Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
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/preterm infants: global CNS depression, cardiac toxicity, respiratory complications	Exact frequency unknown, but ethanol and propylene glycol toxicity at therapeutic LPV/r dose reported in premature neonates	Prematurity Low birth weight Age <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of at least 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.
Neuropsychiatric symptoms and other CNS manifestations	EFV	Onset: 1–2 days after initiating treatment Most symptoms subside or diminish by 2–4 weeks (but may persist in a minority of patients) Presentation: May include one or more of the following: dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, suicidal ideation, seizures (including absence seizures) CNS side effects may be more difficult to detect in children because neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders may be difficult to assess.	Variable, depending on age, symptom, assessment method Children: 24% for any EFV-related CNS manifestations in one case series with 18% requiring drug discontinuation Adults: >50% for any CNS manifestations of any severity 2% for EFV-related severe CNS manifestations	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	Provide reassurance about the likely time-limited nature of symptoms. Consider EFV trough level if symptoms excessive or persistent. If EFV trough level >4 mcg/mL, consider dose reduction, preferably with expert pharmacologist input or drug discontinuation.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated November 1, 2012; last reviewed November 1, 2012) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention / Monitoring	Management
	RAL	Presentation: Increased psychomotor activity, headaches, insomnia, depression	Children: Psychomotor activity reported in one child Adults: Headache, insomnia (<5% in adult trials)	Elevated RAL concentrations Prior history of insomnia or depression	Use with caution in the presence of drugs that increase RAL concentration	Consider drug discontinuation in case of severe insomnia.
Intracranial hemorrage	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 patient-years or 0.04–0.22/100 patient-years in a retrospective review of 2 large patient databases	Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.
Cerebellar ataxia	RAL	Onset: As early as 3 days after starting RAL Presentation: Tremor, dysmetria, ataxia	Two cases reported in adults during post marketing period	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (such as drug-drug interaction) identified and removed.

Key to Acronyms: ARV = antiretroviral, CNS = central nervous system, CYP = cytochrome P, EFV = efavirenz, ICH = intracranial hemorrhage, LPV/r = lopinavir/ritonavir, RAL = raltegravir, TDM = therapeutic drug monitoring, UGT = uridine diphosphate-glucurononyl transferase, TPV = tipranavir, ATV = atazanavir

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