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 14, 2020; last reviewed April 14, 2020) (page 1 of 4)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
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</table>
| **Global CNS Depression** | LPV/r oral solution (contains both ethanol and propylene glycol as excipients) | **Onset:**  
• 1–6 days after starting LPV/r | 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 unless no other alternatives are available; see Lopinavir/Ritonavir. | Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once the patient is 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 symptoms may persist in a significant proportion of patients. | Variable, depending on age, symptoms, and assessment method  
**Children:**  
• 24% of patients experienced any EFV-related CNS manifestation in one case series, with 18% of participants requiring drug discontinuation.  
• Five of 45 participants (11%) experienced new-onset seizures in one study of 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 T/T genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants)  
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 is >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 input from an expert pharmacologist). |
### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  
_Last updated April 14, 2020; last reviewed April 14, 2020_ (page 2 of 4)

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| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | RPV | **Onset:**  
Most symptoms occur in the first 4–8 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 (most were Grade 1). Depressive disorders of all severity grades were reported in 9% of patients; 1% 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 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt.  
- Somnolence was reported in five of 36 children (14%). | 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 3–4 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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<tbody>
<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</td>
<td>DTG</td>
<td>Onset:</td>
<td>• 7–30 days after starting DTG</td>
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<td>For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists.</td>
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<td></td>
<td></td>
<td>Presentation</td>
<td>Neuropsychiatric Symptoms:</td>
<td></td>
<td></td>
<td>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</td>
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<tr>
<td></td>
<td></td>
<td>• Depression or exacerbation of preexisting depression</td>
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<td></td>
<td></td>
<td>• Anxiety</td>
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<td></td>
<td></td>
<td>• Suicidal ideation or attempted/completed suicide</td>
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<td></td>
<td></td>
<td>• Drowsiness</td>
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<td></td>
<td></td>
<td>• Neurocognitive deficits (lower total competence and school performance)</td>
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<td>Other CNS Manifestations (Generally Mild):</td>
<td></td>
<td>• Sleep disturbances</td>
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<td></td>
<td></td>
<td>• Dizziness</td>
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<td></td>
<td></td>
<td>• Headache</td>
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<tr>
<td>Children:</td>
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<td>Onset:</td>
<td>Present in a retrospective cohort analysis, neuropsychiatric events that resulted in discontinuation occurred in two of 29 (6.8%) children who initiated DTG.</td>
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<td>Adults:</td>
<td>• 2.7% of the neuropsychiatric AEs reported in a large prospective cohort resulted in treatment discontinuation.</td>
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<tr>
<td></td>
<td></td>
<td>• Pre-existing depression or other psychiatric illness</td>
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<td></td>
<td></td>
<td>• History of ARV-related neuropsychiatric symptoms</td>
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<td></td>
<td></td>
<td>• Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.</td>
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<td>Prevention/ Monitoring</td>
<td>Use with caution in the presence of psychiatric illness, especially in patients with depression or a history of ARV-related neuropsychiatric symptoms.</td>
<td>Consider morning dosing of DTG.</td>
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<td>Management</td>
<td>For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists.</td>
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<td>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</td>
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<td>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</td>
<td>BIC</td>
<td><strong>Onset:</strong>&lt;br&gt;• 1–63 days after starting BIC (as late as 233 days for schizoaffective disorders)</td>
<td>Data in children and adults come mostly from clinical trials. Overall, the frequency of neuropsychiatric events in BIC and DTG comparator arms appeared similar in adult clinical trials.</td>
<td>Pre-existing depression or other psychiatric conditions</td>
<td>Use with caution in the presence of psychiatric conditions, or in patients with a history of ARV-related neuropsychiatric symptoms.</td>
<td>For persistent or severe neuropsychiatric symptoms, consider discontinuing BIC if a suitable alternative exists. For mild symptoms, continue BIC and counsel patient that symptoms will likely resolve with time.</td>
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<tr>
<td><strong>Presentation</strong>&lt;br&gt;Neuropsychiatric Symptoms:</td>
<td></td>
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<td></td>
<td>History of ARV-related neuropsychiatric symptoms</td>
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<td>• Depression or exacerbation of pre-existing depression</td>
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<tr>
<td>• Schizoaffective disorders</td>
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<tr>
<td>• Abnormal dreams</td>
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<td>• Dizziness</td>
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<td>• Insomnia</td>
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**Key:** ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; 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


