

SECTION 4: DIAGNOSIS AND MANAGEMENT OF ADVERSE EVENTS

Principles of managing adverse events

- Establish whether the adverse event is due to antiretroviral agents, other medication or other illness.
- Never stop only one antiretroviral drug (the patient should always be on 3 drugs).
- Individual drugs may be switched due to intolerance as shown on Table 22, page 69.
- If there is a need to discontinue ART, all antiretroviral medications must be stopped together.
- Clinicians may continue ART if there is a Grade I or II adverse reaction.
- Clinicians should consider terminating treatment in Grade III reactions. Treatment should be stopped if there is a Grade IV adverse event (see Tables 18 – 20).
- Adverse events should be recorded and reported regularly to the HIV/AIDS programme at Head Office. Serious adverse events (SAEs) should be reported within 48-72 hours (Grade IV or death) to the MCC. Adverse event forms on yellow paper will be made available at all centres.

Report serious or unexpected suspected adverse reactions or suspected drug interactions to the National Adverse Drug Event Monitoring Centre, MCC, phone (012) 312-0000 Pretoria; or (021) 447-1618, fax: (021) 448-6181 Cape Town.

N.B.

Contact your local Medicines Information Centre for advice regarding potential interactions and recommendations for dosage adjustment.

Adverse reactions will be graded according to the AIDS Clinical Trial Groups (ACTG and PACTG) grading. Consider grading both laboratory and clinical abnormalities, and manage them as in the tables on page 59 – 62.

Grading of adverse reactions in adults and adolescents

Table 18: Laboratory adverse events in adults (ACTG)

LABORATORY TEST ABNORMALITIES				
ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Haemoglobin	8.0-9.4 g/dL	7.0-7.9 g/dL	6.5-6.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1-1.5 x 10 ⁹ /L	0.75-0.99 x 10 ⁹ /L	0.5-0.749 x 10 ⁹ /L	<0.5 x 10 ⁹ /L
ALT	1.25-2.5 x upper normal limit	>2.5-5 x upper normal limit	>5.0-10 x upper normal limit	>10 x upper normal limit
Triglycerides	3-4.51 mmol/L	4.52-8.48 mmol/L	8.49-13.56 mmol/L	>13.56 mmol/L
Cholesterol	>1.0-1.3 x upper normal limit	>1.3-1.6 x upper normal limit	>1.6-2.0 x upper normal limit	>2.0 x upper normal limit
MANAGEMENT	Continue ART. Repeat test 2 weeks after the initial test and re-assess.		Continue ART. Repeat test 1 week after initial test and reassess; if ALT still Grade III, consult expert about stopping ART.	Consult expert immediately before stopping ART.
	Lipid imbalances could be managed with diet, exercise and pharmacologically with the use of fibrates.			
IF IN DOUBT, ALWAYS SEEK EXPERT ADVICE				

ADVERSE EVENTS

N.B.

The repeat tests may require additional patient's visits over and above the routine monitoring visits.

DIAGNOSIS AND MANAGEMENT OF ADVERSE EVENTS

Table 19: Clinical adverse events in adults

ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Paraesthesia (burning, tingling, etc.)	Mild discomfort; no treatment required	Moderate discomfort; non-narcotic analgesia required	Severe discomfort; OR narcotic analgesia required with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-sensory	Mild impairment (decreased sensation, e.g. vibratory, pinprick, hot/cold in big toes) in focal area or symmetrical distribution.	Moderate impairment (moderate decrease in sensation, e.g. vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decrease or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e. upper and lower extremities)	Sensory loss involves limbs and trunk.
Cutaneous/rash/dermatitis*	Erythema, pruritus	Diffuse, maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	Exfoliative dermatitis OR mucous membrane involvement OR erythema multiforme OR suspected Stevens-Johnson syndrome OR necrosis requiring surgery
MANAGEMENT	<ul style="list-style-type: none"> ■ Continue ART. ■ Provide careful clinical monitoring. ■ Consider change of a single drug if condition worsens. 		<ul style="list-style-type: none"> ■ CONSIDER STOPPING ALL DRUGS. ■ CONSULT SPECIALIST IMMEDIATELY. 	

* A rash in a patient on nevirapine with mucosal involvement **OR** associated with fever/systemic symptoms/derangement in liver functions should be treated as Grade IV toxicity. **ALL** antiretroviral drugs should be stopped immediately. Patients at primary care should be referred to a specialist for advice regarding restarting ART.

The patient should never be rechallenged with nevirapine or swapped with efavirenz if Grade IV or Stevens-Johnson syndrome occurs. If the reaction is non life-threatening or <Grade IV, efavirenz can be substituted with close monitoring.

Table 20: Grading the severity of adverse reactions in children (PACTG)

LABORATORY TEST ABNORMALITIES				
ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Haemoglobin >3 months – <2 years	9.0-9.9 g/dL	7.0-8.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Haemoglobin ≥2 years	10-10.9 g/dL	7.0-9.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Absolute neutrophil count	0.75-1.2 x 10 ⁹ /L	0.4-0.749 x 10 ⁹ /L	0.25-0.399 x 10 ⁹ /L	<0.25 x 10 ⁹ /L
ALT (SGPT)	1.1-4.9 x upper normal limit	5.0-9.9 x upper normal limit	10.0-15.0 x upper normal limit	>15 x upper normal limit
Triglycerides	–	1.54-8.46 mmol/L	8.47-13.55 mmol/L	>13.56 mmol/L
Cholesterol	–	4.43-12.92 mmol/L	12.93-19.4 mmol/L	>19.4 mmol/L

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DIAGNOSIS AND MANAGEMENT OF ADVERSE EVENTS

CLINICAL ADVERSE EVENTS				
ITEM	GRADE I TOXICITY	GRADE II TOXICITY	GRADE III TOXICITY	GRADE IV TOXICITY
Peripheral neuropathy	Diagnosis of peripheral neuropathy is difficult in children. Screen motor function against milestones, and refer to specialist if peripheral neuropathy is suspected.			
Cutaneous/skin rash/dermatitis*	-	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR ulcers	Exfoliative dermatitis OR Stevens-Johnson syndrome OR erythema multiforme OR moist desquamation
MANAGEMENT	<ul style="list-style-type: none"> ■ Continue ART. ■ Repeat laboratory test and clinical assessment within 2 weeks. 		<ul style="list-style-type: none"> ■ Continue ART. ■ Repeat test and clinical assessment within 1 week. If Grade III toxicity persists, stop ALL ART and seek expert medical advice. 	

* A rash in a child on nevirapine with mucosal involvement **OR** associated with fever/ systemic symptoms/derangement in liver functions should be treated as Grade IV toxicity. All ART should be stopped immediately. The patient should never be rechallenged with nevirapine or efavirenz after having presented Grade IV toxicity. Patients at primary care should be referred to a specialist for advice regarding restarting ART.

Important adverse reactions

Table 21: Important ART adverse reactions and safety monitoring

Antiretroviral	Adverse Reactions	Recommended safety monitoring
Abacavir (ABC)	<p>A potentially fatal hypersensitivity reaction develops in approximately 3% -5% of patients. Symptoms usually appear within 6 weeks of treatment initiation. Suspect reaction if symptoms from 2 or more of the following groups are present:</p> <ul style="list-style-type: none"> ■ fever ■ maculopapular pruritic generalised rash ■ gastro-intestinal symptoms ■ other symptoms (including pharyngitis, dyspnoea, cough, musculoskeletal disorders, malaise, fatigue, lymphadenopathy and paraesthesia) <p>Never give abacavir to a child who has previously developed an abacavir-hypersensitivity reaction</p>	Fasting cholesterol and triglycerides at baseline, 6 months, and thereafter every 12 months.
Didanosine (ddI)	Pancreatitis, peripheral neuropathy, GIT effects (bloating, flatulence, nausea, diarrhoea), lactic acidosis.	Clinical
Efavirenz (EFV)	CNS disturbances (dysphoria, vivid dreams, distractedness, dizziness) GIT symptoms. Skin rash, <i>congenital anomalies – avoid during 1st trimester of pregnancy.</i>	Clinical
Lamivudine (3TC)	Diarrhoea, pancreatitis, lactic acidosis	Clinical

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Antiretroviral	Adverse reactions	Recommended safety monitoring
Lopinavir/ Ritonavir	GIT symptoms, lipid abnormalities (5%), lipodystrophic changes.	Fasting cholesterol and triglycerides at baseline, 6 months and thereafter every 12 months.
Nevirapine (NVP)	Skin rash (16%), nausea, vomiting, hepatitis (can be fatal).	ALT at baseline and at week 2, 4, and 8, and thereafter, every 6 months (taken with CD4 and viral load or when symptomatic).
Ritonavir	Bad taste, GIT symptoms, especially diarrhoea. Raised liver enzymes, raised cholesterol and triglycerides, lipodystrophic changes.	Fasting cholesterol and triglycerides at baseline, 6 months, and thereafter every 12 months.
Stavudine (d4T)	Peripheral neuropathy, hepatic steatosis, lactic acidosis, pancreatitis.	Clinical
Zidovudine (AZT)	Bone marrow suppression (anaemia, neutropenia), GIT symptoms, myopathy, lactic acidosis. Cardiomyopathy in children.	FBC with differential count at baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load).

N.B.

Other adverse reactions not listed on this table may occur.

Management of specific adverse reactions

Stop all therapy if there is severe hepatitis, pancreatitis, lactic acidosis or Stevens-Johnson syndrome suspected.

Nausea

- Nausea due to antiretroviral medication must be actively managed, or adherence will suffer.
- Anti-emetics taken half an hour before the antiretroviral dose up to 3 times daily, may be helpful. If the nausea does not settle, refer for expert advice.

Rashes on first-line therapy

- Do a clinical assessment to rule out any other causes of the rash. Enquire about systemic symptoms, and check the temperature in any patient presenting with a rash.
- Do a grading of the rash, and refer to tables for management.
- Both nevirapine and efavirenz may cause skin reactions. This usually occurs within the first 2 months of treatment. Concomitant (simultaneous) TB therapy may confuse the situation as these drugs can cause similar adverse events.

Abdominal pain

- Abdominal pain in a patient on ART can be caused by a number of serious problems, and should never be ignored.
- Important causes include lactic acidosis, pancreatitis, hepatitis, hyperlactataemia (increased serum lactate) and disseminated tuberculosis.
- Recommended investigations: liver functions, lipase and serum lactate. Refer for further investigations as needed.
- Seek expert help if you are unsure of the cause of the pain.

Hyperlactataemia and lactic acidosis

- Asymptomatic elevation of lactate is common in patients taking antiretroviral drugs (up to 20% per year). Routine monitoring of lactate is not recommended if the patient is asymptomatic.
- Patients on ART can occasionally develop symptomatic hyperlactataemia (1-2% per year), and, more rarely, lactic acidosis (0.1-0.2% per year).
- Risk factors for lactic acidosis include:
 - female gender
 - obesity
 - prolonged ART and excellent adherence
 - chronic renal failure
 - pregnancy
- Symptoms are non-specific:
 - unwellness, generalised fatigue, weakness
 - gastro-intestinal symptoms (nausea, vomiting, abdominal pain, abdominal distension and bloatedness)
 - shortness of breath, dyspnoea, tachypnoea
 - neurologic symptoms (disequilibrium, motor weakness)
- Confirmed laboratory test (hyperlactatemia).

Management of hyperlactatemia in adults

- Lactate 2-5 mmol/L: monitor monthly, and be alert for clinical symptoms and signs described above.
- Lactate 5-10 mmol/L with symptoms: STOP all ART and seek urgent expert help. Other causes of raised lactate must be excluded:
 - sepsis
 - renal failure
 - diabetic ketoacidosis

- Lactate >10 mmol/L: STOP all antiretroviral drugs immediately and seek urgent expert help (30% mortality in case series).
- Metabolic acidosis with raised lactate: STOP all ART and seek urgent expert help.
- After recovery, seek expert advice regarding antiretroviral selection. Stavudine and didanosine should be avoided.

Management of hyperlactatemia in children

- Discuss with a treatment expert.
- ART should be discontinued in patients with these symptoms.
- Symptoms associated with lactic acidosis may continue or worsen following discontinuation of ART.
- Therapy is primarily supportive: fluid, bicarbonate administration and respiratory support.

Lipodystrophy

- HIV-associated lipodystrophy include fat loss and/or fat accumulation in distinct regions of the body. This includes increased fat around abdomen, buffalo hump, breast hypertrophy, and fat loss from limbs, buttocks and face.
- Association with antiretrovirals: lipodystrophy more common in individuals taking NRTIs or protease inhibitors.
- Management: There are no established methods for treating lipodystrophy, but the following is recommended:
 - encourage exercise to reduce fat accumulation.
 - some patients improve if switched from a protease inhibitor to an NNRTI.
 - fibrates are effective at lowering cholesterol and triglyceride levels.
 - insulin resistance can be improved with anti-diabetic agents.

Hyperlipidaemia

- Patients on lopinavir/ritonavir who develop hyperlipidaemia should be counselled about lifestyle modification:
 - weight loss if obese
 - increasing exercise
 - stopping smoking
 - reducing cholesterol and saturated fat intake
 Refer to a dietician, if available, for dietary advice.

- Severe hyperlipidaemia may require drug management. If triglyceride >5.6 mmol/L after dietary changes or LDL >4.9 mmol/L or LDL >3.4 mmol/L with 2 or more other ischaemic heart disease risk factors, commence fibrates (or atorvastatin).

Zidovudine related anaemia or neutropenia

- If the patient develops a Grade III or IV anaemia or neutropenia on zidovudine, the dose can be reduced to 200 mg 12 hourly.
- If the anaemia or neutropenia does not improve after dose adjustment, then zidovudine may have to be replaced with stavudine (seek expert advice).

Substitutes for intolerance in adults

For children, consult expert before switching drugs.

All switches should be made by a doctor trained in ART.

Table 22: Recommended substitutions for specific side-effects (Grade III or IV toxicity)

Regimen	Toxicity	Drug substitution
D4T/3TC/EFZ	<ul style="list-style-type: none"> ■ d4T-related neuropathy or pancreatitis ■ EFZ-related persistent CNS toxicity 	<ul style="list-style-type: none"> ■ Switch d4T to AZT ■ Switch EFZ to NVP
D4T/3TC/NVP	<ul style="list-style-type: none"> ■ d4T-related neuropathy or pancreatitis ■ NVP-related severe hepatotoxicity ■ NVP-related severe rash (but not life-threatening) ■ NVP-related life-threatening rash ■ Stevens-Johnson syndrome ■ Lactic acidosis 	<ul style="list-style-type: none"> ■ Switch d4T to AZT ■ Switch NVP to EFZ (except early pregnancy) ■ Switch NVP to EFZ ■ Switch NVP to EFV or lopinavir/ritonavir ■ Switch to lopinavir/ritonavir ■ Consult expert
AZT/ ddI / lopinavir / ritonavir	<ul style="list-style-type: none"> ■ AZT related anaemia or neutropenia ■ ddI related GIT side effects ■ ddI related pancreatitis or hepatitis ■ LPV/r related GIT symptoms ■ LPV/r related hypercholesterolaemia ■ Lipodystrophy ■ Impaired glucose tolerance 	<ul style="list-style-type: none"> ■ Switch AZT to d4T (monitor closely for peripheral neuropathy and lactic acidosis) ■ Switch ddI for enteric coated ddI ■ Consult expert ■ Consult expert ■ Consult expert ■ Consult expert ■ Antidiabetic agents (warning: metformin increases risk of acidosis).

Drug interactions

Protease inhibitors (e.g. lopinavir/ritonavir) and NNRTIs (efavirenz and nevirapine) can interact with a number of other drugs, through changes in drug metabolism in the liver.

Traditional remedies, phytotherapeutics, as well as other complimentary medicines, when used together with ART, could cause liver enzyme induction. They could also bind the drug in the gut, leading to decreased blood levels of ART drugs and ultimately resistance. Little information exists on these interactions and so they are not illustrated here.

Table 23, page 71, shows examples of drugs that should be avoided when administered with efavirenz, nevirapine, lopinavir/ritonavir or all 3 drugs.

N.B.

Beware of other drug interactions that may require dosage adjustment (i.e. anticonvulsant, psychiatric, anti-infective, cholesterol lowering drugs etc.). Seek expert advice if your patient is taking one of these drug combinations.

Table 23: Prohibited drug combinations with specific ART

Agent by class	Agents prohibited with lopinavir/ritonavir	Agents prohibited with ritonavir	Agents prohibited with NVP and EFV
Anti-arrhythmic agents	Flecainide Propafenone	Amiodarone Flecainide Propafenone Quinidine	
Anti-histaminics	Astemizole Terfenadine	Astemizone Terfenadine	Astemizone Terfenadine
Anti-infectives	Rifampicin	Rifabutin	Systemic Ketoconazole
Cholesterol lowering agents	Lovastatin Atorvastatin Simvastatin		
GI motility	Cisapride	Cisapride	Cisapride
Psychiatric medications	St. John's Wort (<i>Hypericum perforatum</i>)		St. John's Wort (<i>Hypericum perforatum</i>)
Sedative/hypnotics	Midazolam Triazolam	Midazolam Triazolam	Midazolam Triazolam
Other	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	Bepiridil (Calcium Channel blocker) Pimozide Ergot derivatives Disulfiram Metronidazole	Dihydroergotamine Ergotamine Methylergonovine