<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
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<th>Management</th>
</tr>
</thead>
</table>
| Global CNS Depression 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 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.  
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 (e.g., tremor, dysmetria, ataxia) | 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. | 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). |
### Neuropsychiatric Symptoms and Other CNS Manifestations, continued

<table>
<thead>
<tr>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults:</td>
<td></td>
<td>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>
</tr>
<tr>
<td>Children:</td>
<td></td>
<td>Prior history of insomnia or depression</td>
<td>Prescreen for psychiatric 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>
</tr>
<tr>
<td>Adults:</td>
<td></td>
<td>Elevated RAL concentrations Co-treatment with TDF, a PPI, or inhibitors of UGT1A1</td>
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<tr>
<td>Children:</td>
<td></td>
<td>Prior history of insomnia or depression</td>
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</tbody>
</table>

#### Neuropsychiatric Symptoms and Other CNS Manifestations:

- **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

- **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)
### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity *(Last updated April 14, 2020; last reviewed April 14, 2020)*

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| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | DTG | Onset:  
• 7–30 days after starting DTG  
**Presentation**  
Neuropsychiatric Symptoms:  
• Depression or exacerbation of preexisting depression  
• Anxiety  
• Suicidal ideation or attempted/ completed suicide  
• Drowsiness  
• Neurocognitive deficits (lower total competence and school performance)  
Other CNS Manifestations (Generally Mild):  
• Sleep disturbances  
• Dizziness  
• Headache | Children:  
• In a retrospective cohort analysis, neuropsychiatric events that resulted in discontinuation occurred in two of 29 (6.8%) children who initiated DTG.  
Adults:  
• 2.7% of the neuropsychiatric AEs reported in a large prospective cohort resulted in treatment discontinuation.  
• 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  
History of ARV-related neuropsychiatric symptoms  
Higher frequency of neuropsychiatric symptoms reported when DTG is 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 in patients with depression or a history of ARV-related neuropsychiatric symptoms.  
Consider morning dosing of DTG. | For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists.  
For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time. |
### Neuropsychiatric Symptoms and Other CNS Manifestations, continued

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric Symptoms</td>
<td>BIC</td>
<td>Onset: • 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.</td>
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<td></td>
<td></td>
<td>Presentation Neuropsychiatric Symptoms: • Depression or exacerbation of pre-existing depression</td>
<td></td>
<td>History of ARV-related neuropsychiatric symptoms</td>
<td></td>
<td>For mild symptoms, continue BIC and counsel patient that symptoms will likely resolve with time.</td>
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<td>Other CNS Manifestations (Generally Mild): • Abnormal dreams</td>
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<td></td>
<td></td>
<td>• Dizziness</td>
<td>• Suicidal ideation or attempted suicide</td>
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<td></td>
<td></td>
<td>• Anxiety</td>
<td>• Schizoaffective disorders</td>
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<td>BIC</td>
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**References**


*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*


