported in one child.</td>
<td>Elevated RAL concentrations Co-treatment with TDF, a PPI, or inhibitors of UGT1A1 Prior history of insomnia or depression</td>
<td>Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.</td>
<td>Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms.</td>
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### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity

(Updated as of April 16, 2019; last reviewed April 16, 2019) (page 3 of 3)

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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. 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 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>
<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. 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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**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


