Adverse Drug Reactions and advanced HIV

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REPUBLIC OF SOUTH AFRICA

NATIONAL DEVELOPMENT PLAN 2030

Outline

- Common Terms & Definitions
- Importance of detecting & reporting suspected ADRs
- Common and severe/serious ADRs associated with ART/TB
- Detecting and managing suspected ADRs
- Reporting suspected ADRs

Drug safety?

There are known knowns.
There are things we know we know.
We also know there are known unknowns;
we know there are some things we do not know.
But there are also unknown unknowns - the ones we don't know we don't know.”

Donald Rumsfeld, 2002

COMMON TERMS & DEFINITIONS

Question 1: Which statement best describes an adverse drug reaction (ADR)?

A. Any medical occurrence that may present during treatment, but which does not necessarily have a causal relationship with treatment.

B. A response to a drug which is noxious and unintended, including lack of efficacy, which occurs at doses normally used in man, and which can result from overdose, misuse or abuse of any drug.

C. Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer.

D. Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine.

COMMON TERMS & DEFINITIONS

A. Any medical occurrence that may present during treatment, but which does not necessarily have a causal relationship with treatment.

ADVERSE DRUG EVENT (ADE)

B. A response to a drug which is noxious and unintended, including lack of efficacy, which occurs at doses normally used in man, and which can result from overdose, misuse or abuse of any drug.

ADVERSE DRUG REACTION (ADR): ADVERSE EFFECT/ ADVERSE REACTION

B. Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer.

MEDICATION ERROR (ME) – PREVENTABLE ADE/ADR

D. Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine.

SIDE EFFECT – TYPE A ADR

Classification of ADRs

Type of reaction	Mnemonic	Features	Examples	Management
A: Dose-related	Augmented	• Common • Related to a pharmacological action of the drug • Predictable • Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants	• Reduce dose or withhold • Consider effects of concomitant therapy
B: Non-dose-related	Bizarre	• Uncommon • Not related to a pharmacological action of the drug • Unpredictable • High mortality	• Immunological reactions: Penicillin hypersensitivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (eg, ampicillin rash)	• Withhold and avoid in future
C: Dose-related and time-related	Chronic	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	• Reduce dose or withhold; withdrawal may have to be prolonged
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia	• Often intractable
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)	• Reintroduce and withdraw slowly
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers	• Increase dosage • Consider effects of concomitant therapy

Related to the pharmacological properties of the drug

NOT related to the pharmacological properties of the drug

Lancet 2000; 356: 1255–59.

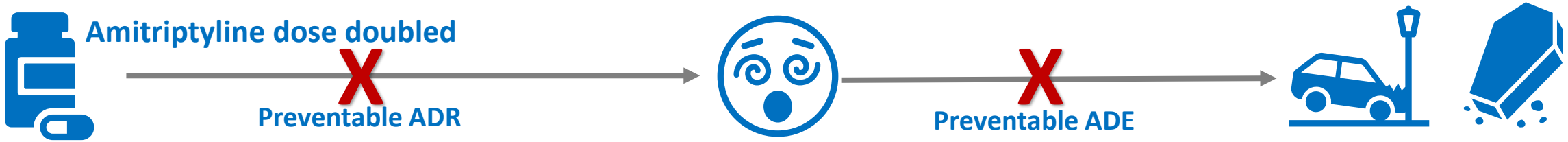
ADVERSE DRUG EVENT - ACCIDENT → DEATH

No causal relationship established between therapy and event

ADVERSE DRUG REACTION (TYPE A: SIDE EFFECT) – DROWSINESS/SLEEP

Causal relationship established

MEDICATION ERROR – AMITRIPTYLINE OVERDOSE



IMPORTANCE OF DETECTING & REPORTING SUSPECTED ADRs

Question 2: Which one of the following statements is incorrect about the importance of reporting suspected ADRs?

A. Reactions that are very common to uncommon reactions (incidence ≥0.1%) are usually observed/reported from clinical studies during clinical development and pre-registration of medicines..

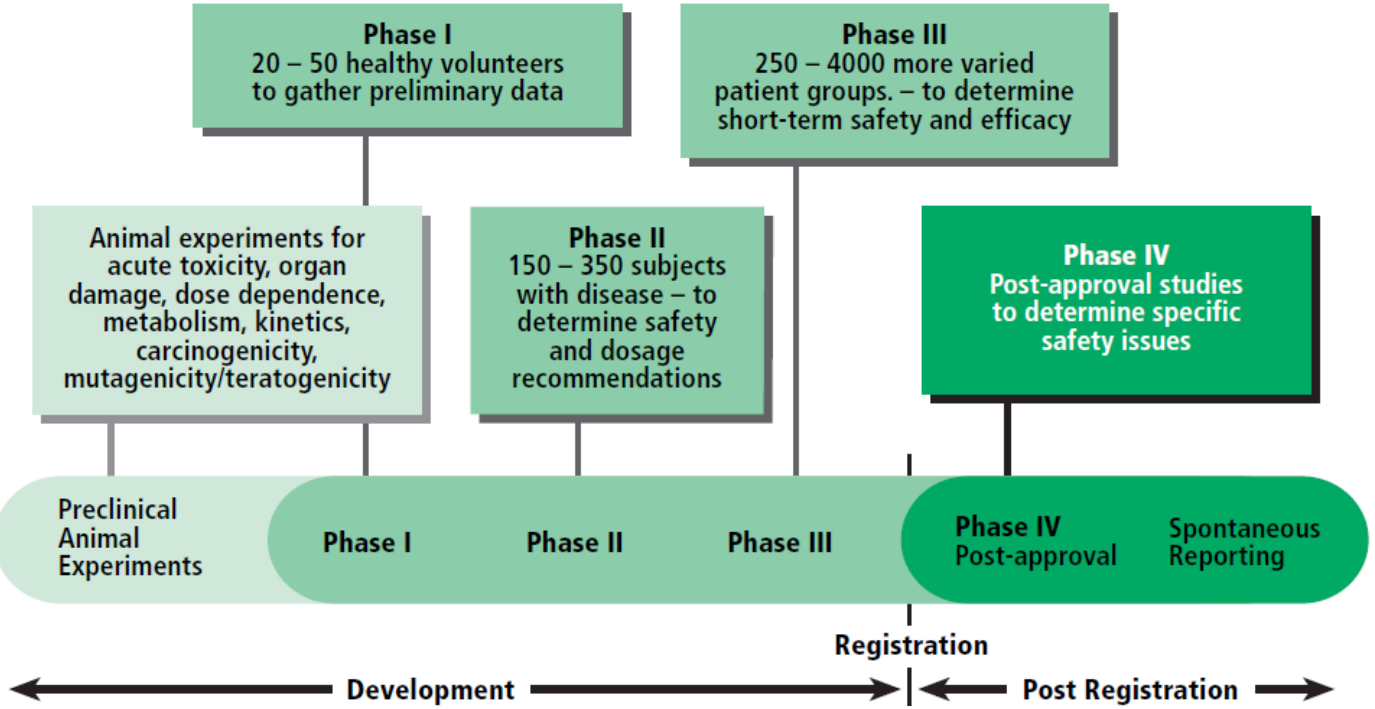
B. Safety information is limited or lacking for drug use in special populations (e.g. pregnancy, breastfeeding, paediatrics, elderly).

C. There is a need for continuous pharmacovigilance throughout the lifecycle of registered medicines to detect any previously unidentified adverse drug reactions.

D. Serious and late onset or long-term reactions are often identified during clinical trials before registering a medicine.

Unidentified ADRs & Risks

Figure 1 Clinical development of medicines

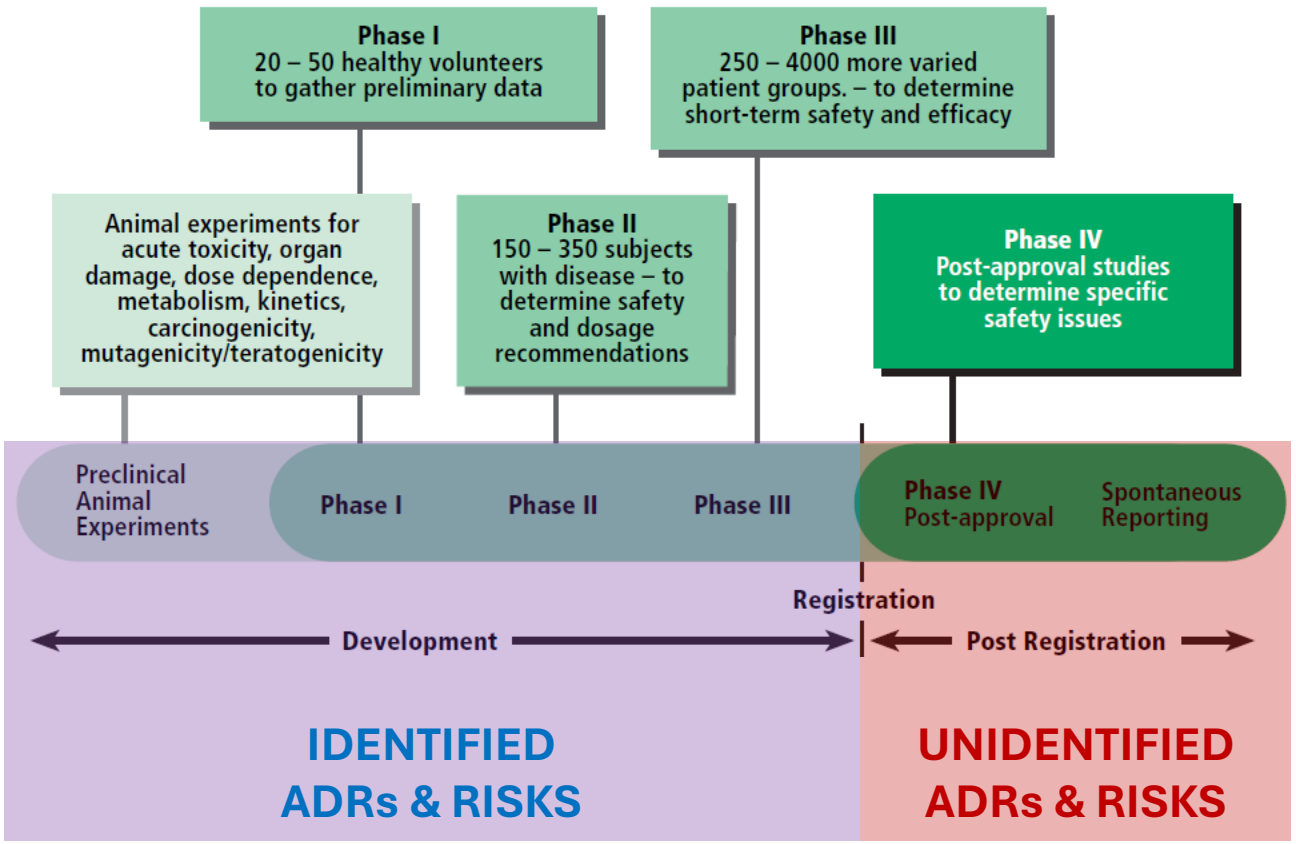


- Small number of patients (< 5000)
- Limited duration, short follow-up
- Conditions and indications differ from those in clinical practice (age, gender, ethnicity, comorbidities)
- Limited /excluded populations (paediatrics, geriatrics, pregnancy, breastfeeding)

WHO. 2004. WHO Policy Perspectives on Medicines. Pharmacovigilance: ensuring the safe use of medicines

Unidentified ADRs & Risks

Figure 1 Clinical development of medicines



FREQUENCY OF ADRs [1]

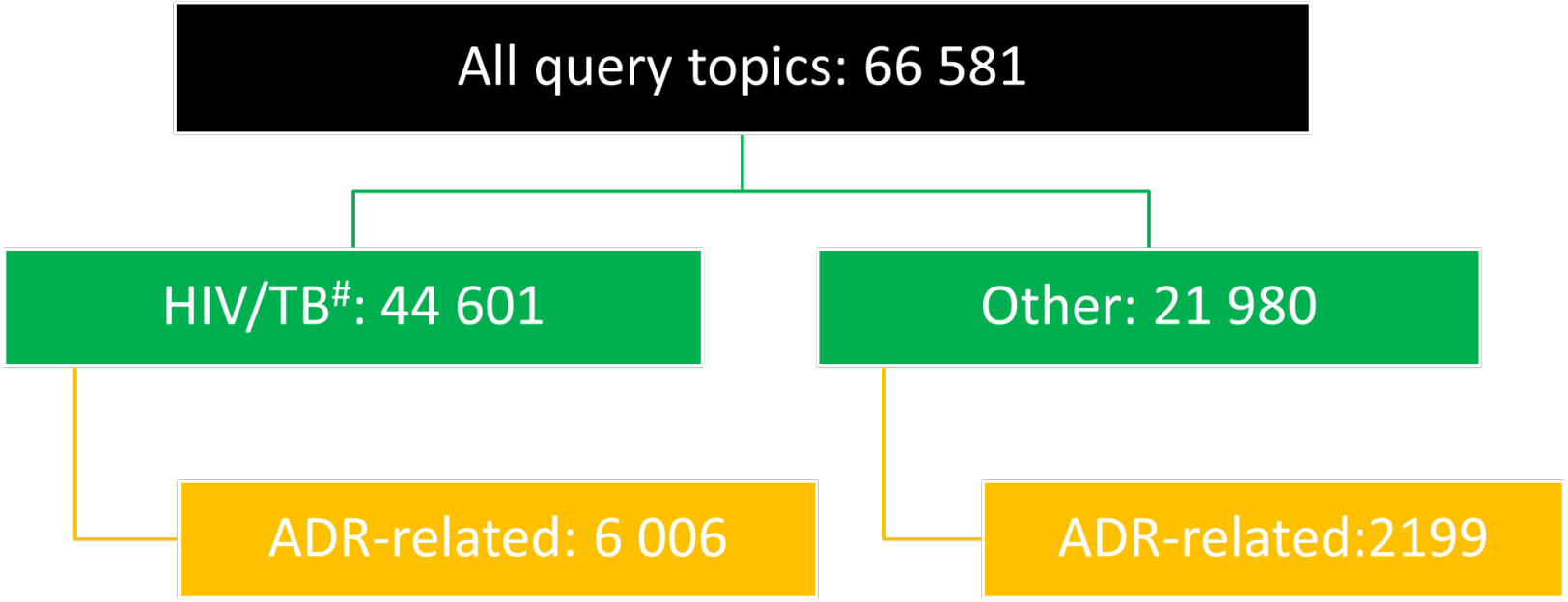
Very common	≥ 10 %	≥ 1/10
Common	1 - 10%	1/100 – 1/10
Uncommon	0.1 - 1%	1/1000 – 1/100
Rare	0.01 - 0.1%	1/10000 - 1/1000
Very rare	< 0.01 %	< 1/10 000

[1] Council for International Organizations of Medical Sciences

Rule of 3:
95% chance of observing 1 occurrence of an event in a population 3 times the size of the event's frequency

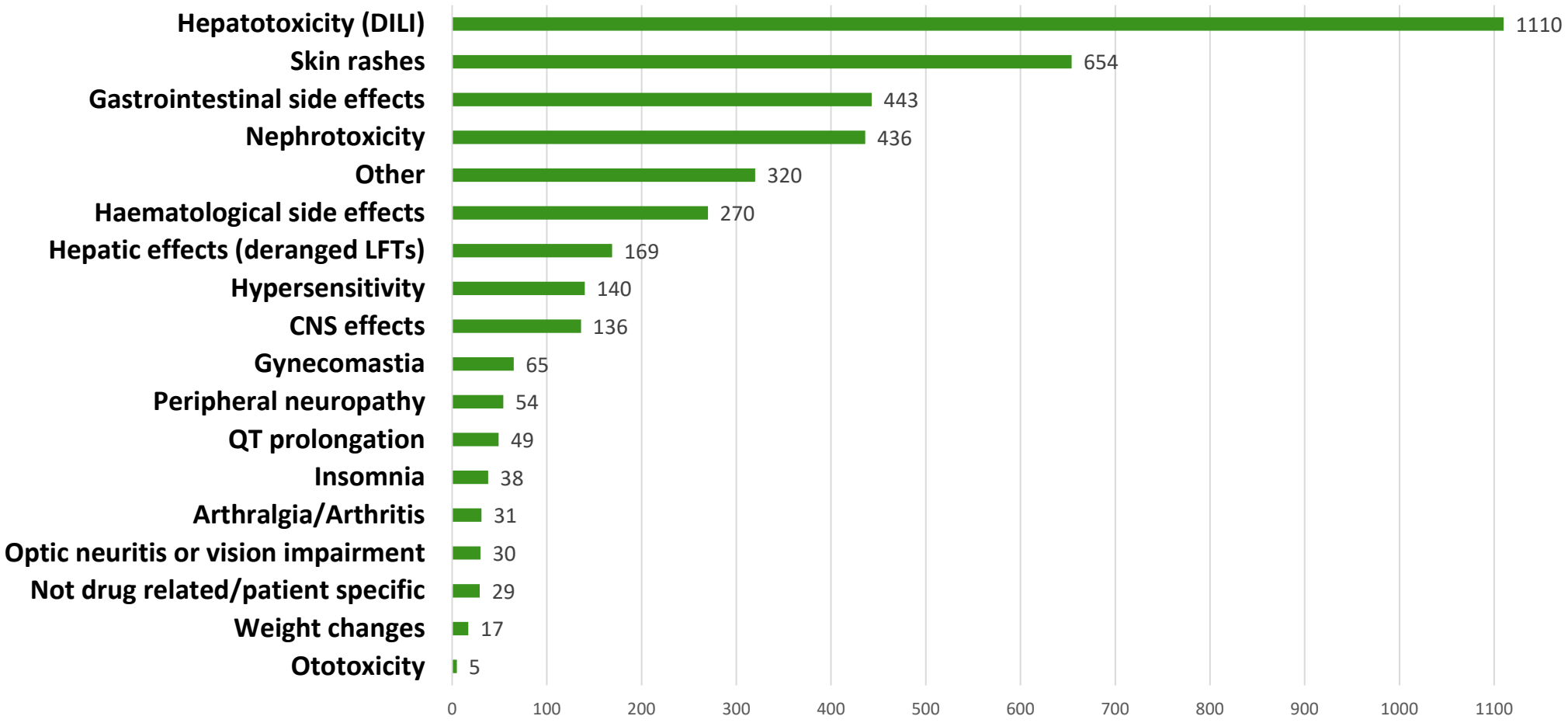
WHO. 2004. WHO Policy Perspectives on Medicines — Pharmacovigilance: ensuring the safe use of medicines

MIC ADR-related queries: 1 Jan 2015 - 1 Jun 2024

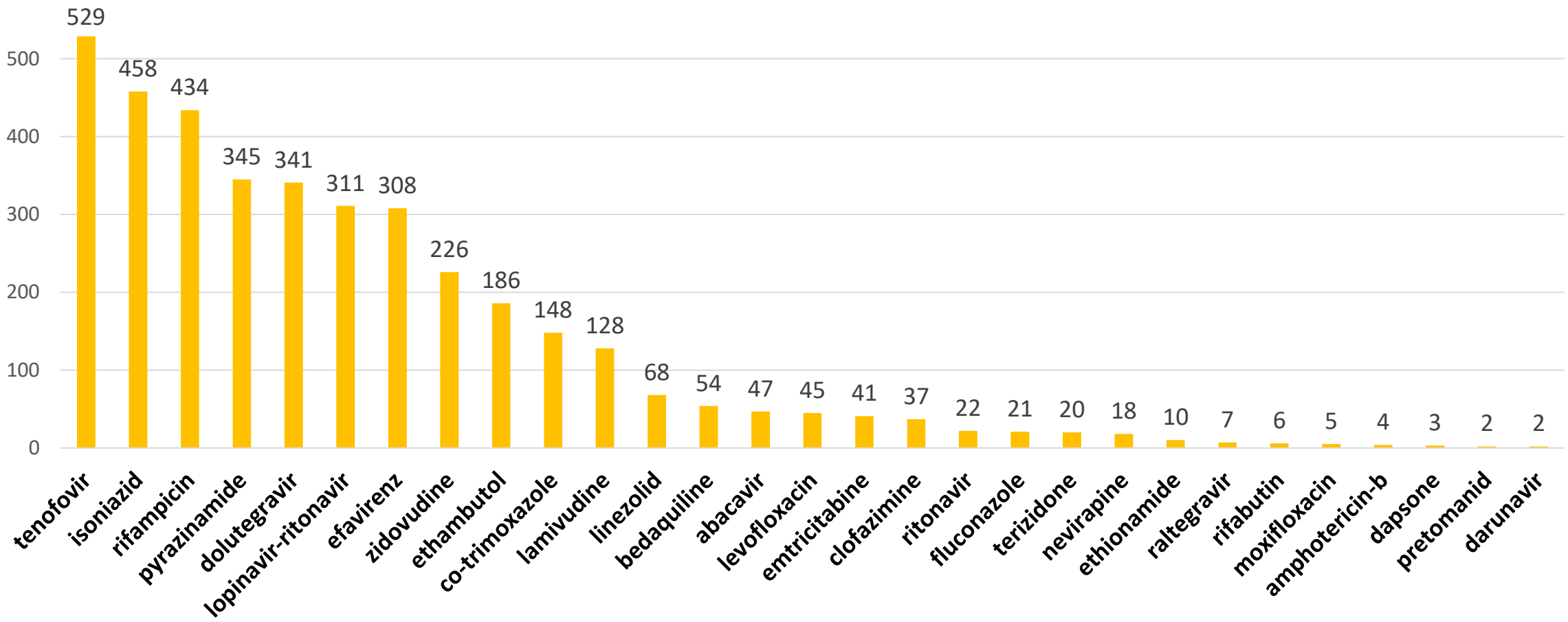


People treated for HIV, TB and/or other related opportunistic infections

ADR-related queries received by the MIC in treatment and prevention of HIV, TB and/or other related opportunistic infections (n=3826): 1 Jan 2020 – 1 Jun 2024



Medicines used in treatment and prevention of HIV, TB and opportunistic infections implicated in one or more ADR-related queries received by the MIC: 1 Jan 2020 – 1 Jun 2024 (n = 3826)



ADR-related admissions in South Africa

- 38% of all ADR-related admissions occurred in PLHIV - 32% of these were preventable
- 34% of all ADR-related admissions involved antiretroviral therapy (ART), anti-tuberculous therapy (ATT) and co-trimoxazole.
- Independent risk factors for all ADR-related admissions:
  - Female sex (aOR 1.51, 95% CI 1.06-2.14)
  - Increasing drug count (aOR 1.14 per additional drug, 95% CI 1.09-1.20)
  - Increasing comorbidity score (aOR 1.23 per additional point, 95% CI 1.07-1.41)
  - Use of ART (aOR 1.92 compared with HIV-negative/unknown, 95% CI 1.17-3.14)
- Top 4 ADRs and most implicated drugs in all ADR-related admissions:
  - Renal impairment – tenofovir (TDF)
  - Hypoglycaemia – insulin
  - Drug induced liver injury (DILI) – rifampicin
  - Haemorrhage – warfarin

aOR - adjusted odds ratio; **CI** - confidence interval

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Medicine (Baltimore). 2016 May; 95(19): e3437.
Published online 2016 May 13. doi: 10.1097/MD.0000000000003437
PMCID: PMC4902486
PMID: 27175644

Adverse Drug Reactions Causing Admission to Medical Wards

ADR-related mortality in South Africa

- ADRs contributed 16% of all patient deaths (56/357) and 2.9% of all medical admissions (56/1951)
- 43% of ADR-related deaths were preventable
- Independent risk factors associated with all ADR-related deaths:
  - Patients on ART (adjusted odds ratio (aOR) 4.4, 95% CI 1.6, 12).
  - ≥ 7 drugs taken concomitantly (aOR 2.5, 95% CI 1.3, 4.8).
  - Increasing comorbidity score (aOR 1.3, 95% CI 1.1, 1.7).
- Independent risk factors with ADR-related deaths in PLHIV:
  - ≥ 7 drugs taken concomitantly (aOR 3.6, 95% CI 1.1, 12)
- Top 2 ADRs in all ADR-related deaths:
  - Renal failure – Tenofovir (TDF)
  - Drug induced liver injury (DILI) - rifampicin, isoniazid and/or pyrazinamide

aOR - adjusted odds ratio; **CI** - confidence interval

BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol. 2015 Oct; 80(4): 818–826.
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PMCID: PMC4594724
PMID: 25475751

Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey

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ADRs Among Patients Initiating 2nd-Line ART in South Africa

- 44.5% of patients on 2nd- line ART experienced an AE in the 24 months of observation
- Most common first AE experienced:
  - Anaemia (68%) – 43.6% amongst patients on AZT + 3TC + LPVr/ATVr
  - Decreased kidney function – ABC + 3TC + LPVr/ATV/r more
- Highest AE incidence - ABC + 3TC + LPVr/ATVr (52.7/100 person-years, 95% CI 42.9, 64.8)
- Lowest AE incidence: TDF + FTC/3TC + LPVr (26.4/100 person-years, 95% CI 24.9, 28.3)
- Clinical predictors of AEs:
  - Experiencing AEs when receiving 1st-line ART (aHR) 2.3, 95% CI 1.9, 2.8)
  - Lower CD4 count (0–199 vs. ≥ 350 cells/mm3; aHR 1.4, 95% CI 1.4, 1.8)
  - Switching to 2nd-line therapy from an ABC-containing 1st-line regimen (ABC + 3TC + EFV/NVP vs. TDF + 3TC/FTC + EFV/NVP; aHR 3.4, 95% CI 1.1, 11.1)

aHR - adjusted hazard ratio; **CI** - confidence interval

Onoya D, *et al.* Drug Saf. 2018 Dec;41(12):1343-1353.

Factors which may predispose patients with advanced HIV to ADRs

- **Immunosuppression (low CD4, high VL, advanced HIV staging)**
- **Comorbidities and pre-existing conditions**
- **Polypharmacy**
  - Concomitant drugs with additive/overlapping toxicity profiles (e.g. ART + TB therapy, TDF + Ampho B, AZT + Linezolid)
  - Inducers reduce levels of other drug(s) → therapy failure, drug resistance
  - Inhibitors increase levels of other drug(s) → drug toxicity
  - hepatic/renal impairment affecting metabolism/elimination of toxic drugs + metabolites
- **Organ dysfunction**
- **Prior treatment and ADR history** – sequalae, cross reactivity, inadvertent re-exposure
- **Other factors** – genetics (polymorphism), age, gender, weight, socioeconomic status, accessibi

ART – antiretroviral therapy; ATT – anti-TB therapy, CNS – central nervous system

Factors which may predispose patients with advanced HIV to ADRs

- Immunosuppression
- Comorbidities and pre-existing conditions
- Polypharmacy - drug interactions
- Organ dysfunction
- Prior treatment and ADR history
- Others

COMMON & SEVERE ADRs ASSOCIATED WITH ART

Renal Effects

	Renal effects
NRTI	TDF: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. TAF: Less impact on renal biomarkers and lower rates of proteinuria than TDF
NNRTI	RPV: Inhibits Cr secretion without reducing renal glomerular function
PI	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. ATV: Stone or crystal formation; adequate hydration may reduce risk
INSTI	DTG: Inhibits Cr secretion without reducing renal glomerular function

Question 3: Which one of the following statements is incorrect when comparing tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF)?

A. Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are both prodrugs of tenofovir and effective in suppressing HIV and hepatitis B viral loads.

B. TAF is associated with less renal toxicity and lower impact on bone mineral density due to lower plasma levels of tenofovir compared to TDF.

C. TAF/FTC can be used in renal impairment provided the calculated creatinine clearance (CrCl) or estimated glomerular rate (eGFR) is above 15 mL/min.

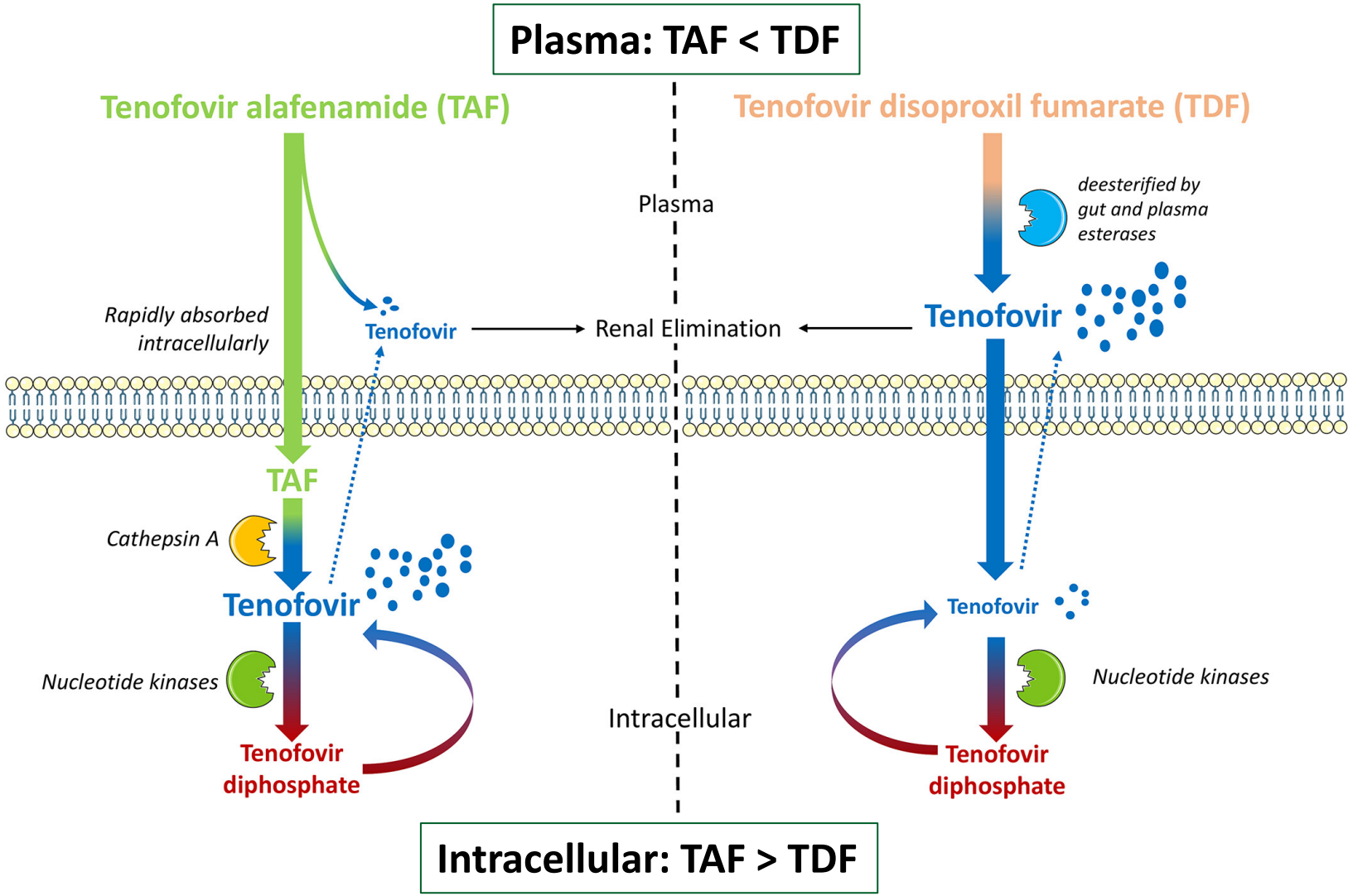
TAF/FTC combination formulation can only be used if eGFR > 30mL/min (cannot adjust FTC dose in combination)

TAF as a single formulation can be used if eGFR > 15mL/min

D. Dosing of TAF and TDF are not the same.

C. TAF has more potential for significant interactions with other medicines which inhibit or induce p-glycoprotein compared to TDF.

Conversion of Tenofovir disoproxil fumarate (TDF) & Tenofovir alafenamide (TAF) to Tenofovir diphosphate (TFV-DP)



Kawuma AN, *et al*. CPT Pharmacometrics Syst Pharmacol. 2023; 12: 821-830.

Tenofovir disoproxil fumarate (TDF) vs Tenofovir alafenamide (TAF)

Differences	TDF	TAF
Pharmacokinetics	Higher plasma vs intracellular tenofovir	▪ Higher intracellular vs plasma tenofovir
Dosing	▪ Usual dose - 300mg daily ▪ eGFR < 50mL /min - avoid use**	▪ Usual dose - 25mg daily ▪ eGFR < 30 mL/min – avoid TAF/FTC ▪ eGFR < 15 mL/min – avoid TAF** or TAF/FTC
Adverse effect profile	Renal and bone toxicity: TDF > TAF	Increased LDL, HDL cholesterol, triglycerides and weight gain
Place in therapy	Only prodrug available for treatment (ART) and prevention (PEP and PrEP) in public sector as of July 2024.	Preferred in patients with chronic hepatitis B, and either an eGFR of 30 to 50mL/min or osteoporosis.
Safety concerns	Avoid in renal impairment (eGFR < 50mL/min)	▪ Not yet approved in public sector Limited use and experience in pregnancy ▪ Interactions with P-gp inhibitors (e.g. ritonavir boosted PIs) and inducers (e.g. rifampicin, rifabutin, carbamazepine, phenobarbitone)

* TAF alone can be used in eGFR as low as 15mL/min, but co-formulation as TAF/FTC limits it use to eGFR no lower than 30 mL/min.
**May be used with adjusted doses if patient is on dialysis

Dosing ARVs and TB drugs in renal impairment (NDoH)

ADULT HIV AND TB DRUG DOSING

INCLUDING RENAL DOSE ADJUSTMENTS

May 2024, Version 3

NEED HELP?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline
0800 212 506 /021 406 6782
Alternatively "WhatsApp" or send an SMS or "Please Call Me" to 071 840 1572
www.mic.uct.ac.za

ANTITUBERCULOUS DRUGS

When used as fixed-dose combination:

Treatment phase	Intensive phase - daily for 2 months	Continuation phase – daily for 4 months		eGFR < 30 mL/min
Body weight (kg)	RHZE (150,75,400,275)	RH (150,75)	RH (300,150)	RH: Unchanged. RHZE: Dosing adjustment needed for pyrazinamide and ethambutol. See individual agents below.
25 – 37.9 kg	2 tablets	2 tablets		
38 – 54.9 kg	3 tablets	3 tablets		
55 – 70.9 kg	4 tablets		2 tablets	
≥ 71 kg	5 tablets		2 tablets	

When used as single agents: (for severely underweight patients please consult the Hotline)

Drug	Target dosing	Standard adult dose	eGFR < 30 mL/min
Amikacin	15 – 20 mg/kg daily	46 – 55.9 kg: 750 – 1000 mg daily ≥ 56 kg: 1000 mg daily	Stop amikacin. If essential, use with therapeutic drug monitoring
Bedaquiline	If bedaquiline treatment interrupted for > 2 weeks, call the hotline for advice on restarting	≥ 30 kg: 400 mg daily for 2 weeks then 200 mg three times a week (M/W/F) until completed **OR** BPaL-L regimen only: 200 mg daily for 8 weeks then 100 mg daily	Unchanged (but dosing not established in severe renal impairment, use with caution)
Clofazimine	2 – 5 mg/kg daily	100 mg daily	Unchanged
Delamanid		30 – 45.9 kg: 50 mg 12 hourly ≥ 46 kg: 100 mg 12 hourly	Unchanged (but dosing not established in severe renal impairment, use with caution)
Ethambutol	15 – 25 mg/kg daily	30 – 45.9 kg: 800 mg daily 46 – 69.9 kg: 1200 mg daily ≥ 70 kg: 1600 mg daily	Standard dose given three times weekly
Ethionamide (can be given in 2 divided doses to improve tolerance)	15 – 20 mg/kg daily	30 – 45.9 kg: 500 mg daily 46 – 69.9 kg: 750 mg daily ≥ 70 kg: 1000 mg daily	Unchanged
Isoniazid (high dose)	10 – 15 mg/kg daily	30 – 45.9 kg: 450 mg daily ≥ 46 kg: 600 mg daily	Unchanged
Levofloxacin	15 – 20 mg/kg daily	30 – 45.9 kg: 750 mg daily ≥ 46 kg: 1000 mg daily	Standard dose given three times weekly
Linezolid	10 mg/kg daily	30 – 35.9 kg: 300 mg daily ≥ 36 kg: 600 mg daily	Unchanged
Moxifloxacin		≥ 30 kg: 400 mg daily	Unchanged
Para-aminosalicylic acid	200 – 300 mg/kg daily	30 – 69.9 kg: 4 g 12 hourly ≥ 70 kg: 4 – 6 g 12 hourly	4 g 12 hourly
Pretomanid		≥ 30 kg: 200 mg daily	Unchanged
Pyrazinamide (dose depends on which tablet strength is available)	20 – 30 mg/kg daily	30 – 35.9 kg: 1200 – 1250 mg daily 36 – 69.9 kg: 1500 – 1600 mg daily ≥ 70 kg: 2000 mg daily	25 – 35 mg/kg three times weekly
Rifabutin		300 – 450 mg daily Reduce dose to 150 mg daily if used in combination with a protease inhibitor.	Unchanged (but consider a dose reduction of 50% if toxicity is suspected)
Terizidone	10 – 15 mg/kg daily	30 – 45.9 kg: 500 mg daily ≥ 46 kg: 750 mg daily	250 mg daily or 500 mg three times weekly

ANTIRETROVIRALS

Drug	Standard adult dose	eGFR 30-50 mL/min	eGFR 15-30 mL/min	eGFR < 15 mL/min
Abacavir	600 mg daily OR 300 mg 12 hourly	Unchanged	Unchanged	Unchanged
Atazanavir/ritonavir	300 mg/100 mg daily Cannot be used with rifampicin. Replace rifampicin with rifabutin, and adjust the dose of rifabutin to 150 mg daily. Continue standard dose of atazanavir/ritonavir.	Unchanged	Unchanged	Unchanged
Darunavir/ritonavir	600 mg/100 mg 12 hourly OR 800 mg/100 mg daily (depending on mutations) Cannot be used with rifampicin. Replace rifampicin with rifabutin, and adjust the dose of rifabutin to 150 mg daily. Continue standard dose of darunavir/ritonavir.	Unchanged	Unchanged	Unchanged
Dolutegravir	50 mg daily If also on rifampicin: boosting of DTG required. The dosing frequency of DTG should be increased to 50 mg 12 hourly. If on TLD FDC, then add DTG 50 mg 12 hours after TLD. Continue boosting until 2 weeks after rifampicin discontinued.	Unchanged	Unchanged	Unchanged
Efavirenz	600 mg at night (or 400 mg if < 40 kg) The use of efavirenz with bedaquiline is contraindicated.	Unchanged	Unchanged	Unchanged
Etravirine	200 mg 12 hourly	Unchanged	Unchanged	Unchanged
Lamivudine	300 mg daily OR 150 mg 12 hourly	Unchanged	150 mg daily	50 mg daily
Lopinavir/ritonavir	400 mg/100 mg 12 hourly If also on rifampicin: Increase LPV/r to 800/200 mg twice daily slowly over 2 weeks with ALT monitoring. Continue double dose for 2 weeks after stopping rifampicin.	Unchanged	Unchanged	Unchanged
Rilpivirine	25 mg daily	Unchanged	Unchanged	Unchanged
Tenofovir alafenamide (TAF)	25 mg daily	Unchanged	Unchanged	Avoid *
Tenofovir disoproxil fumarate (TDF)	300 mg daily	Avoid	Avoid	Avoid *
Zidovudine	300 mg 12 hourly	Unchanged	Unchanged	300 mg daily

DRUGS FOR PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS

Drug	Standard adult dose	eGFR 10-50 mL/min	eGFR < 10 mL/min
Co-trimoxazole	800/160 mg daily	400/80 mg daily	400/80 mg three times per week
Dapsone	100 mg daily	No recommendation	No recommendation
Fluconazole	200 mg daily	100 mg daily	100 mg daily

ASSESSING RENAL FUNCTION

- Creatinine is a waste product filtered by the kidneys. If serum creatinine (SCr) rises it is a sign that the kidneys are not working properly. As serum creatinine rises, the eGFR falls.
- The GFR can be estimated using various formulae, e.g. Modified Cockroft-Gault, MDRD, CKD-EPI. The important point to remember is to consistently use the same formula for the same patient.
- For pregnant women with SCr > 85, discuss with an expert.

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Largely based on NDoH Management of rifampicin-resistant TB guidelines, Sept 2023. Additional references available on request. ALT = alanine aminotransferase; FDC = fixed dose combination; RHZE = fixed dose combination of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E); RH = fixed dose combination of rifampicin and isoniazid; TLD = tenofovir + lamivudine + dolutegravir

* May be used if patient is on haemodialysis

Skin Reactions

Skin reaction	NRTI	NNRTI	PI	INSTI
Rash	FTC*	All	ATV/r, DRV/r, LPV/r	All
Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrosis (TENS)	-	**NVP** > EFV, ETR, RPV	ATV/r, DRV/r, LPV/r (rare reports)	RAL > DTG (rare)
Hypersensitivity reaction (HSR) excluding rash alone or SJS/TENS	**ABC** # (HLA-B*5701 gene)	**NVP** ##	-	RAL, DTG (rare)

All the first-line TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) and co-trimoxazole are associated with rashes including SJS/TENS/DRESS

ABC HSR symptoms (in descending frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhoea, vomiting, abdominal pain, dyspnoea, arthralgia, and respiratory symptoms

NVP HSR symptoms: Fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy

*Hyperpigmentation

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv.

Question 4: Which one of the following statements is incorrect about managing suspected drug-induced skin reactions?

A. TB treatment, ART, co-trimoxazole and other non-essential medicines should be immediately stopped if the patient presents with a rash and any one of the following: systemic illness/feeling unwell, fever, hepatitis, skin blistering, eosinophilia (raised eosinophil count), or mucosal involvement of the eyes, mouth, or genitalia

B. Stop Nevirapine (NVP) or Efavirenz (EFV) in patients who develop serious skin reactions and do not reinitiate (rechallenge) either medicine after recovering.

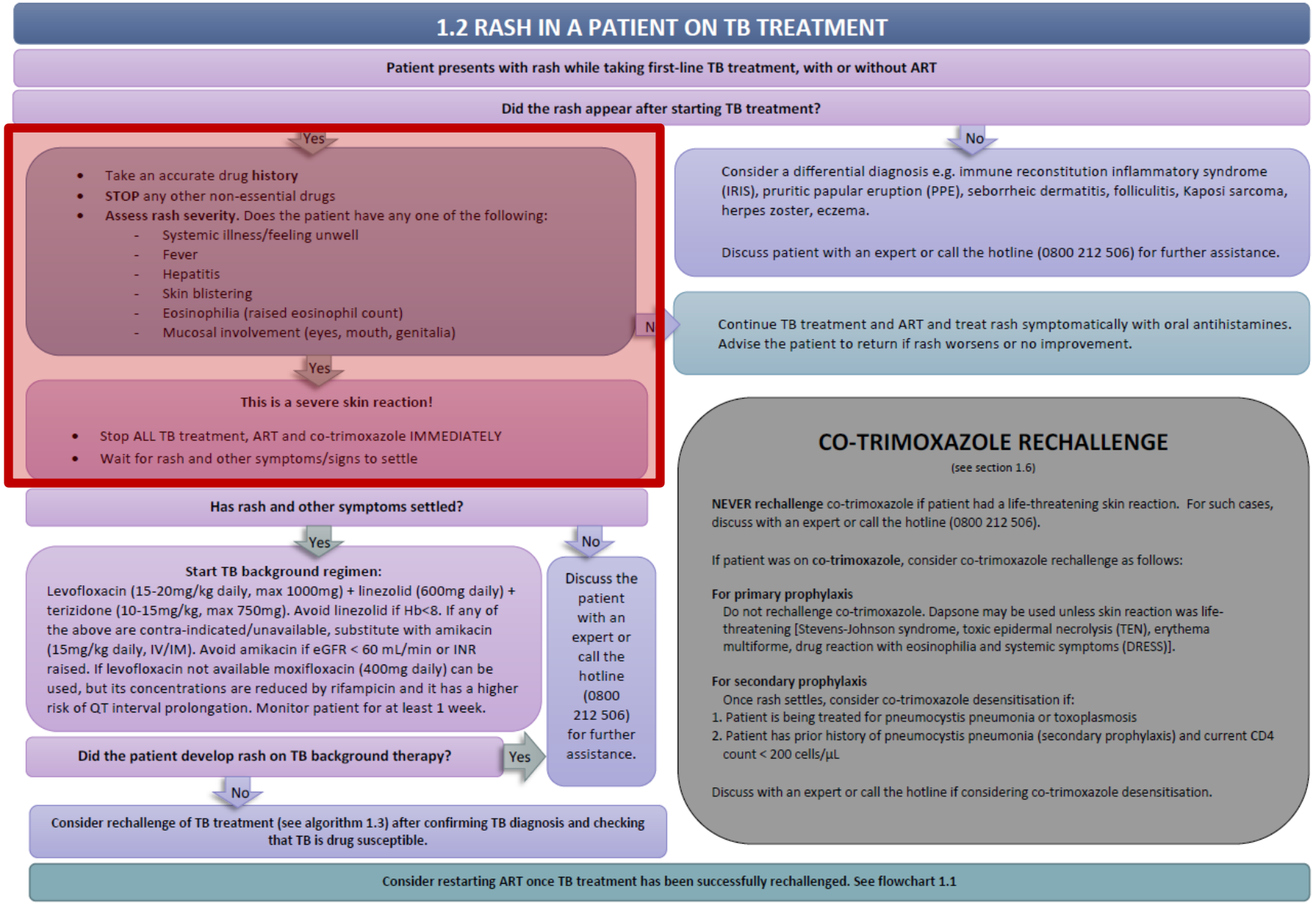
C. If the patient was on 1st line TB therapy, stop Rifafour and switch to a liver-friendly regimen consisting of Ethambutol (EMB), Levofloxacin (LFX) and Linezolid (LZD).

Ethambutol also causes serious skin reactions and should be stopped with rifampicin + isoniazid + pyrazinamide.

'Liver-friendly' is misleading and 'background regimen' is preferred to be used.

D. Wait for the rash and other symptoms/signs to settle before considering reintroduction (rechallenge) of TB treatment.

Skin Reactions



Hepatic effects

	Hepatic effects
NRTI	TAF, TDF, 3TC, FTC: Hepatic flares when withdrawn in HBV/HIV coinfection AZT: Steatosis
NNRTI	EFV: Increase in transaminases (common), fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm3 and men with pre-NVP CD4 counts >400 cells/mm3. EFV and NVP are not recommended in patients with hepatic insufficiency (Child-Pugh class B or C).
PI	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported. ATV: Jaundice due to indirect hyperbilirubinemia
INSTI	DTG: higher risk of DTG-associated hepatotoxicity in patients with HBV or HCV coinfection .

CASE

45-year female, 58kg, HIV/TB coinfected presents to her local clinic complaining of nausea, vomiting and yellowing of eyes for 4 days. She was admitted to hospital for further workup and management of suspected ADR.

Medication history:

- TLD (TDF/3TC/DTG) 1 tablet at night (4 months)
- DTG 50mg taken 12 hours after TLD (5 weeks)
- Co-trimoxazole 2 tablets daily (1 month)
- Rifafour (RIF/INH/PZA/EMB) (5 weeks)
- Pyridoxine (Vit B6) 25mg daily (5 weeks)

Laboratory results on admission:

- LFTs: ALT 422, AST 185, ALP 223, GGT 125, Bilirubin total 68, INR 1.18
- HepBsAg negative
- CD4 187
- eGFR > 60

Question 5: In the case, which medicine/s should be stopped and suspected of causing or contributing to the suspected DILI?

A. All medicines except pyridoxine (Vit B6)

B. Only Rifafour (RIF/INH/PZA/EMB)

C. Rifafour and co-trimoxazole

D. All other drugs except TLD + DTG

Hepatic effects

Southern African Journal of HIV Medicine
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AOSIS

Page 1 of 7 Guideline

Management of drug-induced liver injury in people with HIV treated for tuberculosis: 2024 update

CrossMark

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE
0800 212 506

Management of suspected drug-induced rash, kidney injury and liver injury in adult patients on TB treatment and/or antiretroviral treatmen

July 2020
2nd Edition

MEDICINES INFORMATION CENTRE
DIVISION OF CLINICAL PHARMACOLOGY
UNIVERSITY OF CAPE TOWN

Cardiac Effects

Cardiac Effect	NRTI	NNRTI	PI	INSTI
Cardiovascular disease	**ABC** – MI? risk greatest in patients with traditional CVD risk factors.	-	Boosted DRV and LPV/r: associated with cardiovascular events in some cohorts	-
Dyslipidaemia	**d4T > AZT > ABC**: ↑ TG + LDL **TAF**: ↑ TG + LDL + HDL (no change in TC:HDL ratio) **TDF**: lower lipid levels than ABC or TAF	**EFV**: ↑ TG + LDL + HDL	**LPV/r > DRV/r > ATV/r:** ↑ TG + LDL + HDL Risk: Lower risk with PIs requiring lower RTV boosting dose	-
Cardiac conduction	-	**RPV, EFV**: ↑ QTc	**ATV/r, LPV/r**: PR prolongation. Risk factors: pre-existing CVD, concomitant meds that may cause PR prolongation.	-

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services.

Dyslipidaemia

Implicated drugs

LPV/r > DRV/r, ATV/r, EFV, AZT

Monitoring

Lipids 3 months after initiating PI based regimen. Repeat only in patients with CV risk factors

Management

1. Diet and lifestyle modification (↑ TG: restrict of total TG < 30 g/day)
2. Address any other CV risk factors (smoking, diabetes, hypertension)
3. Rule out secondary causes (e.g. diabetes, nephrotic syndrome, alcohol abuse and hypothyroidism)
4. Switch to alternative: LPV/r → ATV/r, DRV/r or DTG; EFV → RPV or DTG
5. Lipid lowering therapy: ↑TG = fibrate ; ↑TC = statin

Dyslipidaemia

Indications for fibrate therapy

- TG > 10 mmol/L - Fibrates can be stopped after 1 month, followed by reassessment within 4–6 weeks.

Indications for statin therapy

- Isolated elevated cholesterol: TC > 7.5 mmol/L or LDL-C > 5mmol/L) - Framingham heart disease risk score
- Patients with CV risk factors (smoking, diabetes, hypertension) – Framingham heart disease risk score.
- Established atherosclerotic disease or familial hypercholesterolaemia
- Type 2 diabetes with CKD / Age> 40 years / diabetes > 10 years + 1 or more additional CV risk factors

Drug Interactions: PIs + Statins = ↑statin concentrations = ↑myopathy + rhabdomyolysis

- Avoid simvastatin, lovastatin and rosuvastatin (reduced efficacy)
- Pravastatin or Fluvastatin preferred if therapy is required (no clinically relevant interaction expected)
- Atorvastatin if limit dose to 10mg/day with close monitoring

Lipodystrophy – Lipoatrophy & Lipohypertrophy

Lipoatrophy

Loss of subcutaneous fat in the arms, legs, face and buttocks

Implicated drugs: d4T > AZT

Management: Early detection and switch from AZT/d4T → ABC/TDF. Cosmetic surgery?

Lipohypertrophy

Accumulation of fat in the abdomen, viscera, breasts, cervical area (bull neck) or dorsocervical area (buffalo hump)

Implicated drugs: EFV, PI and RAL? - causal relationship has not been established

Management: Diet and exercise (reduce visceral fat accumulation), Metformin (if insulin resistance), and cosmetic surgery

CNS effects

	CNS effects
NRTI	NA
NNRTI	Neuropsychiatric events: EFV > RPV, DOR, ETR EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors. RPV: Depression, suicidality, sleep disturbances DOR: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm
PI	N/A
INSTI	All: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.

DETECTING AND MANAGING SUSPECTED ADRs

Detecting & recognising a suspected ADR

Plausible causal relationship?

- Ensure that the drugs(s) were actually administered/taken prior to or during onset of the suspected ADR.
- Verify onset date/time of suspected ADR (signs, symptoms, abnormal laboratory findings) relative to exposure to medicines administered/taken.
- Determine a temporal relationship from the time interval between the time therapy was taken/administered relative to the onset/duration of the suspected ADR.

Other explanations contributing to the event/reaction?

- Disease/disorder vs other drugs vs interactions.
- Check relevant up-to-date literature to verify if there are previous conclusive reports on the suspected ADR.
  - Note: suspicion should not be ruled out if it is not reported/established.

Managing a suspected ADR

Benefit: risk assessment

- **Nature of the disease/disorder/comorbidities**
  - Severity of disease and progression/prognosis
- **Need for continued drug therapy**
  - Vital vs essential vs non-essential
  - Availability of safe-effective alternatives
- **Nature of reaction and actual/potential harm outcomes**
  - Severity - the intensity of the ADR (DAIDS grading)
  - Seriousness - significance of actual or potential harm and outcomes resulting from any ADR

ADR Severity Grading - DAIDS

Describes the intensity of the ADR (signs & symptoms)

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions

- Grade 1 = mild • Grade 2 = moderate event • Grade 3 = severe • Grade 4 = potentially life-threatening
- Grade 5 = death (grade is not specifically listed on each page of the grading table).

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

U.S. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Corrected Version 2.1. [July 2017].

ADR Seriousness

Describes the significance of actual/ potential harm and outcomes/progression from any ADR

- Requires intervention to resolve/ prevent harm
- Requires hospitalisation (initial/prolonged)
- Results in persistent or significant disability/impairment
- Results in congenital anomaly/ birth defect
- Life threatening (at risk of death at time of event)
- Results in Death

Managing a suspected ADR

Interventions to resolve/prevent harm

A. Continue suspect drug(s):

- Monitor
- Treat symptomatically
- Decrease dose

B. Discontinue suspect drugs (de-challenge)

Reaction resolves after discontinuation of suspect medicine/s = positive dechallenge

Reaction does not resolve after discontinuation of suspect medicine/s = negative de-challenge

- Temporary vs permanent based on severity & seriousness of reaction, risk for recurrence, cross-reactivity
- Time to recovery varies based on nature of reaction/abnormality

Managing a suspected ADR

Interventions to resolve/prevent harm

C. Reintroduce suspect drug/s following recovery (rechallenge)

Positive rechallenge - same or similar reaction recurs following reintroduction of suspect drug/s

Negative rechallenge - same or similar reaction does not recur following reintroduction of suspect drug/s

- Rechallenge is NOT compulsory: contraindicated with severe/serious reactions, hypersensitivity reactions
- Only consider in exceptional cases (e.g. no safe-effective alternatives for vital/essential drugs) with close monitoring and under experienced supervision (e.g. immunology)

D. Replace suspected drug/s with alternatives:

- Availability of safe, equally effective alternatives

- Risk of cross reactivity or similar reaction with alternative
- Drug interactions
- Single ARV drug class switch with unsuppressed VL – resistance - failure

REPORTING SUSPECTED ADRs

Reporting ADRs in South Africa - SAHPRA

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

https://www.sahpra.org.za/

Form

E-mail:
adr@sahpra.org.za

Internet

E-reporting portal:
https://primaryreporting.who-umc.org/ZA

Mobile App

Google Play (Android) | App Store (iOS):
Med Safety App (Web-RADR)

SAHPRA ADR Reporting Form

Doc Number: GLF-CEM-PV-06A *[Old Doc no. 6.04]*	**ADVERSE DRUG REACTION (ADR)/ PRODUCT QUALITY PROBLEM REPORT FORM** (PUBLIC AND PRIVATE SECTOR) (Including Herbal Products)	SAHPRA South African Health Products Regulatory Authority
Revision: 3.0		Effective date: 11 October 2023

See Page 2 for CONSENT CLAUSE, more information regarding reporting of PRODUCT QUALITY PROBLEMS and ADVERSE EVENTS FOR VACCINES

Reporting Health Care Facility/Practice

Building A, Loftus Park 402 Kirkness Street, Arcadia, Pretoria Tel: (012) 501 0311 E-mail: adr@sahpra.org.za	Facility/Practice				
	District		Tel		
	Province		Fax		

Patient Details

Patient Initials		File/Reference Number			Date of Birth/Age				
Sex	☐M ☐F ☐Unk	Race		Weight (kg)		Height (cm)		Pregnant?	☐N ☐Y
Allergies			☐ **Follow up report** **Reference number:** _____					Estimated gestational age at time of reaction	

Suspect Medicine(s) [Medicines suspected to have caused the ADR], Concomitant [Other medicines taken together with the suspect medicine(s)] OR Interacting [Other medicines taken together with the suspect medicine(s) and may have interacted with the suspect medicine(s)] [Including over the counter and herbal products].

Trade Name [Active Ingredient if Trade Name is unknown]	Medicine role (Please tick the applicable box)	Route	Dose (mg) and Interval	Date Started/ Given	Date Stopped	Reason for use	Batch Number	Expiry Date
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							
	☐ Suspect ☐ Concomitant ☐ Interacting							

Adverse Drug Reaction/Product Quality Problem

Date and time of onset of reaction		Date reaction resolved	

Please describe Adverse Event/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention (Tick all that apply)	**Patient Outcomes (Tick all that apply)**	**ADR seriousness criteria (Tick all that apply)**
☐ No intervention. ☐ Intervention unknown. ☐ Patient counselled/non-medical treatment. ☐ Discontinued suspect drug; **Replaced with:** _____ ☐ Decreased suspect drug dosage; **New Dose:** _____ ☐ Treated ADR – with: _____ ☐ Referred to hospital; **Hospital name** _____ ☐ Other intervention (e.g., dialysis): _____	☐ ADR recovered/resolved. ☐ Recovering/resolving. ☐ Not recovered/not resolved. ☐ Recovered with sequelae. ☐ ADR resolved after suspect medicine was stopped: ☐N ☐Y. ☐ ADR reappeared after restarting suspect drug/similar drug (rechallenge): ☐N ☐Y ☐ Not done ☐ Unknown	☐ Resulted in death. Date of death: _____ ☐ Patient hospitalised or hospitalisation prolonged. ☐ Life threatening. ☐ Impairment/disability. ☐ Congenital anomaly/ birth defect. ☐ Other medically important condition.

Laboratory Results			**Additional Laboratory Results**		
Lab Test	**Test Result**	**Test Date**	**Lab Test**	**Test Result**	**Test Date**

Co-morbidities/Other Medical Condition(s)

Reported by

Name		E-mail	
Designation	☐Nurse ☐Pharmacist ☐Doctor ☐Other:	Telephone	
Date reported:		Signature	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:
- medications (medicines and biologicals),
- complementary / alternative medicines (including traditional, herbal remedies, etc).

Please report especially:
- adverse drug reactions to newly marketed products,
- serious reactions and interactions with all products,
- adverse drug reactions which are not clearly reflected in the package insert.

Report Product Quality Problems such as:
- suspected contamination,
- questionable stability,
- defective components,
- poor packaging or labelling,
- therapeutic failures.

Report even if:
- you're not certain the product caused the event,
- you don't have all the details.

Report adverse events experiences with Medical Device via:
- phone: 012 501 0476
- mdvigilance@sahpra.org.za

Report Adverse Events Following Immunisation (AEFI) experienced with vaccines on:
- the dedicated Case Reporting Form accessed from SAHPRA portal: https://www.sahpra.org.za/health-products-vigilance/
- forward the dedicated form to AEFI@health.gov.za
- phone: 0800 02 9999.

Report Product Quality Problems via:
- phone: 0800 204 307

SAHPRA portal: https://www.sahpra.org.za/complaints-relating-to-medicine-and-medical-devices/

Other reporting tools available at SAHPRA include:

Med Safety Application

The Med Safety Application is a mobile application designed for the public and healthcare professionals to report suspected ADRs/adverse event following immunisations (AEFIs). It is the preferred reporting tool by SAHPRA and allows for a seamless electronic submission of ADR/AEFI reports directly from the source into SAHPRA's reporting systems. The app can be downloaded onto a smart mobile phone directly from the SAHPRA website, https://medsafety.sahpra.org.za.
For more reporting channels please visit SAHPRA website, https://www.sahpra.org.za

CONSENT CLAUSE

By the signature above, the reporter hereby provides consent to the processing of personal information provided for the purpose of reporting a suspected adverse reaction. The reporter acknowledges that this information may be used a) to access all medical and clinical records for the purpose of gathering additional information for a clinical meaningful data, when required; b) in the generation of statistics; and c) to make policy decisions relating to safe use of medicines.

SAHPRA's Vigilance unit undertakes to collate the personal information contained in this form and collected during the process of reporting of suspected adverse drug reaction in a manner that adheres to the Protection of Personal Information Act, so that your personal data is processed fairly, lawfully and transparently, adequate, relevant, and limited to what is necessary, processed for specific and legitimate purposes, accurate and kept up to date where necessary, kept in an identifiable form no longer than necessary for the purpose and processed securely . SAHPRA has placed appropriate technical and organisational measures to safeguard your information. The information will not be stored for any longer than is necessary to achieve the purpose for which it was collected, unless the unit has a lawful basis to do so. If the reporter wishes to access and/or rectify their personal information, they may do so by contacting SAHPRA's Vigilance unit at 012 501 0311 or via email: adr@sahpra.org.za.

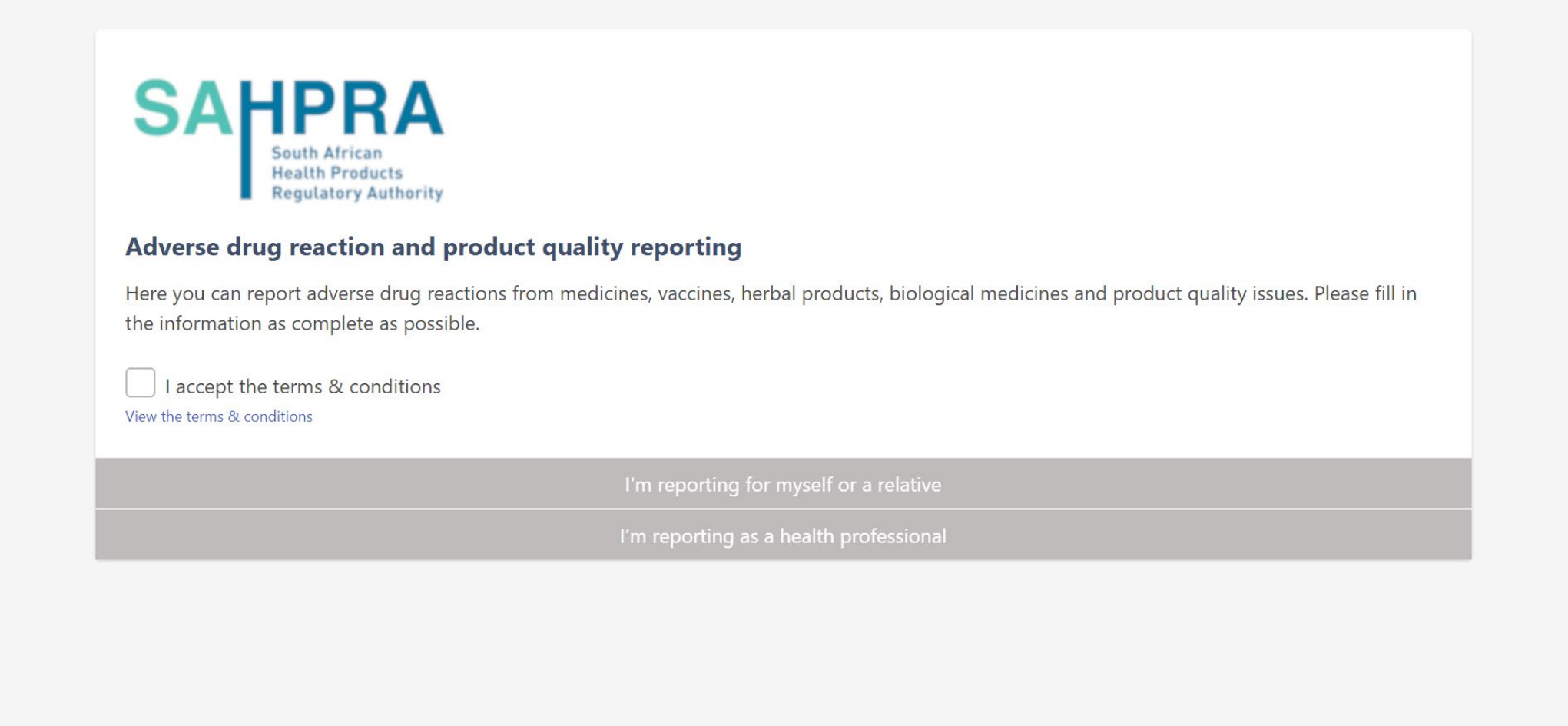
Confidentiality:

Identities of the reporter and patient will remain strictly confidential.

Your support of the South African Health Products Regulatory Authority's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

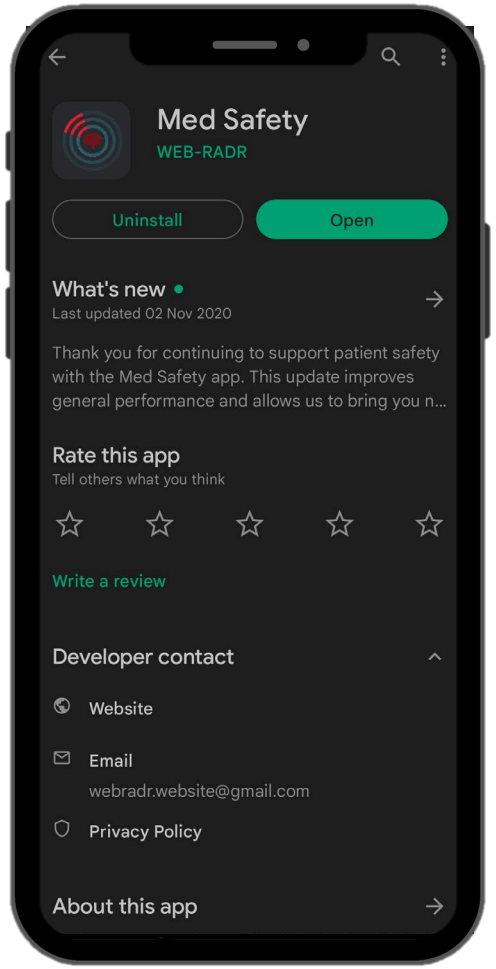
Approved for use!

SAHPRA ADR e-reporting portal (internet)



Website link: https://primaryreporting.who-umc.org/ZA

SAHPRA Medsafety App



Watch how to use the Medsafety App
Website link: https://www.youtube.com/watch?v=uIGGy1OSgIY

Download the Med Safety mobile app from Google Play or App store.
It should read “Med Safety” Web-RADR.
Website link: https://medsafety.sahpra.org.za/#download1

Question 6: Which statement is incorrect about reporting suspected ADRs?

A. Report all serious reaction/s; result in death; are life-threatening; require patient hospitalisation or prolongation of existing hospitalisation; results in an abortion, premature delivery, or congenital anomaly/birth defects; or results in persistent or significant disability/incapability

B. Report even if you are unsure which medicine/s caused or contributed to the suspected ADR/s

C. Only report if the reaction/s are listed in the package insert/s of the medicine/s taken by the patient.

A suspected reaction not listed/documented in a package insert of a medicine does not exclude it from causing or contributing, especially if the reaction is rare, occurs after long-term use, or was not previously described/documented

D. Report all reactions which occur in paediatrics, elderly and during pregnancy or breastfeeding.

Report What?

All Adverse events or experiences with:

- ❑ Registered and unregistered medicines
- ❑ Medical devices | In-vitro diagnostics
- ❑ Vaccines | Biologicals
- ❑ Complementary | Alternative | Traditional | Herbal | Natural products

Serious reactions resulting in:

- ✓ Any intervention to prevent impairment/harm
- ✓ Hospitalisation (initial/prolonged)
- ✓ Disability/impairment
- ✓ Congenital anomaly/ birth defect
- ✓ Life threatening
- ✓ Death

Significant reactions:

- ✓ Children, elderly and during pregnancy/breastfeeding
- ✓ Foetal or infant exposures during pregnancy/breastfeeding
- ✓ Newly marketed products (< 5 years)
- ✓ ADRs not clearly stated in package inserts
- ✓ ADRs occurring more frequently than previously reported
- ✓ ADRs resulting from interactions (drug, food, disease)
- ✓ Therapeutic failures

Should I Report?

Do you suspect an ADE/ADR?

YES ↓

Reaction is serious/severe or significant? — YES → **REPORT**

NO ↓

Is the patient a child, elderly, pregnant or breastfeeding? — YES → **REPORT**

NO ↓

Is it a new product (< 5 years from registration)? — YES → **REPORT**

NO ↓

Reaction is well described in the PI/SmPC? — NO / UNSURE → **REPORT**

YES ↓

Not necessary to report ADR

****Report even if you are unsure or in doubt****
*****Reporter and patient details are confidential*****
A report does not constitute an admission that medical personnel or a product caused or contributed to the event

Serious reactions resulting in:

- ✓ Any intervention to prevent impairment/harm
- ✓ Hospitalisation (initial/prolonged)
- ✓ Disability/impairment
- ✓ Congenital anomaly/ birth defect
- ✓ Life threatening
- ✓ Death

Significant reactions:

- ✓ In children, elderly, pregnancy, breastfeeding
- ✓ Foetal/infant exposures during pregnancy/breastfeeding
- ✓ Newly marketed products (< 5 years)
- ✓ Not clearly stated in package inserts
- ✓ Occurring more frequently than previously reported
- ✓ Resulting from interactions (drug, food, disease)
- ✓ Therapeutic failures

PHARMACOVIGILANCE THROUGH PRODUCT LIFECYCLE

PREVENTION

Inform + Prevent
Guidelines
Policies & Protocols
Restriction
Medicine alerts/ recalls
Withdrawal/suspension
Media statements
Training & education

REGULATOR

POLICY MAKERS

Estimate + Understand
Further studies
Seriousness and severity
Trends, risk factors
Incidence and prevalence

Review + Update
Rescheduling/restrictions
Labelling/packaging
PIL, PI updates

UNDERSTANDING

PATIENT

Complaint/concern
Adverse drug event

DETECTION

PHARMACEUTICAL

Collect + Research
Pre- & post-marketing
safety information

HEALTHCARE WORKER

Manage & Report
Suspected ADE/ADR

ASSESSMENT

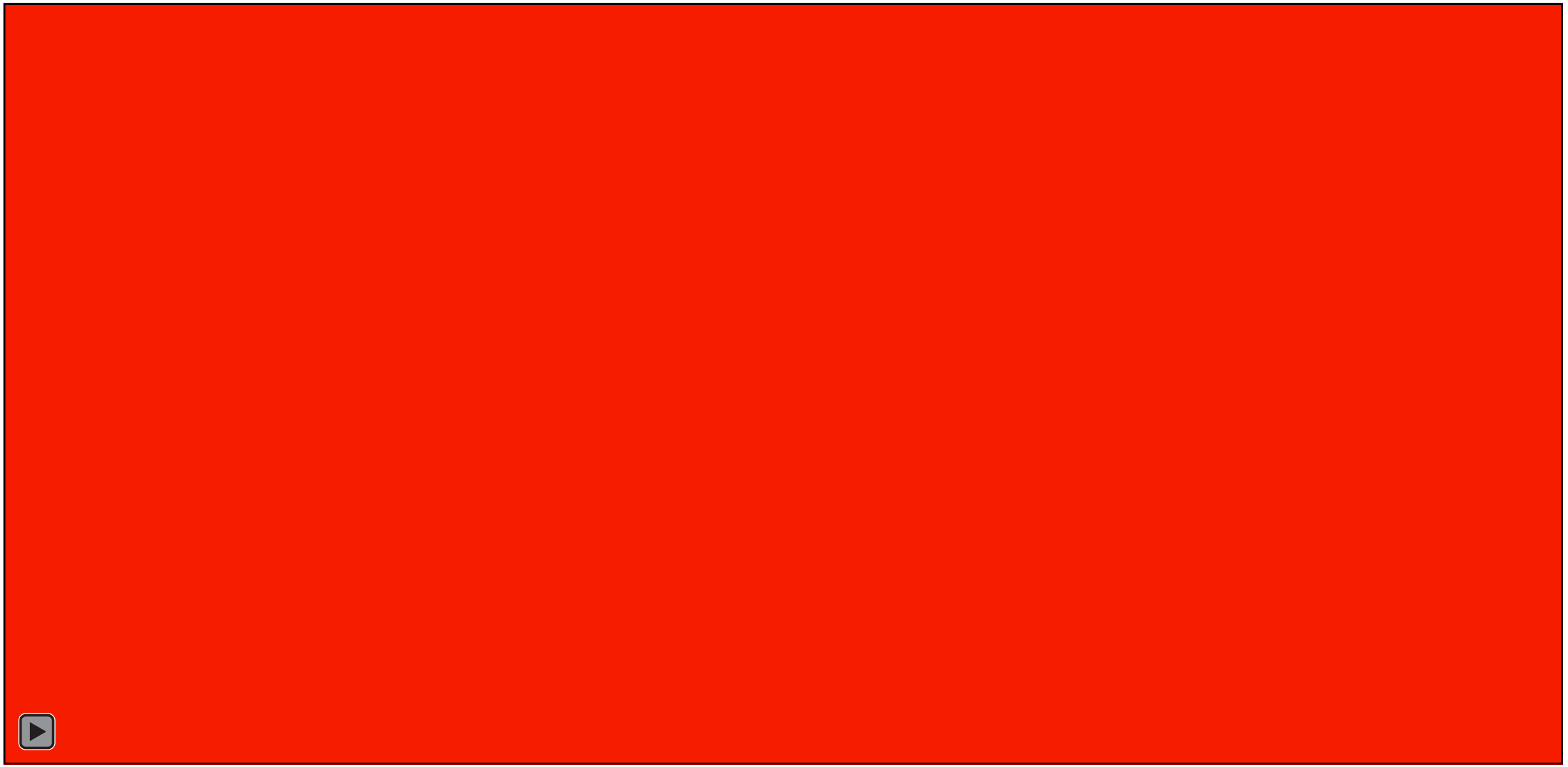
SAHPRA
South African
Health Products
Regulatory Authority

PHARMACOVIGILANCE CENTRE

Collect + Assess + Research
Causality & Preventability
Signal detection, trends, risk factors

Train + Educate
Pharmacovigilance & ADE reporting

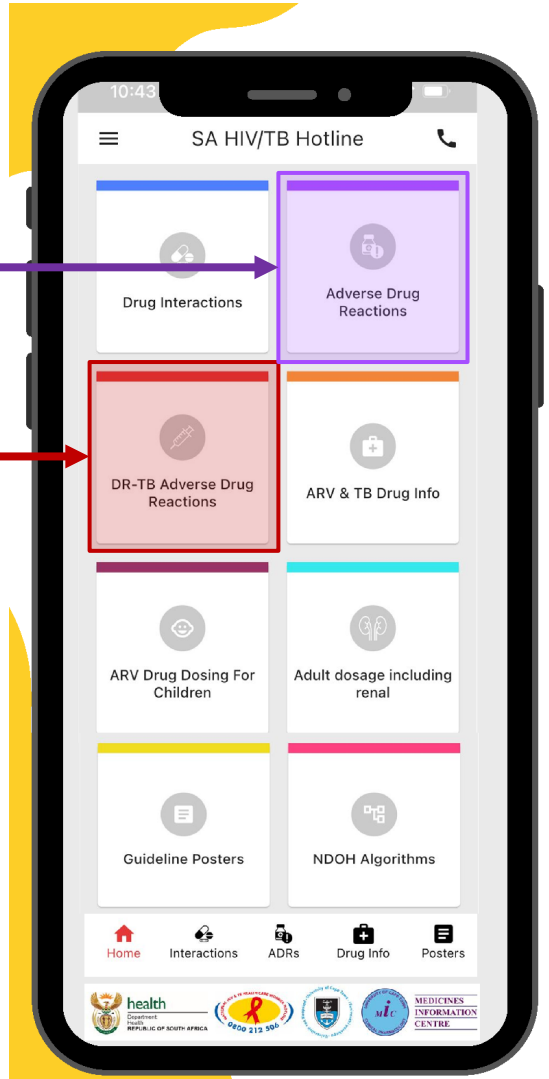
Visit our website for useful resources on managing ADRs with ART and TB therapy



Download the FREE SA HIV/TB HCW HOTLINE APP

Adverse Drug Reactions
Management of rashes, kidney injury and liver injury with ARV therapy, DS-TB and co-trimoxazole therapy

DR-TB Adverse Drug Reactions
Management of common & serious ADRs
- View by ADR and associated DR-TB Drugs
- View by DR-TB Drug and associated ADRs



NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE
0800 212 506

SA HIV/TB Hotline App

Developed by the Medicines Information Centre, Division of Clinical Pharmacology, University of Cape Town

AVAILABLE FOR FREE

- Can be used offline
- Printable/shareable posters
- Clinical support available
- Up-to-date ART and TB information
- Multiple drug interaction checker
- Adult and paediatric dosing tool
- Stepwise approach to management of common adverse drug reactions

Scan QR code to download the app

Scan QR code to see how the app works

www.mic.uct.ac.za

Medicines Information Centre

National HIV & TB Health Care Worker Hotline

We are available Monday to Friday 08:30 – 16:30

The is a free service for all health care workers

0861 100 531 Toll-free | 021 406 6829
071 840 1572 SMS | WhatsApp | Call back

pha-mic@uct.ac.za

www.mic.uct.ac.za

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NATIONAL HIV & TB HEALTH CARE WORKER HOTLINE
0800 212 506

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MEDICINES
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NATIONAL DEVELOPMENT PLAN
2030

THANK YOU