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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<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>
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| 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.  
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). | 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). |

Neuropsychiatric Symptoms and Other CNS Manifestations | 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 (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 <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. | 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 | 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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<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 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</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>RAL</td>
<td>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)</td>
<td>Children: • Increased psychomotor activity was reported in one child. Adults: • Headache • Insomnia (&lt;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</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  *(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  
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) | 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


