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 May 22, 2018; last reviewed May 22, 2018)*

<table>
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<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
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| Global CNS Depression | LPV/r oral solution (contains both ethanol and propylene glycol as excipients) | Onset:  
1–6 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 | Prematurity  
Low birth weight  
Aged <14 days (whether premature or term) | Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days. | 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). |
| Neuropsychiatric Symptoms and Other CNS Manifestations | EFV | 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.  
Presentation (May Include 1 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) | Variable, depending on age, symptom, and assessment method  
Children:  
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 <36 months, 2 of whom had alternative causes for seizures.  
Cases of cerebellar dysfunction have been reported in children in association 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. | Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL  
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)  
Prior history of psychiatric illness or use of psychoactive drugs | Administer EFV on an empty stomach, preferably at bedtime.  
Prescreen for and avoid use in the presence of psychiatric illness, including depression or suicidal thoughts.  
Avoid concomitant use of psychoactive drugs.  
TDM can be considered in the context of a child with mild or moderate EFV-associated toxicity. | 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 suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input). |
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<td><strong>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</strong></td>
<td>EFV, continued</td>
<td>• Cerebellar dysfunction (tremor, dysmetria, ataxia)</td>
<td>• 1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported.</td>
<td>Prior history of neuropsychiatric illness</td>
<td>Monitor carefully for depressive disorders and other CNS symptoms.</td>
<td>Consider drug substitution in cases of severe symptoms.</td>
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<tr>
<td><strong>RPV</strong></td>
<td>Onset: • Most symptoms occur in the first 4–8 weeks of treatment</td>
<td>Presentation</td>
<td>Neuropsychiatric Symptoms: • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares</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, and were severe, requiring RPV discontinuation in 1% of patients.</td>
<td>Children: • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including 1 suicide attempt.</td>
<td>Monitor carefully for depressive disorders and other CNS symptoms.</td>
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<tr>
<td></td>
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<td>Other CNS Manifestations: • Headache • Dizziness • Insomnia • Somnolence</td>
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<td>Elevate RAL concentrations Co-treatment with TDF or PPI or inhibitors of UGT1A1 Prior history of insomnia or depression</td>
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<td>Use with caution in the presence of drugs that increase RAL concentration.</td>
<td>Consider drug substitution (RAL or co-administered drug) in cases of severe insomnia or other neuropsychiatric symptoms.</td>
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<td><strong>RAL</strong></td>
<td>Onset: • As early as 3–4 days after starting RAL</td>
<td>Presentation:</td>
<td>Increased psychomotor activity reported in 1 child.</td>
<td>Adults: • Headache • Insomnia (&lt;5% in adult trials)</td>
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<td></td>
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<td>• Increased psychomotor activity</td>
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<tr>
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<td></td>
<td>• Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)</td>
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<td><strong>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</strong></td>
<td>DTG</td>
<td><strong>Onset:</strong>&lt;br&gt;• 7–30 days after starting DTG</td>
<td><strong>Children:</strong>&lt;br&gt;• CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.</td>
<td>Pre-existing depression or other psychiatric illness</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. For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</td>
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<td><strong>Presentation</strong>&lt;br&gt;Neuropsychiatric Symptoms:&lt;br&gt;• Depression or exacerbation of preexisting depression&lt;br&gt;• Anxiety&lt;br&gt;• Suicidal ideation or attempted/completed suicide</td>
<td><strong>Adults:</strong>&lt;br&gt;• 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>Higher frequency of neuropsychiatric symptoms reported when co-administered with ABC</td>
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<td>Other CNS Manifestations (Generally Mild):&lt;br&gt;• Insomnia&lt;br&gt;• Dizziness&lt;br&gt;• Headache</td>
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<td><strong>Intracranial Hemorrhage (ICH)</strong></td>
<td>TPV</td>
<td><strong>Onset:</strong>&lt;br&gt;• 7–513 days after starting TPV</td>
<td><strong>Children:</strong>&lt;br&gt;• No cases of ICH reported in children.</td>
<td>Unknown; prior history of bleeding disorder or risk factors for bleeding reported for most patients in case series.</td>
<td>Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.</td>
<td>Discontinue TPV if ICH is suspected or confirmed.</td>
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<td><strong>Adults:</strong>&lt;br&gt;• 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.</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; 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...


