Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution which contains both ethanol (42.4% v/v) and propylene glycol (15.3% w/v) 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 when 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	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	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	Avoid use of EFV for initial ARV treatment in children and adolescents to prevent EFV-associated CNS side effects. See What to Start: Regimens Recommended for Initial Therapy of Antiretroviral -Naïve Children In situations where EFV treatment may be indicated,	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).

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• 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) **Note:** CNS side effects (e.g., impaired concentration, abnormal dreams, sleep disturbances) may be more difficult to assess in children.	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.	516 G/T and 983 T/C variants) History of psychiatric illness or use of psychoactive drugs	consider the following: • 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.	
	RPV	**Onset:** • Most symptoms occur in the first 4–8 weeks of treatment.	**Adults:** • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (most were	History of neuropsychiatric illness	• Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares *Other CNS Manifestations:* • Headache • Dizziness • Insomnia • Somnolence	Grade 1). Depressive disorders of all severity grades were reported in 9% of patients; 1% of patients discontinued RPV because of severe depressive disorders. Higher frequency of depression and dizziness reported when coadministered with DTG. **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 5 of 36 children (14%).			
	RAL	**Onset:** • As early as 3–4 days after starting RAL **Presentation:** • Increased psychomotor activity • Headaches • Insomnia • Depression	**Children:** • Increased psychomotor activity was reported in one child. **Adults:** • Headache • Insomnia (<5% in adult trials)	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.

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)	• Rare case reports of cerebellar dysfunction in adults			
	DTG	**Onset:** • 7–30 days after starting DTG **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Self-harm thoughts, 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 2 of 29 (6.8%) children who initiated DTG. • Significantly higher frequency of self-harm or suicidal thoughts reported in children in the ODYSSEY trial receiving DTG (23%) compared to SOC ARVs (5%). They were transient, self-resolved, and did not lead to treatment changes **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.	Preexisting depression or other psychiatric illness History of ARV-related neuropsychiatric symptoms Higher frequency of overall neuropsychiatric symptoms reported when DTG is coadministered with ABC; and of depression and dizziness when DTG is coadministered with RPV. However, evidence is conflicting for ABC association.	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 likely will resolve with time.
	BIC	**Onset:** • 1–63 days after starting BIC (as late as 233 days	**Children:** • One child (1%) had Grade 2 insomnia and anxiety that	Preexisting depression or other	Use with caution in the presence of psychiatric conditions	For persistent or severe neuropsychiatric symptoms, consider

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		for schizoaffective disorders) **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Suicidal ideation or attempted suicide • Schizoaffective disorders • Anxiety *Other CNS Manifestations (Generally Mild):* • Sleep disturbances • Dizziness • Insomnia	led to drug discontinuation in clinical trials. **Adults:** • Overall, the frequency of neuropsychiatric events in BIC and DTG comparator arms appeared similar in adult clinical trials. • Abnormal dreams, dizziness, and insomnia occurred in 1% to 5% of adults. • Suicidal ideation, suicide attempts, schizoaffective disorders, and depression occurred in <1% of adults. • A recent study reported a 3.3% short term BIC-related discontinuation rate due to neuropsychiatric AEs after ART switch in a large cohort of adults living with HIV in routine clinical practice setting.	psychiatric conditions History of ARV-related neuropsychiatric symptoms	or in patients with a history of ARV-related neuropsychiatric symptoms.	discontinuing BIC if a suitable alternative exists. For mild symptoms, continue BIC and counsel patient that symptoms likely will resolve with time.

Key: ABC = abacavir; AE = adverse event; ARV = antiretroviral; BIC = bictegravir; CNS = central nervous system; CYP2B6 = cytochrome P450 2B6; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; SOC = standard of care; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; UGT1A = uridine diphosphate(UDP)-glucuronosyltransferase Family 1 Member A Complex; % v = volume; w = weight

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