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>
<thead>
<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>
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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  
Presentation: Neonates/Premature Infants: • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) | Unknown, rare case reports   | Prematurity  | 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). |
### Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  
(Last updated May 22, 2018; last reviewed May 22, 2018)  
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| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | EFV, continued | • 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. | **1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported.** | | | |
| | | | | | | |
| | 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 (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.  
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.  
• Somnolence reported in 14% (5/36) of children. | Prior 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) | Adults:  
• Headache  
• Insomnia (<5% in adult trials)  
• Rare case reports of cerebellar dysfunction in adults  
Children:  
• Increased psychomotor activity reported in 1 child. | Elevated RAL concentrations  
Co-treatment with TDF or PPI or inhibitors of UGT1A1 | 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 co-administered drug) in cases of severe insomnia or other neuropsychiatric symptoms. |
Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity *(Last updated May 22, 2018; last reviewed May 22, 2018)*  (page 3 of 3)

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| **Neuropsychiatric Symptoms and Other CNS Manifestations, continued**<sup>a</sup> | DTG | Onset:  
• 7–30 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 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 <1% patients in Phase 3 trials, but these severe symptoms are reported with increasing frequency (4% to 10%) in recent post-marketing reports. | Pre-existing depression or other psychiatric illness  
Higher frequency of neuropsychiatric symptoms reported when co-administered with ABC | Use with caution in the presence of psychiatric illness, especially depression.  
For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.  
Discontinuation resulted in resolution of neuropsychiatric symptoms in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation).  
For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time. |
| **Intracranial Hemorrhage (ICH)** | TPV | Onset:  
• 7–513 days after starting TPV | Children:  
• No cases of ICH reported in children.  
Adults:  
• 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. | Unknown; prior history of bleeding disorder or risk factors for bleeding reported for most patients in case series.  
Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery. | Discontinue TPV if ICH is suspected or confirmed. |

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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


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

References


*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* K-10

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