

DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (> 3 MONTHS OF AGE) ADVERSE EXPERIENCES
April 1994

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HEMATOLOGY				
Hemoglobin > 3 mo.- < 2 y.o.	9.0-9.9	7.0-8.9	<7.0	Cardiac Failure 2ndary to anemia
Hemoglobin >= 2 y.o.	10-10.9	7.0-9.9	<7.0	Cardiac Failure 2ndary to anemia
Abs Neutrophil Ct	750-1200	400-749	250-399	<250
Platelets		50,000-75,000	25,000-49,999	<25,000 or bleeding
PT	1.1-1.25xN	1.26-1.5xN	1.51-3.0xN	>3xN
PTT	1.1-1.66xN	1.67-2.33xN	2.34-3.0xN	>3xN
GASTROINTESTINAL				
Bilirubin	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN
AST (SGOT)	1.1-4.9xN	5.0-9.9xN	10.0-15.0xN	>15.0xN
ALT (SGPT)	1.1-4.9xN	5.0-9.9xN	10.0-15.0xN	>15.0xN
GGT	1.1-4.9xN	5.0-9.9xN	10.0-15.0xN	>15.0xN
Pancreatic Amylase	1.1-1.4xN	1.5-1.9xN	2.0-3.0xN	>3.0xN
Total Amylase + Lipase*	1.1-1.4xN	1.5-2.4xN	2.5-5.0xN	>5.0xN
Uric Acid	7.5-9.9	10-12.4	12.5-15.0	>15.0 or Gout
CPK	See Neuromuscular Toxicity			
Abdominal Pain	Mild	Moderate- No Rx Needed	Moderate- Rx Needed	Severe- Hospital and Rx
Diarrhea	Soft stools	Liquid stools	Liquid Stools and Mild Dehydration Bloody stools	Dehydration requiring IV therapy or Hypotensive Shock
Constipation	Mild	Moderate	Severe	Distention and Vomiting
Nausea	Mild	Moderate- Decreased po intake	Severe- Little po intake	Unable to ingest food or fluid for >24 hours
Vomiting	<1 episode/day	1-3 episodes/day or duration >3d	>3 episodes/day or duration >7d	Intractable Vomiting

* Both amylase and lipase must be elevated to the same grade or higher (i.e. if total amylase is Grade 4, but lipase is only Grade 1, the Toxicity Grade is 1. In pediatric HIV patients, the most common source of serum amylase is the salivary glands. Salivary amylase elevations are generally not clinically significant. When amylase is released from damaged pancreatic cells, it can be a marker of pancreatitis. In most cases of clinical pancreatitis, lipase will also be elevated. However, lipase is also a non-specific marker. Combined elevation of amylase and lipase (each >5 x normal) often indicates pancreatic disease and requires evaluation. However, in the absence of pancreatic disease, drug can be resumed even at Grade 3 and 4 toxicities.

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RENAL AND ELECTROLYTES				
CREATININE				
2 Month-2 Years	0.6-0.8	0.9-1.1	1.2-1.5	>1.5
2 Years-Adolescent	0.7-1.0	1.1-1.6	1.7-2.0	>2.0
Adolescents	1.0-1.7	1.8-2.4	2.5-3.5	>3.5
Creatinine Clearance	60-75 cc/min/1.73 m ²	50-59 cc/min/1.73 m ²	35-49 cc/min/1.73 m ²	<35 cc/min/1.73 m ²
ELECTROLYTES				
High Sodium	145-149		150-155	>155 or mental status changes
Low Sodium	130-135		129-124	<124 or mental status changes
High Potassium	5.0-5.9	6.0-6.4	6.5-7.0	>7.0 or Cardiac arrhythmias
Low Potassium	3.0-3.5	2.5-2.9	2.0-2.4	<2.0
High Calcium	10.5-11.2	11.3-11.9	12.0-12.9	>=13.0
Low Calcium	7.8-8.4	7.0-7.7	6.0-6.9	<6.0
Low Magnesium	1.2-1.4	0.9-1.1	0.6-0.8	<0.6 or Cardiac arrhythmias
Hypoglycemia	55-65	40-54	30-39	<30 or Mental status changes
Hyperglycemia	116-159	160-249	250-400	>400 or Ketoacidosis
Proteinuria	Tr-1+ <150 mg/day	2+ 150-499 mg/day	3+ 500-1000 mg/day	4+, or nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >=25 cells/hpf	Gross	Obstruction or Transfusion requirement
Comments Calcium values are corrected for albumin concentration. CrCl values do not apply to infants <2 months old.				
OTHER				
Allergy	Pruritis without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)		38.5-40	>40	Sustained Fever: >40, >5 days
Cutaneous		Diffuse maculo-papular rash, dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Stevens-Johnson or Erythema multiforme, Moist desquamation
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: requires IV fluids

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SYMPTOM	GRADE 1	GRADE 2	GRADE 3	GRADE 4
CENTRAL NERVOUS SYSTEM				
Seizures	None	1 Uncomplicated Sz +/- Temp Elevation	1 Sz/Month for >=2 Consecutive Months Or 3 Sz over 6 Months; No Temp Elevation	>1 Sz/Month; No Temp Elevation; No Decrease in Sz Frequency Despite dose reduction
Seizures are a ubiquitous symptom of numerous systemic or CNS disturbances; alternative explanations should be vigorously sought and eliminated. Status epilepticus represents a severe end of the seizure spectrum, but should be considered as a single seizure event. The need for chronic or acute anticonvulsant medication should be made on a clinical basis. Seizures as a manifestation of drug toxicity are usually primarily generalized. Focal (partial onset) seizures are suggestive of focal central nervous system pathology and should be appropriately investigated, although they may be a manifestation of drug toxicity. Beware of focal seizures which secondarily generalize; these should be approached diagnostically as partial onset seizures. Children with underlying epileptic conditions who experience persistent breakthrough seizures despite maximal anticonvulsant therapy coincident with beginning the trial medication should be considered Grade 4.				
Headache	<=1/Month <2 Hrs duration Mild	>1/Month >2 Hrs Duration Moderate to Severe Responds to non-narcotic analgesia or prophylaxis	>2/Month >2 Hrs Duration Moderate to Severe Responds to narcotic analgesia, or does not respond to prophylaxis	>4/Month; >2 Hrs Duration; Moderate to Severe; Non-Responsive to narcotic Analgesia; or persistently Recurrent despite prophylaxis No decrease in frequency or Severity despite dose reduction
Headache is a non-specific symptom, but may be a symptom of CNS/intracranial pathology. Appropriate diagnostic measures should be pursued. Duration refers to the waxing and peak phases, not to the resolution/waning phases of the headache. Mild refers to a grade of headache pain which does not affect function or activity. Moderate to severe refers to a grade of headache which affects function or activity.				
Mental Status And Behavior	Changes which do not Affect Function	Changes requiring pharmacologic or other therapy; or mild lethargy, sedation or somnolence which resolves with rest	Changes not improved by drugs or other therapies; or onset of confusion, memory impairment, lethargy, sedation, or somnolence which does not respond to rest	Onset of delirium, obtundation, coma, or psychosis, or Grade 3 toxicity which does not respond to dose reduction
Behavior refers to the development of attention deficits with or without hyperactivity, depression, mania, agitation, sleep disorders, phobias, obsessive-compulsive behaviors, or anxiety. Mental status refers to the level of consciousness, memory function, language and analytical operations, and non-dominant hemisphere functioning. Alternative explanations should be sought.				
Balance & Posture	None	None	Ataxia, dizziness, vertigo, tremor, impaired postural balance	Onset of movement disorder; or Grade 3 toxicity which does not respond to dosage adjustment
"Ataxia" can be mistakenly diagnosed in the face of central weakness or peripheral neuropathy, which should not be considered a drug toxicity of this category. Movement disorders refer to tardive or other dyskinesias, dystonias, chorea, or ballismus. Alternative explanations should be sought.				

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Visual	None	Blurriness, diplopia, or horizontal nystagmus of < 1 hour duration, with spontaneous resolution	> = 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 Sx lasting 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis, or Grade 3 Sx which persist after dose reduction
Many of the symptoms in this category can be the result of CNS pathology, or alternatively can be an external (i.e., non-CNS) neuro-ophthalmologic disorder. Appropriate diagnostic investigations should be pursued.				
Myelopathy	None	None	None	Myelopathic/spinal cord symptoms, such as: Pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction
HIV can cause spinal cord syndromes rarely in children. Other infectious agents can cause myelopathies as well. Alternative explanations should be sought.				
PERIPHERAL NERVOUS SYSTEM				
Neuropathy/ Lower Motor Neuronopathy	None	Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness. Grade 3 symptoms which do not resolve with dose reduction
Infectious agents other than HIV can precipitate a neuropathy and should be considered, especially CMV. Neuropathies which do not resolve after dose reduction or discontinuation should be pursued for alternative infectious or non-infectious etiologies, since drug-related neuropathies will usually resolve after dose reduction or drug discontinuation. It should be borne in mind that many subjects will worsen for up to one month after drug discontinuation prior to improvement ("coasting"). Abnormalities should be confirmed by nerve conduction studies (NCS) +/- electromyographic studies (EMG).				
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x N) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x N)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x N; Consider confirmatory EMG and/or muscle bx	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms (confirm with EMG); or Grade 3 symptoms which do not resolve on dose adjustment; confirm with muscle bx
HIV can produce a myopathy, and should be differentiated. Drug-induced myopathy can be accompanied by normal CPK levels. On occasion, neuropathic or central weakness can mimic myopathic weakness.				

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Clinical symptoms <i>not otherwise specified</i> in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values <i>not otherwise specified</i> in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity. Requires immediate evaluation, treatment, and usually hospitalization. Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than study drug.