

Appendix 4: ARVs for children – side effects and adverse events

Side effects and adverse events of ARVs in children		
Class	Drug	Side effects/adverse events
NRTI	Zidovidine (Retrovir®)	Anaemia, granulocytopenia, myopathy, lactic acidosis
	Didanosine ddI (Videx®)	Common: abdominal pain, nausea and vomiting Uncommon: pancreatitis, peripheral neuropathy, lactic acidosis
	Stavudine (Zerit®)	Common: headache, rash, gastrointestinal Uncommon: pancreatitis and peripheral neuropathy, lactic acidosis
	Abacavir (Ziagen®)	Hypersensitivity reaction (with or without rash) – may be fatal in adults and children
	Lamivudine (3TC)	Common: headache, fatigue and abdominal pain Uncommon: pancreatitis and peripheral neuropathy, lactic acidosis
NNRTI	Nevirapine (Viramune®)	Skin rash, sedative effect and diarrhoea LIVER TOXICITY
	Efavirenz (Stocrin®)	Skin rash CNS – Sleep disturbance, confusion, abnormal thinking. Teratogenic in primates
PI	Ritonavir (Norvir®)	Nausea, vomiting, diarrhoea Hypercholesterolaemia and hypertriglyceridaemia
	Nelfinavir (Viracept®)	Diarrhoea Can exacerbate chronic liver disease Hypercholesterolaemia and hypertriglyceridaemia
	Kaletra®	Nausea, vomiting, diarrhoea Hypercholesterolaemia and hypertriglyceridaemia

APPENDICES

Appendix 5: Grading of adverse events

Feature	Grade 1	Grade 2	Grade 3	Grade 4
Haematology				
Haemoglobin (g/dL) Age >2 yrs	10–10.9	7–9.9	<7.0	Cardiac failure 2° to anaemia
Absolute neutrophil count	0.750 – 1.2	0.400–0.749	0.25–0.399	<0.250
Platelets (cells/mm)		50 000–75 000	25 000–49.999	<25 000 or bleeding
Gastro-intestinal				
Bilirubin	1.1–1.9 x N*	2.0–2.9 x N	3.0–7.5 x N	>7.5 x N
AST	1.1–4.9 x N	5.0–9.9 x N	10.0–15.0 x N	>15.0 x N
ALT	1.1–4.9 x N	5.0–9.9 x N	10.0–15.0 x N	>15.0 x N
GT	1.1–4.9 x N	5.0–9.9 x N	10.0–15.0 x N	>15.0 x N
Pancreatic Amylase	1.1–1.4 x N	1.5–1.9 x N	2.0–3.0 x N	>3.0 x N
Abdominal pain	Mild	Moderate No Rx needed	Moderate Rx needed	Hospital and Rx
Diarrhoea	Soft stools	Liquid stools	Liquid stools + mild dehydration, bloody stools	Severe dehydration or hypotensive shock
Constipation	Mild	Moderate	Severe	Distention + vomiting
Nausea	Mild	Moderate	Severe, little oral intake	Unable to take any food or fluid for >24 hrs
Vomiting	<1 episode/day	1–3 episodes/day or duration >3 days	>3 episodes/day or duration >7 days	Intractable vomiting
Allergic/dermatological				
Allergy	Itch without rash	Itchy rash	Mild urticaria	Severe urticaria Anaphylaxis, angioedema
Drug fever		38.5–40.0°C	>40°C	Sustained fever: >40°C >5 days
Cutaneous		Diffuse maculopapular rash dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Steven-Johnson or E. multiforme, moist desquamation

Feature	Grade 1	Grade 2	Grade 3	Grade 4
Nervous system				
Mental status or behaviour	Changes with normal function	Changes requiring drugs or other therapy: or mild lethargy, sedation, or somnolence that resolves with rest	Changes not improved with drugs or other therapy: or onset of confusion, memory loss, lethargy, sedation, or somnolence not resolved by rest	Delirium, obtundation, coma or psychosis or Grade 3 toxicity with no response to dose reduction
Neuropathy/ lower motor neuropathy	None	Mild transient paresthesia	See below**	See below***
Other				
Clinical symptoms not otherwise specified above	No therapy, monitor condition	May require minimal intervention and monitoring	Requires care or possible hospitalisation	Requires active medical intervention, hospitalisation or hospice care

* N = normal

** Persistent or progressive paresthesias, burning sensation of feet or mild dysesthesia, no weakness, mild tendon reflex changes, no sensory loss.

*** Onset of significant weakness, decrease or loss of DTR, sensory loss in stocking-glove distribution, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness, Grade 3 features not resolving on drug dose reduction.

Appendix 6: Guidelines for adverse drug reaction (ADR) reporting

National Pharmacovigilance Programme

The Medicines Control Council (MCC) has a responsibility to ensure the safety, efficacy and quality of all medicines used by the South African public. The National Pharmacovigilance Programme is co-ordinated by the MCC and has two dedicated Units responsible for the monitoring of the safety of medicines. The National Adverse Drug Event Monitoring Centre (NADEMC) in Cape Town monitors the safety of all registered medicines in South Africa. In addition, a focused surveillance unit at MEDUNSA is responsible for monitoring the safety of antiretroviral (ARV) medicines and complementary medicines. The unit at MEDUNSA is also responsible for monitoring the safety of unregistered medicines used during clinical trials.

What is pharmacovigilance?

Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. adverse drug reactions or ADRs). The goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.

What is an ADR?

The Medicines Control Council (MCC) defines an adverse drug reaction (ADR) or adverse reaction as a response to a medicine which is noxious and unintended, including lack of efficacy. It can occur at any dosage and can also result from overdose, misuse or abuse of a medicine.

Who should report ADRs?

All health-care workers, including doctors, dentists, pharmacists, nurses and other health professionals are encouraged to report all suspected adverse reactions to medicines (including vaccines, X-ray contrast media, traditional and herbal remedies). This is especially important when the reaction is not in the package insert, is potentially serious or clinically significant.

What happens to a report?

All ADR reports are entered into a national ADR database. Each report is evaluated to assess the causal relationship between the event and the medicine. A well-completed adverse drug reaction/product quality form submitted could result in any of the following:

- Additional investigations into the use of the medicine in South Africa
- Educational initiatives to improve the safe use of the medicine
- Appropriate package insert changes to include the potential for the reaction
- Changes in the scheduling or manufacture of the medicine to make it safer

The purpose of ADR reporting is to reduce the risks associated with the use of medicines and to ultimately improve patient care.

Will reporting have any negative consequences on the health worker or the patient?

An adverse drug reaction report does not constitute an admission of liability or that the health professional contributed to the event in any way. The outcome of a report, together with any important or relevant information relating to the reaction, will be sent back to the reporter as appropriate. The details of a report are stored in a confidential database. The names of the reporter or any other health professionals named on a report and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. The information is only meant to improve the understanding of the medicines used in the country.

Is the event possibly an ADR?

The following factors should be considered when an adverse drug reaction is suspected:

1. What exactly is the nature of the reaction?
(Describe the reaction as clearly as you can, and where possible provide an accurate diagnosis.)

APPENDICES

2. Did the reaction occur within a reasonable time relationship to starting treatment with the suspected medicine?
(Some reactions occur immediately after administration of a medicine while others take time to develop.)
3. Is the reaction known to occur with the particular medicine as stated in the package insert or other reference?
(If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine.)
4. Did the patient recover when the suspected medicine was stopped?
(Some reactions can cause permanent damage, but most reactions are reversible if the medication is stopped.)
5. Did the patient take the medicine again after the reaction abated (i.e. rechallenge). If so, did the same reaction occur again?
(In most situations it is not possible or ethical to rechallenge the patient with the same medicine. If such information is available or if such a rechallenge is necessary, recurrence of the event is a strong indicator that the medicine may be responsible.)
6. Can this reaction be explained by other causes (e.g. underlying disease(s); other medicine(s); toxins or foods)?
(It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is. A medicine-related cause should be considered, when other causes do not explain the patient's condition.)

What types of reactions should be reported?

The following ADRs should be reported:

- All ADRs to newly marketed drugs or new drugs added to the EDL
- All serious reactions and interactions
- ADRs that are not clearly stated in the package insert
- All adverse reactions to or poisonings from traditional or herbal remedies

Report even if you are not certain that the medicine caused the event.

What product quality problems should be reported?

The following product quality problems should be reported:

- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labelling
- Therapeutic failures

How can ADRs be prevented from occurring?

Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines.

How are ADRs reported?

An Adverse Drug Reaction/Product Quality Report Form is enclosed in this book and should be completed in as much detail as possible before returning it by fax or post to any of the addresses provided below. Additional forms can be obtained by contacting the MCC at these addresses. Report forms may also be accessed via the following website: <http://www.mccza.com>

1. The Registrar of Medicines
Medicines Control Council, Department of Health, Private Bag X828, Pretoria, 0001 Tel: (012) 312-0925; Fax: (012) 312-0925
2. The National Adverse Drug Event Monitoring Centre (NADEMC)
*c/o Division of Pharmacology, University of Cape Town, Observatory, 7925 Tel: (021) 447-1618; Fax: (021) 448-6181
For spontaneous reporting, including HIV and AIDS*
3. MEDUNSA Pharmacovigilance Unit
*Tel. (012) 521-4358; Fax (012) 521-4335
For adults and adolescents*
4. University of Free State Pharmacovigilance Unit
*For pregnant women and children
Not yet operational*

Adverse Drug Reaction and Product Quality Problem Report Form

(Identities of reporter and patient will remain strictly confidential)

NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE

Medicines Control Council, The Registrar of Medicines,
Department of Health

Tel : (021) 447-1618
Fax: (021) 448-6181

In collaboration with the WHO International Drug Monitoring Programme

PATIENT INFORMATION

Name (or initials):..... Age:..... Weight (kg):.....

Sex: M F Date of birth:..... / / Height (cm):.....

ADVERSE REACTION/PRODUCT QUALITY PROBLEM

Adverse and/or Product Date of onset of reaction:...../...../.....
reaction¹ Quality Problem² Time of onset of reaction:.....h.....min

Description of reaction or problem (Include relevant tests/lab data, as well as dates):

1. ADVERSE REACTION PROBLEM

MEDICINES/VACCINES/DEVICES (include all concomitant medicines)

Trade Name (Asterisk* suspected product)	Batch No.	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

- death
- life-threatening
- disability
- hospitalisation
- congenital anomaly
- other.....
- required intervention to prevent permanent impairment/damage

Event reappeared on rechallenge: Y N

Rechallenge not done Y N

Treatment (of reaction):

.....

.....

.....

Recovered: Y N

Sequelae: Y N

Describe sequelae:

.....

.....

.....

COMMENTS: (e.g. relevant history, allergies, previous exposure, baseline test results/lab data)

2. PRODUCT QUALITY PROBLEM

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation? Y N

Reporting doctor/pharmacist etc:

Name: Qualifications:.....

Address:

Signature:..... Date:..... Tel: (.....).....

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

APPENDICES

Advice about voluntary reporting

Report adverse experiences with:

- Medications (drugs, vaccines and biologicals)
- Medical devices (including in-vitro diagnostics)
- Traditional and herbal remedies
- For adverse events following immunisation (AEFI), please follow the reporting procedure recommended by the Expanded Programme in Immunisation (EPI)

Please report:

- Adverse drug reactions to recently marketed products
- Serious reactions and interactions with all products
- Adverse drug reactions which are not clearly reflected in the package insert

Report even if:

- You're not certain the product caused the event.
- You don't have all the details.

Report product quality problems such as:

- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labelling
- Therapeutic failures

Important numbers:

Investigational products and product quality problems:

- (012) 326-4344 to fax a report
- (012) 312-0000 to report by phone

Registered medicines and traditional and herbal remedies:

- (021) 448-6181 to fax a report
- (021) 447-1618 to report by phone

Adverse events following immunisation:

- (012) 312-0110 to phone for information
- (012) 321-9882 to fax a report

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of drug safety and therapy in South Africa.

PLEASE POST FORMS TO THE ADDRESS PROVIDED BELOW

Department of Health
Registrar of Medicines
Private bag x828
Pretoria
0001

ACRONYMS AND ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AZT	Zidovudine
CB	<i>Chart Booklet</i> (Integrated Management of Childhood Illness)
ddI	Didanosine
D4T	Stavudine
ELISA	Enzyme-linked Immunosorbent Assay
GIT	Gastrointestinal Tract
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IMCI	Integrated Management of Childhood Illnesses
IRIS	Immune Reconstitution Inflammatory Syndrome
LIP	Lymphocytic Interstitial Pneumonitis
MAC	<i>Mycobacterium avium</i> Intracellulare
NDoH	National Department of Health
NVP	Nevirapine
OI	Opportunistic Infection
ORS	Oral Rehydration Salts
PCP	<i>Pneumocystis jiroveci</i> Pneumonia <i>Pneumocystis carinii</i> Pneumonia
PCR	Polymerase Chain Reaction
PHC	Primary Health Care
SSS	Sugar Salt Solution
STI	Sexually Transmitted Infection
TB	Tuberculosis
3TC	Lamivudine

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

