DRUGS ON THE GO

THE AURUM INSTITUTE

A Prescribers Guide for Managing TB & HIV

Version 3 – 1 April 2016

The Aurum Institute

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- The content of this booklet is deemed correct and up-to-date as of April 2016
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- Doses may change based on new data
- Not all drug interactions are listed in this publication
- Always investigate potential drug interactions with concomitant therapy, especially when prescribing NNRTIs and PIs (*see* - www.hiv-druginteractions.org)
- Not all side-effects are listed in this pocket book and prescribers should only use this as a guide – the authors of the book cannot be held responsible for any omissions
- The information was thoroughly reviewed by several specialists in the field but could still contain unforeseen errors
- Dose adjustments may be necessary in patients with renal or hepatic impairment, and should be referred to a specialised institution

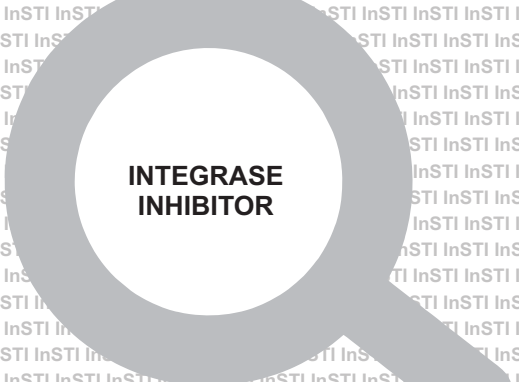
Important Contact Details:

- Adverse events should be reported to the MCC through the existing channels (www.mccza.com or 012-395 9288)
- National HIV Health Care Worker Hotline: 0800 212 506 / 021 406 6782

ABBREVIATIONS

ART	Antiretroviral Therapy
ARV	Antiretroviral
C/I	Contraindicated
CNS	Central Nervous System
bd	Twice Daily
EC	Enteric Coated
ENT	Ear, Nose and Throat
FBC	Full Blood Count
FDC	Fixed Dose Combination
GIT	Gastro-intestinal Tract
Hb	Haemoglobin
HCW	Health Care Worker
IM	Intramuscular
IV	Intravenous
LFT	Liver Function Test
MAC	*Mycobacterium Avium* Complex
NDoH	National Department of Health
OC	Oral Contraceptive
od	Once Daily
PR	Per rectum
SC	Subcutaneous
TB	Tuberculosis
tds	Three Times Daily
qid	Four Times Daily
SAMF	South African Medicines Formulary
WHO	World Health Organization


ANTI-RETROVIRAL
DRUGS


INTEGRASE
INHIBITOR

RALTEGRAVIR, RAL (Integrase Inhibitor)

Doses:

Adult:

- 400mg bd, oral
- If co-administered with rifampicin: 800mg bd, oral

Paediatric:

Not approved in children <16 years

Formulation:

Film-coated Tablets: 400mg

Contraindications:

Known hypersensitivity

Side-effects:

- Generally well tolerated
- **Most common**: insomnia, headache, nausea and fatigue
- GIT upset
- Creatine kinase elevations, myopathy and rhabdomyolysis reported
- Pruritis, rash including Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity reactions have been reported

Interactions:

Food-Drug:

Take with or without food

Drug-Drug:

- Drugs with potential to cause myopathy
- Rifampicin: reduces raltegravir concentrations (see doses section)

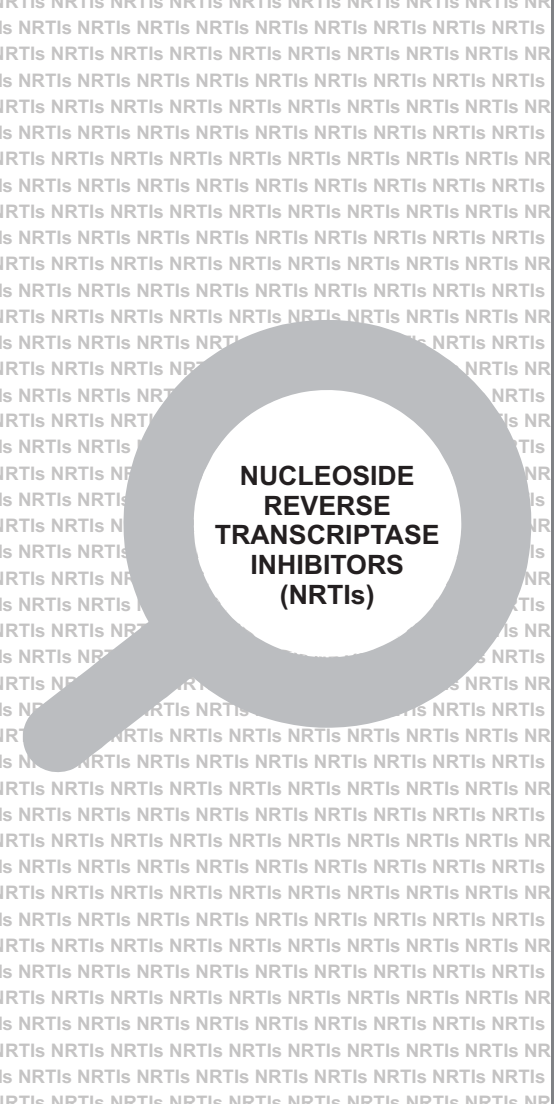
Practical Tips:

- Used in treatment-experienced patients with virological failure despite ART
- Genotype resistance testing result and prior drug exposure should be considered prior to use

Practical Tips Continued:

- May not be effective in patients with multiple PI mutations
- Can be used in first/second-line or third-line treatment if there is intolerance to other drug classes. Must be combined with fully sensitive NRTIs
- Film-coated tablets must be swallowed whole
- Use with **caution** in patients at increased risk of myopathy or rhabdomyolysis

Storage:
Room temperature, cool, dry and dark place


NUCLEOSIDE
REVERSE
TRANSCRIPTASE
INHIBITORS
(NRTIs)

ABACAVIR, ABC (NRTI)

Doses:

Adult:

- 300mg bd **OR** 600mg od, oral
- Significant liver impairment: reduce adult dose to 200 mg bd

Paediatric:

Weight range (kg)	Dosage	
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates and infants weighing <3kg	
3 - 4.9	2ml bd	
5 - 6.9	3ml bd	
7 - 9.9	4ml bd	
Choose only one option below		
10 - 13.9	6ml bd **OR** 2 x 60mg tabs bd	12ml od **OR** 4 x 60mg tabs od
14 - 19.9	8ml bd **OR** 2.5 x 60mg tabs bd	5 x 60mg tabs od **OR** 15ml od
20 - 22.9	10ml bd **OR** 3 x 60mg tabs bd	1 x 300mg tab +1 x 60mg tab od
23 - 24.9	10ml bd **OR** 3 x 60mg tabs bd	1 x 300mg tab + 2 x 60mg tabs od
≥ 25	1 x 300mg tab bd	2x 300mg tabs od **OR** 1 x ABC/3TC 600/300mg tab od

Formulation:

Oral Solution: 20mg/ml

Tablets: 60mg (scored dispersible), 300mg (not scored), ABC/3TC 600/300mg

FDC tablets: ABC/3TC 600/300mg,ABC/3TC/AZT 300/150/300mg

Contraindications:

Prior hypersensitivity to the drug, presence of HLA-B*5701, severe liver impairment

Side-effects:

- **Most common in adults:** nausea, vomiting, headache, malaise, fatigue, dream/sleep disorders
- **Most common in paediatrics:** fever and/or chills, nausea, vomiting, rash, ENT infections

- Low potential to cause NRTI class effects (hyperlactataemia and steatohepatitis)
- Potentially fatal hypersensitivity reaction (+/-5%, more likely in **Caucasians** and HLA-B*5701- positive individuals). Usually occurs in first 6 weeks.
  - symptoms from **≥2 of the following groups usually occur:**
    1. fever
    2. maculopapular pruritic rash
    3. GIT (including nausea, vomiting, diarrhoea, abdominal pain)
    4. constitutional (including generalised malaise, fatigue, achiness)
    5. respiratory symptoms (including dyspnoea, cough, pharyngitis)
  - laboratory changes may include increased creatinine kinase, lymphopaenia, leukopenia, elevated LFTs
- Other: pancreatitis, possible risk of myocardial infarction
- Lipodystrophy (particularly lipoatrophy) occurs with NRTI class but unclear whether it occurs with ABC at all

Interactions:

Food-Drug:
Take with or without food

Drug-Drug:
Low potential for drug interactions

Practical Tips:

- Avoid initiating ABC and cotrimoxazole at the same time due to similar side-effects
- Avoid combining ABC and NVP in a regimen as both drugs can potentially cause hypersensitivity reactions and it will be difficult to identify the causative drugs. Both drugs will have to be stopped.
- ***Hypersensitivity Reaction:***
  - Counsel caregivers on the signs and to contact a HCW immediately should they occur
  - Stop all ART immediately if signs and symptoms develop and admit
  - Rash or GIT symptoms alone without other symptoms does not warrant discontinuation
  - Do not initiate ABC during intercurrent symptoms to avoid confusion
  - Symptoms tend to worsen in the hours immediately after the dose and worsen with each subsequent dose

Practical Tips Continued:

- Hypersensitivity severity increases if abacavir is rechallenged – **DO NOT RECHALLENGE**
- Genetic testing for HLA-B*5701 virtually eliminates the risk, but patients should still be counselled

- Currently available tablet formulations (except for the 60mg) must not be chewed, divided or crushed but swallowed whole with or without food
- Discard solution 2 months after opening

Storage:

- Room temperature (20-25^{0}C), cool, dry and dark place
- Solution may be refrigerated but must not be frozen

EMTRICITABINE, FTC (NRTI)
Currently available only as an FDC in SA

Doses:

Adult:
- TDF/FTC 300/200mg: one tablet od
- TDF/FTC/EFV 300/200/600mg: one tablet od

Paediatric:
- Not registered for use in SA

Formulation:

FDC Tablets:
- TDF 300mg, FTC 200mg- FDC
- TDF 300mg, FTC 200mg and EFV 600mg- FDC

Contraindications:

Known hypersensitivity to the drug

Side-effects:
- **Most common:** headache, diarrhoea, nausea, fatigue, dizziness, depression, insomnia, abnormal dreams, rash, abdominal pain, asthenia, increased cough, rhinitis
- **Most common in paediatrics:** similar to adults, hyperpigmentation more frequent
- Skin hyperpigmentation (particularly in dark-skinned individuals, palms and/or soles)
- Low potential to cause NRTI class effects (hyperlactataemia, steatohepatitis)

Interactions:

Food-Drug:
Take with or without food

Drug-Drug:
None of clinical consequence

Practical Tips:
- In patients with chronic hepatitis B infection, there is a risk of rebound hepatitis if FTC is discontinued or if hepatitis B resistance develops to FTC
- Patients with a positive hepatitis B surface antigen should have either TDF and 3TC **or** TDF and FTC in their regimen

Practical Tips Continued:

- **Caution** in hepatic and renal impairment

Storage:

Both FDCs should be stored at room temperature, in a cool, dry, dark place

LAMIVUDINE, 3TC (NRTI)

Doses:

Adult:

- 150mg bd
- If creatinine clearance 10-50ml/min: 150mg od
- If creatinine clearance <10ml/min: 50mg od

Paediatric:

Weight range (kg)	Dosage	
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates and infants weighing <3kg	
3 - 4.9	2ml bd	
5 - 6.9	3ml bd	
7 - 9.9	4ml bd	
Choose only one option below		
10 - 13.9	6ml bd	12ml od
14 - 19.9	½ x 150mg tab bd **OR** 8ml bd	1 x 150mg tab od **OR** 15ml od
20 - 24.9	1 x 150mg tab bd **OR** 15ml bd	2 x 150mg tab od **OR** 30ml od
≥25	1 x 150mg tab bd	2 x 150mg tabs od **OR** 1xABC/3TC 600/300mg tab od

Formulation:

Oral Solution: 10mg/ml
Tablets: 150mg (scored)
FDC tablets: ABC/3TC 600/300mg, 3TC/AZT 150/300mg

Contraindications:

Known hypersensitivity to the drug

Side-effects:

- Adverse effects are infrequent

- **Most common in adults**: headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhoea, cough
- **Most common in paediatrics**: fever and cough
- Low potential to cause NRTI class effect (hyperlactataemia, steatohepatitis)
- Anaemia (including pure red cell aplasia) rare
- Peripheral neuropathy, pancreatitis rare
- Other: upper abdominal pain, paraesthesia, muscle disorders, alopecia

Interactions:

Food-Drug:
Take with or without food

Drug-Drug:
Low potential for drug interactions

Practical Tips:

- **Caution** in liver and renal impairment
- In patients with chronic hepatitis B infection, there is a risk of rebound hepatitis if 3TC is discontinued or if hepatitis B resistance develops to 3TC
- Patients with a positive hepatitis B surface antigen should have either TDF and 3TC **or** TDF and FTC in their regimen
- Tablets are scored and can be easily divided; may be crushed and mixed with a small amount of water or food and immediately ingested.

Storage:

- Room temperature, cool, dry and dark place
- Oral solution may be stored at room temperature.

STAVUDINE, d4t (NRTI)

Doses:

Adult:

- 30mg bd, oral
- If creatinine clearance 10-50ml/min: 15mg bd
- If creatinine clearance <10ml/min: 15mg od

Paediatric:

Weight range (kg)	Dosage
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates and infants < 3kg
3 - 4.9	6ml bd
5 - 6.9	7.5mg bd (open 15mg capsule into 5ml water and give 2.5ml)
7 - 9.9	10mg bd (open 20mg capsule into 5ml water and give 2.5ml)
10 - 13.9	15mg bd (open 15mg capsule into 5ml water)
14 - 24.9	20mg bd (open 20mg capsule into 5ml water if child is unable to swallow a capsule)
≥ 25	30mg bd

Formulation:

Oral powder for solution: 1mg/ml
Capsules: 15mg, 20mg, 30mg

Contraindications:

Known hypersensitivity to the drug

Side-effects:

- **Most common:** headache, diarrhoea, peripheral neuropathy, rash, nausea, vomiting
- High potential to cause NRTI class effect (hyperlactataemia, steatohepatitis)
- Lipodystrophy, particularly lipoatrophy of face and limbs
- Hepatic toxicity, pancreatitis
- HIV-associated neuromuscular weakness syndrome (HANWS): ascending motor weakness, usually in setting of lactic acidosis

- Other: dyslipidaemia, insomnia, myalgia, haematological effects including neutropenia, thrombocytopenia

Interactions:

Food-Drug:
Take with or without food

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):
- **AZT:** antagonistic effect
- Drugs that can cause peripheral neuropathy including isoniazid, dapsone, ethambutol, ethionamide
- Drugs that can cause pancreatitis including valproate, pentamidine

Practical Tips:
- **In children change d4t to ABC if viral load undetectable**
- Inform patients of symptoms of hyperlactatemia (including weight loss, nausea and vomiting) and to consult a HCW should these occur
- **Caution** if history of pancreatitis or peripheral neuropathy, hepatic disease, renal impairment. porphyria
- In adults switch to less toxic NRTI e.g. TDF if mitochondrial toxicities occur or if at high risk (including high BMI or pregnant)
- Content of capsules can be dissolved in 5ml water – can be kept at room temperature for 24 hours and can be used for 2 doses
- Higher doses for patients >60kg no longer recommended
- TDF should not routinely be used in children <15 years in South Africa

Storage:
- Reconstituted solution: 2-8°C for up to 30 days
- Capsules: room temperature, cool, dry, dark place

ZIDOVUDINE, AZT (NRTI)

Doses:

Adult:

- 300mg bd, oral
- If creatinine clearance <10ml/min: 300mg od, oral
- Significant liver disease : decrease dose by 50% or double dosage interval

Paediatric:

Weight band (kg)	Dosage
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates and infants <3kg
3-5.9	6ml bd
6-7.9	9ml bd
8-13.9	1 cap bd **OR** 12ml bd
14-19.9	2 caps am 1 cap pm **OR** 15ml bd
20-24.9	2 caps bd **OR** 20ml bd
≥ 25	1 x 300mg tab bd **OR** 1 x AZT/3TC 300/150mg tab bd

Formulation:

Oral Solution: 50mg/5ml
Capsules: 100mg, 250mg
Tablets: 300mg (film-coated, not scored), AZT/3TC 300/150mg
FDC tablets: AZT/3TC 300/150mg

Contraindications:

Significant anaemia (Hb less than 8g/dl) or neutropenia, known hypersensitivity to the drug

Side-effects:

- **Most common in adults:** headache, malaise, nausea, anorexia, vomiting

- **Most common in paediatrics:** fever, cough, digestive disorders; anaemia and neutropenia in neonates
- Intermediate potential to cause NRTI class effects (hyperlactatemia, steatohepatitis)
- Haematological effects include anaemia (usually after 4-6 weeks), leucopoenia, neutropenia, macrocytosis (platelets usually unaffected, may rise)
- Symptomatic myopathy with prolonged use
- Other: lipodystrophy (particularly lipoatrophy), altered taste, myalgia, fingernail discolouration, hepatotoxicity

Interactions:

Food-Drug:

- Take with or without food
- Take tablet or capsule with adequate fluid to prevent oesophageal ulceration

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- Valproate: increased AZT levels
- Myelosuppressive agents (including ganciclovir, interferon, ribavirin) and radiotherapy: increased bone marrow suppression
- **d4T**, **doxorubicin:** both are antagonistic

Practical Tips:

- **Monitoring:** FBC should be monitored. Current NDoH guidelines:
  - Do Hb or FBC prior to AZT initiation
  - FBC at month 3 & 6 on ART in adults
  - Hb or FBC at month 1, 2, 3 & annually in children
- Monitor Hb closely when given with other bone marrow suppressive drugs
- In adults who develop anaemia/neutropenia:
  - reduce dose if Hb drops to < 8g/dL (to 200mg bd)
  - switch AZT if Hb drops to < 6.5 g/dL
  - consider reduced dose if neutrophil count < $1x10^9$/L
  - switch AZT if neutrophil count < $0.5x10^9$/L
    (No clear guidelines on dose reduction in children who develop anaemia/neutropenia, consider differential diagnosis, switch to another drug if possible)
- **Caution** in renal/hepatic impairment, porphyria

Practical Tips Continued:

- May be useful in HIV-associated neurocognitive disorder, useful in idiopathic thrombocytopenic purpura
- Tablets currently available are film-coated and not scored. They must be swallowed whole and not chewed, divided or crushed.
- Capsules: can be opened and dispersed in water or onto a small amount of food e.g. yoghurt and immediately ingested
- PMTCT: given to neonates for the first 6 weeks of life (consult paediatrician)

Storage:

Room temperature, cool, dry, dark place


NON-NUCLEOSIDE
REVERSE
TRANSCRIPTASE
INHIBITORS
(NNRTIs)

EFAVIRENZ, EFV (NNRTI)

Doses:

Adult:
600mg od (nocte), oral

Paediatric:

Weight range (kg)	Dosage
<10	Avoid using when <10kg or <3 years (dosing not established)
10-13.9	200mg nocte *(1 x 200mg cap or tab)*
14-24.9	300mg nocte *(200mg cap/tab + 2x 50mg cap or tab)*
25-39.9	400mg nocte *(2 x 200mg caps/tabs)*
≥40	600mg tab nocte

Formulation:
Tablets: 50mg, 200mg, 600mg (not scored)
Capsules: 50mg, 200mg
FDC tablets: TDF/FTC/EFV 300/200/600mg

Contraindications:
Known hypersensitivity to EFV, severe liver disease, significant psychiatric co-morbidity

Side-effects:

- **Most common**: rash, dizziness, nausea, headache, fatigue, insomnia, vomiting
- **Most common in paediatrics**: similar to adults, higher incidence of rash
- Side effects occur commonly within the first 2-6 weeks of treatment.
- Mild to moderate maculopapular rash- common, blistering, desquamation, fever and mucosal involvement -rare and require discontinuation of EFV
- CNS effects common: usually start on 1st or 2nd day of treatment and resolve in 2-4 weeks, include vivid dreams, headache, insomnia, somnolence, impaired concentration, dizziness, hallucinations
- Psychiatric symptoms including depression, anxiety, nervousness
- Other: fatigue, GIT effects, gynaecomastia, dyslipidaemia (increased total cholesterol and triglycerides), hepatotoxicity

(especially if underlying liver disease), convulsions (usually in patients known with seizures), pancreatitis

Interactions:

Food-Drug:

Avoid fatty meals (increases absorption and thus side effects), best taken on empty stomach

Drug-Drug:

(In bold: Co-administration is not recommended or C/I)

- **Cisapride, midazolam, triazolam, ergot derivatives, pimozide**, **St John's wort, bepridil**
- Protease inhibitors: plasma levels of fosamprenavir, atazanavir, lopinavir, saquinavir decreased while ritonavir levels increased (PIs may require dose adjustments - see section on PIs)
- Rifampicin: minimal effect on EFV concentrations , no dose adjustment required
- Rifabutin levels decreased: increase rifabutin dose to 450mg/day
- Clarithromycin: rash and reduced clarithromycin levels - consider alternatives e.g. erythromycin or azithromycin
- Warfarin effect may be increased or decreased: monitor INR and dose adjust
- Calcium channel blockers: levels may be decreased - adjust dose of calcium channel blocker based on clinical response
- Phenytoin, carbamazepine, phenobarbital: levels of EFV and anticonvulsants may be reduced, monitor anticonvulsant levels
- Sertraline and bupropion levels decreased: increase dose based on clinical response (do not exceed recommended dose of bupropion)
- Anti-fungals: Voriconazole (increase voriconazole maintenance dose to 400mg bd and decrease EFV to 300mg nocte but avoid if possible), insufficient data on itraconazole (consider alternative), **posaconazole** levels decreased
- Levels of simvastatin, atorvastatin and pravastatin decreased: increased dose of statin may be needed but not beyond recommended maximum
- Immunosuppressants including cyclosporin, tacrolimus, sirolimus: levels of immunosuppressant reduced, monitor concentrations, may require dose adjustment
- Hormonal contraceptives: ethinyl estradiol/ norgestimate oral contraceptive and progestin implant – efficacy may be reduced, use additional barrier contraception

- **Bedaquiline: EFV is a CYP3A4 inducer, reduces levels of Bedaquiline**
- Delamanid: EFV has no clinically significant effect on levels of Delamanid

Practical Tips:

- If switching due to a rash, do not switch to NVP
- **Caution** in patients who work night shifts
- **Caution** if history of psychiatric illness (may increase CNS effects), porphyria, history of seizures
- **Caution** in liver disease, **monitor** liver function in patients with hepatic dysfunction or risk factors for hepatotoxicity
- Currently recommended as part of the first line regimen during pregnancy in SA
- Antihistamines, corticosteroids may hasten resolution of rash
- Take at night and on empty stomach to minimise side effects
- Psychoactive drugs and alcohol may increase CNS effects
- Capsules may be opened and powder contents dispersed in water or mixed with a small amount of food (e.g. yoghurt) to disguise peppery taste and should be immediately ingested
- Currently available tablet formulations are film-coated and must be swallowed whole and not chewed, divided or crushed
- EFV has a relatively long half-life. If ART is stopped consider either:
  - stopping EFV 1-2 weeks before the other drugs or
  - replacing EFV with a protease inhibitor before stopping treatment
- There is cross resistance between the first generation NNRTIs. If there is resistance to one, this usually confers resistance to the other
- Should not be used in children exposed to NVP for 6 weeks or longer as part of PMTCT

Storage:
Room temperature, cool, dry and dark place

ETRAVIRINE, ETR (Second Generation NNRTI)

Doses:

Adult:
200mg bd, oral

Paediatric:
Not approved in children

Formulation:
Tablets: 100mg

Contraindications:
Nil

Side-effects:

- **Most common in adults:** rash, peripheral neuropathy
- **Most common in paediatrics:** rash, diarrhoea
- Rash is usually mild to moderate, starts in first 6 weeks and resolves in 1-2 weeks with continued therapy. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme also reported
- Systemic hypersensitivity reactions (rash, constitutional findings, organ dysfunction including hepatic failure)
- Other: diarrhoea, nausea, increased LDL and triglycerides, hepatotoxicity
- Psychiatric effects less than EFV

Interactions:

Food-Drug:
Take after food

Drug-Drug:
(In bold: Co-administration is not recommended or C/I)

- **Fosamprenavir/r, atazanavir/r, protease inhibitors without ritonavir, other NNRTIs**
- Digoxin levels increased: monitor levels of digoxin and titrate dose
- Amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone and quinidine levels may decrease: use with caution, monitor levels if possible
- Warfarin levels may be increased: monitor INR
- **Carbamazepine, phenytoin, phenobarbital**: ETR levels decreased, **AVOID**

- Fluconazole, voriconazole: increased ETR levels, use with caution
- Itraconazole, ketoconazole, posaconazole: increased ETR levels, levels of ketoconazole and posaconazole may be decreased, dose adjustment of the antifungal may be needed
- Clarithromycin: consider azithromycin in treatment of MAC
- **Rifampicin**, **rifapentine**: decreased ETR levels
- Rifabutin:
  - decreased ETR and rifabutin levels, use rifabutin dose 300mg od
  - if ETR co-administered with darunavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir - do not use rifabutin
- Diazepam levels increased: diazepam dose may need to be decreased
- Dexamethasone(systemic): ETR levels decreased, consider alternative
- **St John's wort**: decreased ETR levels
- HMG CoA reductase inhibitors:
  - atorvastatin levels decreased: adjust dose based on clinical response
  - lovastatin and simvastatin levels reduced, may require dose adjustment
  - fluvastatin and pitavastatin levels may be increased, may require dose adjustment
  - no interaction with pravastatin or rosuvastatin
- Cyclosporin, sirolimus, tacrolimus levels may be decreased
- Buprenorphine levels decreased: monitor for withdrawal, may require dose adjustment
- Sildenafil levels decreased: adjust dose based on clinical effect
- Clopidrogel: decreased activation to active metabolite, consider alternative

Practical Tips:

- For use in ARV treatment-experienced patients with viral strains resistant to an NNRTI and other ARVs
- History and resistance testing must be considered prior to using ETR. In patients who have had virological failure on an NNRTI-containing regimen, do not use ETR in combination with only NtRTIs

Practical Tips Continued:

- Immediately stop treatment if severe hypersensitivity, severe rash, rash with systemic symptoms or rash with elevated liver transaminases occurs
- Should be used with ritonavir boosted PI
- Tablets may be swallowed whole or may be dispersed in a glass of water

Storage:

Room temperature, cool, dry and dark place

NEVIRAPINE, NVP (NNRTI)

Doses:

Adult:

200mg od* for 14 days then 200mg bd, oral

Paediatric:

Weight (kg)	Dosage
***When initiating nevirapine, begin with once daily lead-in dose for two weeks, then proceed to bd dose**	
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates and infants <3kg
3 - 5.9	5ml bd
6 - 9.9	8ml bd
10 - 13.9	10ml bd
14 - 24.9	1 tab am ½ tab pm **OR** 15 ml bd
≥25	1 tab bd

- *If rash occurs during lead-in period, do not escalate to a bd dose until resolved. Once daily dose can be continued for 28 days maximum at which point an alternative should be sought
- *If treatment interrupted for >7days, restart with once daily lead-in dosing
- *Consider omitting induction dose if on rifampicin or if switching from EFV to NVP

Formulation:

Oral Solution: 50mg/5ml
Tablets: 200mg (scored)

Contraindications:

Hypersensitivity to the drug, moderate or severe hepatic impairment

Side-effects:

- Rash common, usually in first 6 weeks: mild to severe or life-threatening. Rash may be accompanied by fever and hepatitis-hypersensitivity reaction, includes Stevens- Johnson syndrome, toxic epidermal necrolysis.
- Early hepatotoxicity can be severe/fatal:

- usually occurs in first 8 weeks
- appears to be a hypersensitivity reaction
- can occur with rash, fever, eosinophilia, systemic symptoms
- occurs especially at high baseline CD4 counts and in women

- Transaminase elevation may occur later in treatment, usually asymptomatic, more common in patients with chronic hepatitis B or C co-infection
- Rhabdomyolysis has been observed in patients with rash/hepatitis
- Other: nausea, diarrhoea, abdominal pain, granulocytopaenia, headache, fatigue, myalgia

Interactions:

Food-Drug:
Take with or without food

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):

- Rifampicin: decreased NVP levels, hepatotoxicity (see doses section)
- **Ketoconazole, St. John's Wort, rifapentine, atazanavir, itraconazole**
- Efavirenz: appropriate doses not determined
- Clarithromycin: consider alternative if treating MAC
- Hormonal contraception: use alternative/ additional methods
- Fluconazole: increased NVP concentrations, monitor for toxicity
- Protease inhibitor levels may be reduced: LPV/r dose may need to be increased (see section on LPV/r)
- Warfarin levels may increase: monitor INR
- Rifabutin levels increased: monitor for toxicity, rifabutin dose 300mg od
- The doses of the following drugs may be reduced:
  - amiodarone, disopyramide, lidocaine, carbamazepine, clonazepam, ethosuximide, diltiazem, nifedipine, verapamil, ergotamine, cyclophosphamide, cyclosporin, tacrolimus, sirolimus, cisapride, fentanyl

Practical Tips:

- Advise patients to inform HCW promptly should rash or symptoms of hepatitis occur
- If nevirapine-associated rash suspected, measure transaminases immediately
- Permanently discontinue NVP if:
  - increased transaminases combined with rash or other systemic symptoms
  - severe skin or hypersensitivity reactions including fever and mucosal involvement
- Try to avoid initiating NVP and co-trimoxazole at the same time due to similar side effects
- Avoid initiation of NVP if CD4 count >250 cells/mm^3 in women or >400 cells/mm^3 in men due to risk of hepatotoxicity (N/A to single-dose PMTCT) unless benefit outweighs risk
- **Monitoring:** liver function
  - Current NDoH Guidelines:
    - do ALT if starting on a NVP-based regimen
    - if ALT raised >100, avoid NVP if possible; if no alternative, closely monitor the patient
    - repeat ALT if rash or symptoms of hepatitis develop
- **Caution** in hepatic impairment, porphyria
- If patient on dialysis, give an additional dose following each dialysis session
- NVP has a long half-life. If a NVP-based regimen is being stopped: continue the 2 NRTIs for 1-2 weeks thereafter (unless the regimen is being stopped for NRTI related toxicity), or replace NVP with a boosted PI 2-4 weeks before stopping regimen
- There is cross resistance between the first generation NNRTIs
- Ensure solution is well shaken before use

Storage:
Room temperature, cool, dry and dark place

RILPIVIRINE, RPV (NNRTI)

Doses:

Adults:
Treatment Naïve: 25mg od
Concomitant therapy with rifabutin: 50mg od

Paediatrics:
Not recommended for children< 18 years

Formulation:
Tablets: 25mg

Contraindications:
Hypersensitivity

Side-effects:
Depression, hepatotoxicity, headache, insomnia, rash

Interactions:

Food-Drug:
Take with food

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

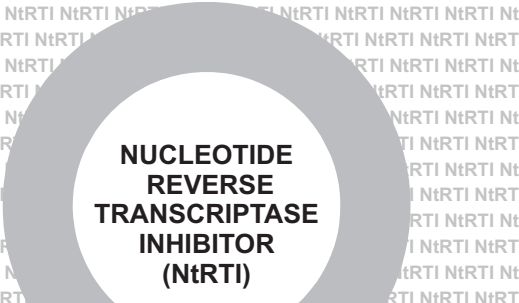
- CYP3A4 inhibitors (erythromycin): may increase levels of Rilpivirine
- CYP3A4 inducers (carbamazepine, phenytoin, rifampicin): decreases levels of Rilpivirine
- Proton Pump inhibitors/ Antacids: decreases levels of Rilpivirine
- **Drugs that Prolong QT interval, Risk of Torsades de Pointes (Bedaquiline, Delamanid, Moxifloxacin, Fluconazole, Atazanavir, Azithromycin): AVOID using with Rilpivirine**

Practical Tips:

- Plasma ½ Life 50 hours
- Indicated for use in Treatment Naïve Adults with a viral load≤ 100 000 copies/mL
- Use with caution in VL> 100 000 copies – increase risk of virological failure
- Liver function monitoring is recommended in patients with hepatic disease
- Severe depression and psychotic-like symptoms have been reported

Storage:

Room temperature, Cool, dry place


NUCLEOTIDE
REVERSE
TRANSCRIPTASE
INHIBITOR
(NtRTI)

TENOFOVIR, TDF (NtRTI)

Doses:

Adult:
300mg od, oral

Paediatric:
Not registered for paediatric use in SA

Formulation:
Tablets: 300mg
FDC tablets:TDF/FTC 300/200mg,TDF/FTC/EFV 300/200/600mg

Contraindications:
Not recommended if creatinine clearance< 50ml/min

Side-effects:
- **Most common:** rash, diarrhoea, headache, pain, depression, asthenia, nausea
- GIT effects include diarrhoea, flatulence, nausea, vomiting
- Nephrotoxicity: renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Very low potential to cause NRTI class effects (hyperlactataemia, hepatosteatosis)
- Reduction in bone mineral density
- Hypersensitivity rare

Interactions:

Food-Drug:
Take without regard to food

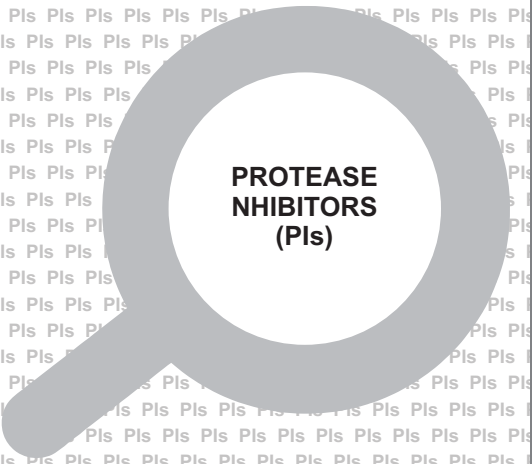
Drug-Drug:
(In bold: Co-administration is not recommended or C/I):
- Atazanavir: decreased atazanavir and increased TDF levels – use with ritonavir and monitor for TDF toxicity
- Lopinavir/ritonavir: TDF levels increased, monitor for toxicity
- Drugs that reduce renal function or compete for active tubular secretion including acyclovir, valacyclovir, ganciclovir, valganciclovir, cidofovir: level of TDF and/or other drug increased, monitor for toxicities
- O**ther nephrotoxic drugs including aminoglycosides**: avoid **Adefovir, combination drugs containing TDF**
- Delamanid: TDF has no clinically significant effect on Delamanid levels

Practical Tips:

- In patients with chronic hepatitis B infection, there is a risk of rebound hepatitis if TDF is discontinued
- Patients with a positive hepatitis B surface antigen should have either TDF and 3TC **or** TDF and FTC in their regimen
- Monitor carefully if history or risk of renal dysfunction
- **Monitoring:** renal function
    - Current NDoH guidelines:
        - do serum creatinine and creatinine clearance at baseline if starting on a TDF-based regimen and at month 3, 6, 12 and then every 12 months if on TDF
- In patients on MDR-TB treatment (which includes aminoglycosides) consider switching TDF for the duration of aminoglycosides use provided HepBsAg is negative and VL lower than detectable. TDF can be reintroduced afterward if CrCl> 50 ml/min. If TDF cannot be stopped, increase monitoring of renal function while on aminoglycoside.

Storage

Room temperature, cool, dry and dark place


PROTEASE
NHIBITORS
(PIs)

ATAZANAVIR, ATV (PI)

Doses:

Adult:

Dosage depends on treatment history and on the use of co-administered medications

- Treatment-naïve patients:
  - ATV 300mg + RTV 100mg od, oral
  - If unable to tolerate RTV:
    - ATV 400mg od, oral can be given if not on TDF
  - If on TDF, H_2 - receptor antagonist or proton pump inhibitor:
    - ATV 300mg + RTV 100mg od should be given
  - If on EFV:
    - ATV 400mg + RTV 100mg od, oral at separate times
- Treatment-experienced patients:
  - ATV 300mg + RTV 100mg od, oral
  - Do not give with proton-pump inhibitors or EFV
  - If on TDF **and** an H_2 - receptor antagonist:
    - ATV 400mg + RTV 100mg od, oral
- Pregnancy:
  - ATV 300mg + RTV 100mg od, oral
  - For treatment-experienced pregnant women during the 2nd or 3rd trimester, if ATV is given with either an H_2 - receptor antagonist OR TDF:
    - ATV 400 mg + RTV 100 mg od
- Treatment-naïve patients with end-stage renal disease on haemodialysis:
  - ATV 300mg + RTV 100mg od, oral (no dose adjustment if renal impairment and not on haemodialysis)
- Moderate hepatic impairment in patients without prior virological failure:
  - consider dose reduction to ATV 300mg od

Paediatric:

Not registered for paediatric use in SA

Formulation:

Capsules: 150mg, 200mg

Contraindications:

Hypersensitivity to the drug, severe hepatic impairment, treatment-experienced patients with end-stage renal disease on haemodialysis

Side-effects:

- **Most common**: unconjugated hyperbilirubinemia/jaundice, nausea, abdominal pain, vomiting, diarrhoea, rash, headache, insomnia, peripheral neuropathy, dizziness, myalgia, depression, fever
- Asymptomatic unconjugated hyperbilirubinemia common, reversible, does not require drug discontinuation; jaundice occurs less often (consider alternative if cosmetic concerns)
- Lower potential for dyslipidaemia, insulin resistance, GIT effects and possibly fat accumulation than LPV/r and older PIs; lipids slightly higher with RTV boosting
- Other: increased transaminases, hepatitis, prolonged PR interval, severe rash including Stevens-Johnson syndrome, nephrolithiasis, increased bleeding in haemophilia

Interactions:

Food-Drug:

Take with food (enhances absorption)

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- **Alfuzosin, triazolam, oral midazolam, ergot derivatives, rifampicin, irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozide, St John's Wort, sildenafil for treatment of pulmonary artery hypertension, nevirapine, PIs other than RTV, salmeterol**
- Tenofovir levels increased, ATV levels decreased: (see doses section) monitor for TDF adverse events
- Efavirenz: decreased ATV levels (see doses section)
- Antacids and buffered medication (including ddI): give ATV 2 hours before or 1 hour after these medications
- Amiodarone, bepridil, systemic lidocaine, quinidine and tricyclic antidepressant levels may be increased: caution, monitor concentrations of these drugs when used with ATV
- Warfarin: increased anticoagulant effect, monitor INR
- Trazodone concentrations increased: monitor for adverse events and consider lower dose
- Ketoconazole, itraconazole levels increased: caution if dose >200mg/day, **voriconazole:** limited data, avoid
- Colchicine: requires dose adjustment (see package insert), do not use with ATV in renal or hepatic disease
- Rifabutin levels increased: reduce rifabutin dose to 150mg 3 x weekly, monitor for rifabutin side effects

- Parenteral midazolam: increased midazolam levels, consider dose reduction, monitor closely
- Calcium channel blocker levels increased: consider reducing dose of diltiazem by 50%, titrate doses of felodipine, nifedipine, nicardipine, verapamil; monitor ECG
- Atorvastatin and rosuvastatin levels increased, increased risk of myopathy: titrate atorvastatin dose and use lowest possible dose; maximum dose of rosuvastatin 10mg/day
- Bosentan: ATV must be given with RTV, see package insert for bosentan dose adjustments
- H_2 - receptor antagonists: avoid if possible. If used with ATV/r, dose should not exceed a dose comparable to famotidine 40mg bd in treatment-naïve patients and 20mg bd in treatment-experienced patients. Administer ATV at least 2 hours before or 10 hours after the H_2 blocker (see doses section)
- Immunosuppressant (cyclosporin, sirolimus, tacrolimus) levels increased: monitor concentrations
- Fluticasone levels increased: consider alternatives
- Clarithromycin levels increased: consider 50% dose reduction due to risk of QT prolongation; additionally, active metabolite decreased - consider alternative (unless treating MAC)
- Contraception - ethinyl estradiol and norgestimate or norethindrone: if used with ATV/r, OC should contain at least 35 mcg of ethinyl estradiol; if used with ATV, ethinyl estradiol should not exceed 30mcg. Possible safety risk due to increased progesterone. Other hormonal contraceptives not studied, consider alternatives.
- Buprenorphine levels increased: monitor for side effects, consider dose reduction, do not give ATV without RTV
- PDE5 inhibitor levels may be increased**:** reduced doses required (see package insert) **, sildenafil contra-indicated if used for pulmonary artery hypertension**
- Proton pump inhibitors (PPIs) decrease ATV levels: in treatment naïve patients maximum dose is omeprazole 20mg od and PPI must be taken 12 hours prior to ATV/r; **do not use in treatment experienced patients** (see doses section)

Practical Tips:

- **Caution** if pre-existing conduction disease or if given with drugs that can prolong the PR interval
- **Caution** if hepatitis B/C infection or mild to moderate hepatic impairment: risk of increased transaminases, hepatic decompensation
- Discontinue if severe rash
- Do not open the capsules

Storage:

Room temperature, cool, dry and dark place

DARUNAVIR, DRV (PI)

Doses:

Should not be used without ritonavir

Adults:

- Treatment-naïve or treatment-experienced with no DRV resistance associated mutations:
  - DRV 800 mg + RTV 100mg od, oral
- Treatment-experienced adult patients with at least one DRV resistance associated mutation:
  - DRV 600 mg + RTV 100mg bd, oral

Paediatrics:

Not registered for paediatric use in SA

Contraindications:

Not recommended in severe hepatic impairment

Formulation:

Tablets: 300mg, 800mg

Side-effects:

- **Most common**: diarrhoea, nausea, rash, headache, abdominal pain, vomiting
- Hepatitis (increased risk if pre-existing liver dysfunction, including chronic active hepatitis B or C), skin reactions (including Stevens-Johnson syndrome), new onset or exacerbation of pre-existing diabetes mellitus or hyperglycaemia, increased bleeding in haemophilia, lipodystrophy, pancreatitis, hyperlipidaemia, transaminase elevation

Interactions:

Food-Drug:

Take with meals

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- **Alfuzosin, ergot derivatives, cisapride, pimozide, oral midazolam, triazolam, St. John's Wort, lovastatin, simvastatin, rifampicin, sildenafil (for treatment of pulmonary arterial hypertension)**
- **Lopinavir/r, saquinavir:** dosing not established

- Bepridil, systemic lidocaine, quinidine, amiodarone, flecainide, propafenone and digoxin levels increased: monitor concentrations if possible, titrate digoxin and use lowest possible dose
- Warfarin levels decreased: monitor INR
- Carbamazepine levels increased: monitor levels and titrate dose
- Phenobarbital, phenytoin levels decreased: monitor levels
- Trazodone, desipramine levels increased: consider lower dose
- Clarithromycin: adjust dose in renal failure
- Ketoconazole, itraconazole: ketoconazole, itraconazole and DRV levels increased, daily dose of ketoconazole/ itraconazole should not exceed 200 mg
- Colchicine levels increased: requires dose adjustment (see package insert)
- Rifabutin: Reduce dosage of rifabutin to 150mg po daily when used in combination with boosted PI
- Beta-blockers levels increased: may need dose reduction, monitor closely
- Calcium channel blockers levels increased: monitor carefully
- Parenteral midazolam levels increased: monitor closely, consider reduced midazolam dose
- Systemic dexamethasone: decreased DRV levels
- Nasal/inhaled fluticasone levels increased: consider alternatives
- Pravastatin, atorvastatin, rosuvastatin levels increased: titrate and use lowest possible dose, maximum atorvastatin dose 20mg/day
- Cyclosporin, tacrolimus, sirolimus levels increased: monitor concentrations
- Risperidone, thioridazine levels increased: may need dose reduction
- Ethinyl estradiol, norethindrone levels decreased: use non-hormonal contraception
- PDE5 inhibitor levels may be increased**:** reduced doses required, **sildenafil contra-indicated if used for pulmonary artery hypertension**
- Sertraline, paroxetine levels decreased: titrate based on clinical response

Practical Tips:

- **Caution** in sulphonamide allergy (contains sulphonamide moiety)
- **Caution** if pre-existing liver dysfunction including hepatitis B or C co-infection: increased risk for hepatic adverse events
- Discontinue if signs or symptoms of severe skin reactions develop
- Tablets should be swallowed whole
- Genotype resistance testing result and prior ART exposure should be considered prior to use

Storage:
Room temperature, cool, dry dark place

LOPINAVIR/RITONAVIR, LPV/r (PI)

Doses:

Adult:

- 400/100mg bd, oral
- If co-administered with EFV, NVP or amprenavir: consider LPV/r 500/125mg bd if reduced susceptibility to LPV suspected
- If co-administered with rifampicin: double the LPV/r dose, can be done incrementally over 2 weeks to improve tolerability

Paediatric:

Weight range (kg)	Dosage
< 3	Consult with a clinician experienced in paediatric ARV prescribing for neonates and infants <3kg
3 - 4.9	1ml bd
5 - 9.9	1.5ml bd
10 -13.9	2ml bd
CHOOSE ONLY ONE OPTION BELOW	
14 -19.9	2.5ml bd **OR** 100/25mg paeds tabs: 2 bd **OR** 200/50mg adult tabs: 1 bd
20 - 24.9	3ml bd **OR** 100/25mg paeds tabs: 2 bd **OR** 200/50mg adult tabs: 1 bd
25 - 29.9	3.5ml bd **OR** 100/25mg paeds tabs: 3 bd **OR** 200/50mg adult tabs: 1 bd **OR** 100/25mg paeds tabs: 1 bd **OR** 200/50mg adult tabs: 2 tabs am; 1 tab pm

30 - 34.9	4ml bd **OR** 100/25mg paeds tabs: 3 bd **OR** 200/50mg adult tabs: 1 bd **+** 100/25mg paeds tabs: 1 bd **OR** 200/50mg adult tabs: 2 tabs am 1 tab pm
≥35	5ml bd **OR** 200/50mg adult tabs: 2 bd

- If co-administered with rifampicin: boost by adding RTV at 75% of the LPV/r dose in ml, see section on RTV for RTV doses (if RTV unavailable, LPV/r dose can be doubled but this has a higher rate of virological failure)
- Requires dose adjustment when administered with EFV or NVP: see SAMF

Formulation:
Oral Solution: 80/20mg/ml
Tablets: 100/25mg, 200/50mg

Contraindications:
Known hypersensitivity to the drug, porphyria

Side-effects:
- **Most common**: diarrhoea, nausea, abdominal pain, asthenia, vomiting, headache, dyspepsia
- High potential to cause metabolic class side-effects: new onset or exacerbation of pre-existing diabetes, hyperglycaemia; increased total cholesterol, triglycerides
- Lipodystrophy, pancreatitis, hepatotoxicity, PR interval prolongation, QT interval prolongation, increased bleeding in haemophilia

Interactions:
Food-Drug:
- Solution: Take with a meal
- Tablet: Take with or without food (administration with or after meals may improve GIT tolerability)

Drug-Drug:
- TDF levels increased: monitor for toxicity

- EFV or NVP: LPV levels decreased (see doses section)
- Rifampicin: decreased LPV levels (see doses section)
- Amiodarone, bepridil, lidocaine (systemic), quinidine levels increased: caution, monitor levels if possible
- Carbamazepine, phenobarbital, phenytoin: LPV levels reduced, phenytoin levels reduced: caution, monitor levels
- Dexamethasone: caution as LPV levels decreased
- Bedaquiline: caution as LPV/r increases Bedaquiline levels 3-fold
- Other interactions as for ritonavir
- Delaminid: LPV/r has no clinically significant effect on Delamanid levels

Practical Tips:

- RTV inhibits the metabolism of LPV and increases LPV levels
- Think of innovative ways to improve the taste of the solution in children e.g. peanut butter before dose
- Tablets must be swallowed whole and not chewed, divided or crushed
- **Monitoring**: lipid profile and glucose
  - Current NDoH guidelines:
    - Adults - fasting cholesterol and triglycerides at month 3 on LPV/r
    - Children - fasting cholesterol and triglycerides at baseline and annually
- **Caution** in liver disease (including hepatitis B and C, or marked transaminase elevations), pre-existing diabetes, baseline cardiac conduction abnormalities
- **Avoid** LPV/r solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice
- Bedaquiline can be used in patients on second line ART but QTc should be monitored more frequently (weekly)

Storage:

Solution: 2-8°C (can be kept at room temperature for 42 days). Avoid exposure to high heat.
Tablet: Room temperature, cool, dry and dark place

RITONAVIR, RTV (PI)

Doses:

- Use only as a booster dose for other protease inhibitors (see 1° protease inhibitor for dose)
- Dose should be increased if rifampicin is co-prescribed

Paediatrics:
Dosage when used as booster for LPV/r when on rifampicin

Weight range (kg)	Dose
3 - 4.9	1ml bd
5 - 13.9	1.5ml bd
14 - 19.9	2ml bd
20 - 24.9	2.5ml bd
25 - 34.9	3ml bd
≥35	4ml bd

Contraindications:

Known hypersensitivity to the drug

Formulation:

Oral Solution: 80mg/ml
Soft Capsules: 100mg

Side-effects:

- **Most common:** abdominal pain, asthenia, headache, malaise, anorexia, diarrhoea, dyspepsia, nausea, vomiting, paraesthesia, circumoral paraesthesia, peripheral paraesthesia, dizziness, taste perversion
- High potential to cause class effects i.e. metabolic abnormalities including hyperglycaemia, new-onset and exacerbation of pre-existing diabetes, increased total cholesterol and triglycerides
- Lipodystrophy
- Other: hepatotoxicity, pancreatitis, hypersensitivity/allergic reactions, PR interval prolongation, increased bleeding in haemophilia

Interactions:

Food-Drug:
Take with meals (improves absorption & tolerability)

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):

- **Alfuzosin, amiodarone, flecainide, propafenone, quinidine, ergot derivatives, cisapride, St. John's Wort, lovastatin, simvastatin, pimozide, oral midazolam, triazolam, voriconazole, sildenafil when used for pulmonary arterial hypertension**
- Disulfiram, metronidazole: disulfiram-like reactions as RTV capsules contain alcohol
- Warfarin: monitor INR frequently
- Rifampicin: RTV levels decreased, requires increased dose, see doses section and or section on LPV/ritonavir
- Levels of the following drugs may be decreased:
  - phenytoin, lamotrigine, divalproex, theophylline, atovaquone: monitor levels if possible, consider increased dose
  - ethinyl estradiol: consider alternative contraceptive methods
  - bupropion: monitor for effect
- Levels of the following drugs may be increased, monitor for side effects and monitor levels where possible:
  - protease inhibitors: atazanavir, darunavir, fosamprenavir, saquinavir (RTV used as a booster with these drugs)
  - disopyramide, lidocaine, mexiletine
  - anti-cancer agents: vincristine, vinblastine, dasatinib, nilotinib (may require dose adjustments/regimen change, see package inserts)
  - consider decreasing dose of: tramadol, propoxyphene, trazadone, desipramine, carbamazepine, clonazepam, ethosuximide, dronabinol, SSRIs, tricyclics, quinine, beta-blockers, calcium channel blockers, neuroleptics (including perphenazine, risperidone, thioridazine), parenteral midazolam, diazepam, buspirone, zolpidem
  - Colchicine: see package insert for dosing, do not give with RTV in renal or hepatic impairment
  - Clarithromycin: adjust dose if renal impairment, see package insert
  - Ketoconazole, itraconazole: doses >200mg not recommended
  - Rifabutin: reduce dose by at least 75% e.g.150 mg 3 x per week
  - Digoxin: monitor closely
  - Bosentan: adjust dose, see package insert
  - Atorvastatin, rosuvastatin: titrate dose carefully and use lowest possible dose

- Cyclosporin, tacrolimus, sirolimus: monitor
- Steroids**: fluticasone** - decreased cortisol levels, **salmeterol** - risk of cardiac events, consider reduced doses of dexamethasone, prednisone, fluticasone
- Fentanyl: monitor carefully
- **Sildenafil C/I for treatment of pulmonary artery hypertension**; sildenafil (for other indications), tadalafil, vardenafil may require dose adjustment, see package insert
- **Delaminid: Ritonavir-containing regimens can cause modest QT prolongation - monitor closely using ECG**

Practical Tips:

- Oral solution is bitter, use peanut butter, milk powder before dose to improve tolerability
- RTV is not recommended to use as an ARV on its own, due to toxicity at therapeutic doses and rapid selection of PI mutations
- The washout period for rifampicin's effect on CYP450 is 14 days
- **Caution** in underlying liver disease (including hepatitis B and C, or marked transaminase elevations), cardiac disease, diabetes
- Frequently observed adverse events, such as mild to moderate gastrointestinal disturbances and paraesthesias, may diminish as therapy is continued

Storage:

- Solution: room temperature, cool, dry and dark place. Do not store in the fridge.
- Capsules: 2-8°C (can be kept at room temperature, cool, dry, dark place for 30 days)


FIXED DOSE
COMBINATIONS
ART

Fixed Dose Combinations (FDCs) for Antiretroviral Treatment

FDC	Strength (mg)	Dosing Interval
Abacavir/Lamivudine	600/300	OD
Tenofovir/Emtricitabine	300/200	OD
Tenofovir/Emtricitabine/Efavirenz	300/200/600	OD
Zidovudine/Lamivudine	300/150	BD

TENOFOVIR/EMTRICITABINE/EFAVIRENZ

Doses:

Adult:

- TDF/FTC/EFV 300/200/600mg 1 tablet nocte

Paediatrics:

- Tenofovir is currently not registered for use in paediatric populations in South Africa

Contraindications:

- As for the individual drugs
- Note that this combination cannot be used in patients weighing < 40kg as they require 400mg of efavirenz

Formulation:

- Tablet: 300mg tenofovir, 200mg emtricitabine and 600mg efavirenz

Side-effects:

- Side effects are expected to be the same as for each individual drug

Interactions:

Food-Drug:

Take on an empty stomach

Drug-Drug:

As for the individual drugs

Practical Tips:

- Reducing the pill burden of the first-line regimen may improve adherence
- The FDC should not be crushed or dissolved
- 3TC and FTC are interchangeable
- Patients who are virologically suppressed on TDF, 3TC and EFV can be changed to the FDC
- Patients who are on D4T, 3TC and EFV can be changed to the FDC provided that they are virologically suppressed and their GFR is greater than 50ml/min – this can be considered a single drug substitution

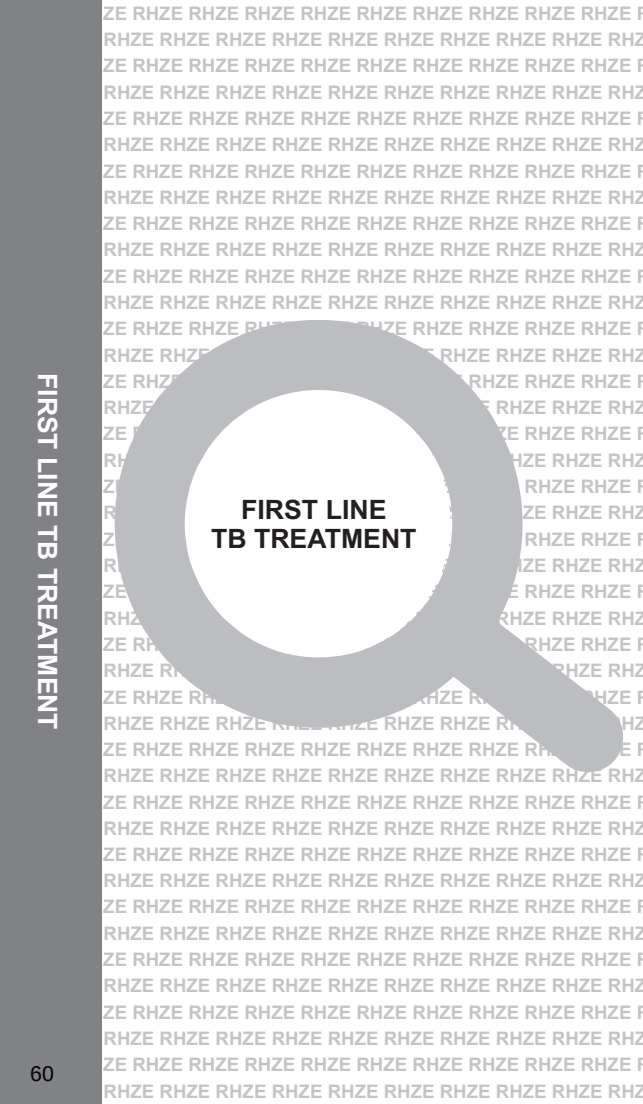
Practical Tips Continued:

- **Monitoring:** as for the individual drugs; ensure that creatinine clearance is done at month 3, 6, 12 and then annually
- In patients who develop side effects necessitating discontinuation of a single drug, the FDC will have to be replaced with individual drugs - the 2 tolerated drugs plus an alternative to replace the offending drug
- In patients on MDR-TB treatment (which includes aminoglycosides) consider switching the TDF-containing FDC for the duration of aminoglycoside use. Alternatively, increase monitoring of renal function while on the aminoglycoside
- Both TDF and FTC are active against hepatitis B. Discontinuation of TDF or FTC in patients with Hep B (surface antigenaemia) and HIV has been associated with acute exacerbations of hepatitis B

Storage:

Room temperature, cool, dry and dark place


TB DRUGS


FIRST LINE
TB TREATMENT

ADULT REGIMENS

Regimen 1: New Cases for Adults and Previously Treated patients

Pre-treatment body weight (kg)	Intensive phase (daily for 2 months)	Continuation phase (daily for 4 months)	
	RHZE 150,75, 400,275	RH 150,75	RH 300,150
30-37	2 tabs	2 tabs	
38-54	3 tabs	3 tabs	
55-70	4 tabs		2 tabs
>70	5 tabs		2 tabs

PAEDIATRIC REGIMENS

Regimen 3A: For uncomplicated TB with low bacillary load

Children up to 8 years

Pre-treatment body weight (kg)	Intensive Phase (daily for 2 months)			Continuation Phase (daily for 4 months)
	RH	PZA	PZA	RH
	60,60	150mg/150mg/3ml	500mg	60/60
2–2.9	½ tablet	1.5ml	expert advice on dose	½ tablet
3–3.9	¾ tablet	2.5ml	¼ tablet	¾ tablet
4–5.9	1 tablet	3 ml	¼ tablet	1 tablet
6–7.9	1½ tablet		½ tablet	1½ tablets
8–11.9	2 tablets		½ tablet	2 tablets
12–14.9	3 tablets		1 tablet	3 tablets
15–19.9	3½ tablets		1 tablet	3½ tablets
20–24.9	4½ tablets		1½ tablet	4½ tablets
25–29.9	5 tablets		2 tablets	5 tablets

- PLUS: Pyridoxine 12.5mg daily x 6 months if HIV infected or malnourished

Children > 8 years and Adolescents

Pre-treatment body weight (kg)	Intensive Phase (daily for 2 months)	Continuation phase (daily for 4 months)	
	RHZE 150,75,400, 275	**RH 150,75**	**RH 300,150**
30–37	2 tabs	2 tabs	
38–54	3 tabs	3 tabs	
55–70	4 tabs		2 tabs
≥71	5 tabs		2 tabs

- PLUS Pyridoxine 12.5mg daily x 6 months if HIV infected or malnourished

Regimen 3B: For Complicated TB

(Severe forms of TB such as TB Pericarditis, abdominal TB, osteo-articular TB and high bacillary load PTB)

Children Up to 8 years

	Intensive Phase (daily for 2 months)				Continuation phase (daily for 4 months)
Weight (kg)	**RH 60,60**	**PZA 500mg**	**PZA150mg or 150mg/3ml***	**EMB 400mg or 400mg/8ml****	**RH 60,60**
2 – 2.9	½ tablet	Expert advice on dose	1.5ml	1ml	½ tablet
3 – 3.9	¾ tablet	¼ tablet	2.5ml	1.5ml	¾ tablet
4 – 5.9	1 tablet	¼ tablet	3ml	2ml	1 tablet
6 – 7.9	1½ tablet	½ tablet		3ml	1½ tablets
8 –11.9	2 tablets	½ tablet		½ tablet	2 tablets
12 –14.9	3 tablets	1 tablet		¾ tablet	3 tablets
15 –19.9	3½ tabs	1 tablet		1 tablet	3½ tablets
20 –24.9	4½ tabs	1½ tablets		1 tablet	4½ tablets
25 –29.9	5 tabs	2 tablets		1½ tablets	5 tablets

- PLUS Pyridoxine 12.5mg daily x 6months if HIV-infected or malnourished

- *For each dose, dissolve 150mg dispersible (1 tablet) in 3mL of water to prepare a concentration of 50mg/mL (150mg/3mL). Only Pyrazinamide 150mg or 500mg tablets may be given at a time depending on availability but NOT both
- **400mg tab OR crush 400mg tablet & dissolve in 8 ml water to prepare a concentration of 400mg/8ml

Children > 8 Years and adolescents:

Pre-treatment body weight (kg)	Intensive Phase (daily for 2 months)	Continuation Phase (daily for 4 months)	
	RHZE 150,75, 400, 275	**RH 150,75**	**RH 300, 150**
30–37	2 tabs	2 tabs	
38–54	3 tabs	3 tabs	
55–70	4 tabs		2 tabs
>71	5 tabs		2 tabs

- PLUS: Pyridoxine 12.5mg daily x 6 months if HIV infected or malnourished
- Adjust treatment dosages to body weight. If calculating dosages, rather give ½ tablet more than ½ tablet less
- All previously treated children must be assessed and investigated for drug resistant TB. If drug susceptible TB, treat with Regimen 3B and monitor closely for clinical response and adverse events.

TB Meningitis

Duration: 6-9 months

Drug	Dose
Rifampicin	20mg/kg od
Isoniazid	20mgkg od
Pyrazinamide	40mg/kg od (max 2000mg daily)
Ethionamide	20mg/kg od (max 1000mg daily)

Use of steroids is indicated with the following types of TB:

- TB Meningitis
- TB Lymphadenitis- obstructing the airway
- Severely ill children with disseminated TB (Miliary)

Recommended dose: Prednisone 2mg/kg orally over 4 weeks (max dose 60mg/day) Dose to be tapered to stop over 2 weeks

ETHAMBUTOL, E, EMB

Drug Properties

Bacteriostatic, low potency, targets all bacterial populations

Doses:

See pages 60-65 for NDoH weight band dosing tables

Adult:

- 15 (15-20) mg/kg od, oral
- Usual dose range: 1000 - 1200mg daily
- Maximum dose: 2g od, oral
- Creatinine clearance < 30 ml/min or for patients receiving haemodialysis: 15–25 mg/kg/dose three times per week (not daily)

Paediatric:

- 20 (15-25) mg/kg od, oral
- Maximum dose: 1.2g od
- Safe for use in children of all ages provided dose does not exceed 25 mg/kg

Formulation:

Tablets: 400mg

Contraindications:

Hypersensitivity to the drug, optic neuritis, advanced renal failure

Side-effects:

- Optic neuropathy: related to dose and duration of treatment (<1% with 15mg/kg/day, <5% with 25mg/kg/day), can present as decreased visual acuity, scotomata, colour blindness, and/or constricted fields, usually presents in 2nd month of treatment, can be reversible if drug stopped promptly but can cause irreversible blindness
- Hyperuricemia, arthralgia, acute gout
- Hepatotoxicity rarely
- Peripheral neuropathy, rash, pruritus, dermatitis, hypersensitivity reaction, mild gastrointestinal events, dizziness, confusion, interstitial nephritis, haematological effects including leukopenia, neutropenia, thrombocytopenia, eosinophilia

Interactions:

Food-Drug:

May be taken with food or on an empty stomach

Drug-Drug:

- Neurotoxic agents: increased risk of optic and peripheral neuritis
- Diuretics, pyrazinamide: increased serum urate
- Aluminium hydroxide containing antacids: reduced ethambutol absorption, take these antacids >4 hours after ethambutol

Practical Tips:

- To mask bitter taste, tablet can be crushed, mixed with apple juice, refrigerated and used within 24 hours. Shake well before use.
- **Caution** in patients with eye defects, hyperuricaemia, renal impairment
- Advise patients to report any visual disturbance to their health care worker immediately
- Enquire about vision at each visit; assess visual fields and colour discrimination monthly
- If the client complains about visual disturbance, stop treatment immediately
- Poor CNS penetration

Storage:

Room temperature, cool, dry and dark place

ISONIAZID, H, INH

Drug Properties:
Bactericidal, high potency

Doses:
See pages 60-65 for NDoH weight band dosing tables

Adult:
- TB Treatment:
  - 5 (4-6) mg/kg od, oral
  - Maximum dose: 300mg od
  - Dose may be increased to overcome resistance
- TB prophylaxis:
  - 300 mg od, oral (duration based on result of tuberculin skin test – see NDOH guidelines)
  - Maximum dose: 300mg od, oral

Paediatric:
- TB Treatment: 10 (10-15) mg/kg od, oral
- Maximum dose: 300mg od, oral
- TB Meningitis in children: 20mg/kg od (see page 65 for regimen)
- TB prophylaxis: 10 (10-15) mg/kg od, oral (max 300mg) for between 6 and 36 months depending on tuberculin skin test status
  - Weight band dosage recommendations for INH preventive therapy in children

Body weight (kg)	Daily INH 100mg tablet
2 - 3.4	¼ tablet
3.5 - 6.9	½ tablet
7 - 9.9	1 tablet
10 - 14.9	1 ¼ tablets
15 - 19.9	1 ½ tablets
20 - 24.9	2 tablets
25 - 29.9	2 ½ tablets
≥30	3 tablets

Formulation:
Tablets: 100mg
Oral Solution: 50mg/5ml

Contraindications:

Severe hypersensitivity reaction to INH, acute hepatic disease

Side-effects:

- **Most common**: neurological effects, hepatotoxicity
- Hepatotoxicity: transient increase in transaminases in 10-20%, hepatitis in <2%
- Neurotoxicity: peripheral neuropathy, seizures, psychosis, optic neuritis, encephalopathy; neurotoxicity can be reversed with pyridoxine
- Haematological effects: agranulocytosis, haemolytic anaemia, sideroblastic anaemia, aplastic anaemia, thrombocytopenia, eosinophilia
- Drug-induced lupus erythematosus
- Rash: acne-form eruptions common, pellagra-type dermatitis in malnourished patients which responds to niacin
- GIT effects: nausea, vomiting, epigastric distress
- Other: hypersensitivity reactions, fever, interstitial nephritis rare, arthralgia

Interactions:

Food-Drug:

Absorption is better on an empty stomach. However, this is not always practical and patients may experience fewer GIT effects if taken after food.

Drug-Drug*: (inhibits cytochrome P450)*

- Anticonvulsant (e.g. phenytoin, carbamazepine, valproate) levels increased: anticonvulsant dosages may need reduction
- Warfarin levels increased: may need dose adjustment
- Rifampicin: increased hepatotoxicity but combination recommended
- Theophylline levels may increase
- Alcohol, corticosteroids: increased INH metabolism
- Disulfiram: increased psychosis
- Alcohol and paracetamol: increased hepatotoxicity
- Aluminium containing antacids: decreased INH absorption, should be given $\geq$2 hours apart

Practical Tips:

- Pyridoxine must be given with INH (for TB treatment and IPT) to prevent neurotoxicity
  - Adult dose: 10-50 mg/ day (may increase to 100mg/day for treatment)
  - Children: 12.5mg od
- **Caution** in patients with epilepsy, porphyria, peripheral neuropathy; if possible **monitor** transaminases in patients with pre-existing liver disease
- Safe during pregnancy and breastfeeding
- Advise patients that alcohol may increase risk of hepatotoxicity
- Appropriate proportion of INH tablet can crushed, dissolved in water or multi-vitamin syrup and given to children
- Good CNS penetration

Storage:
Room temperature, cool, dry and dark place

PYRAZINAMIDE, Z, PZA

Drug Properties:
Bactericidal, low potency, achieves sterilising action within 2-3 months. Acts on slow-growing bacteria. CNS levels equal to plasma.

Doses:
See pages 60-65 & 81-82 for NDoH weight band dosing tables

Adult:
- 25 (20-30) mg/kg od, oral
- Maximum dose: 2g od, oral
- Creatinine clearance <30 ml/min or patients receiving haemodialysis: 25–35 mg/kg/dose three times per week (not daily)

Paediatric:
- 35 (30-40) mg/kg od, oral
- Maximum dose: 2g od, oral
- Miliary TB in children < 8 years: 40mg/kg od (see page 65 for regimen)

Formulation:
Tablets: 500mg

Contraindications:
Hypersensitivity to the drug, severe hepatic damage, porphyria, acute gout

Side-effects:
- Hepatotoxicity: reversible transaminase elevation more common than overt hepatitis, dose-related – lower risk when doses <30mg/kg
- Asymptomatic hyperuricemia (common), non-gouty arthralgia, acute gout rare
- GIT effects including nausea, vomiting, anorexia
- Haematological: thrombocytopenia, sideroblastic anaemia
- Myalgia
- Hypersensitivity reactions (flushing, pruritus, urticarial rash) rare

Interactions:

Food-Drug:

Absorption is better on an empty stomach. However, this is not always practical and patients may experience fewer GIT effects if taken after food.

Drug-Drug:

- Allopurinol, probenecid: dose adjustment of antigout agents may be required as PZA inhibits urate clearance
- Diuretics, ethambutol: further increase in serum urate

Practical Tips:

- Most hepatotoxic of first-line TB drugs
- If hepatotoxicity has occurred secondary to TB treatment and TB treatment was discontinued, consider re-introducing PZA in patients with severe TB (e.g. miliary, meningitis), drug resistance or intolerance to INH or RIF
- **Caution** in renal impairment, gout, diabetes, pre-existing liver disease or those at increased risk for drug related hepatitis (e.g. alcohol abusers)
- Crush and dissolve tablets for paediatric use
- **Monitoring:**
  - Clients with diabetes should be carefully monitored since blood glucose concentrations may become labile
  - LFTs should be done periodically (every 1-3 months) in patients receiving PZA for extended periods or for patients at risk of or with symptoms of hepatitis
- Good CNS penetration

Storage:

Room temperature, cool, dry and dark place

RIFAMPICIN, R, RIF

Drug Properties

Bactericidal, high potency, most effective sterilising agent. Acts on all populations of bacilli, including dormant bacilli.

Doses:

See pages 60-65 for NDoH weight band dosing tables

Adult:

- 10 (8-12) mg/kg (usual adult dose 600mg/day) od, oral
- Maximum dose: 600mg od, oral
- Renal impairment: doses up to 10mg/kg/day do not accumulate in renal impairment
- Liver impairment: do not use >8mg/kg/day

Paediatric:

- 15 (10-20) mg/kg od, oral
- Maximum dose: 600mg od, oral
- Miliary TB in children <8 years: 20mg/kg od (see page 65 for regimen)

Formulation:

Oral Solution: 100mg/5ml
Capsules: 150mg
Tablets: 450mg, 600mg

Contraindications:

Hypersensitivity to any of the rifamycins, porphyria

Side-effects:

- Hepatotoxicity: isolated jaundice usually clears with ongoing treatment, elevated transaminases common, overt hepatitis rare
- GIT effects include nausea, vomiting, anorexia, abdominal discomfort, diarrhoea
- Can colour urine and body fluids orange to reddish brown (explain to patients that this is normal)
- Flu-like syndrome with fever, chills, headache, dizziness, bone pain, abdominal pain, generalised pruritus (more common if on intermittent or discontinuous treatment)
- Hypersensitivity reactions
- CNS effects include drowsiness, headache, confusion, muscular weakness
- Thrombocytopenia, haemolytic anaemia

- Drug fever

Interactions:

Food-Drug:

Absorption better on an empty stomach; however, this is not always practical and patients may experience fewer GIT effects if taken after food.

Drug-Drug:

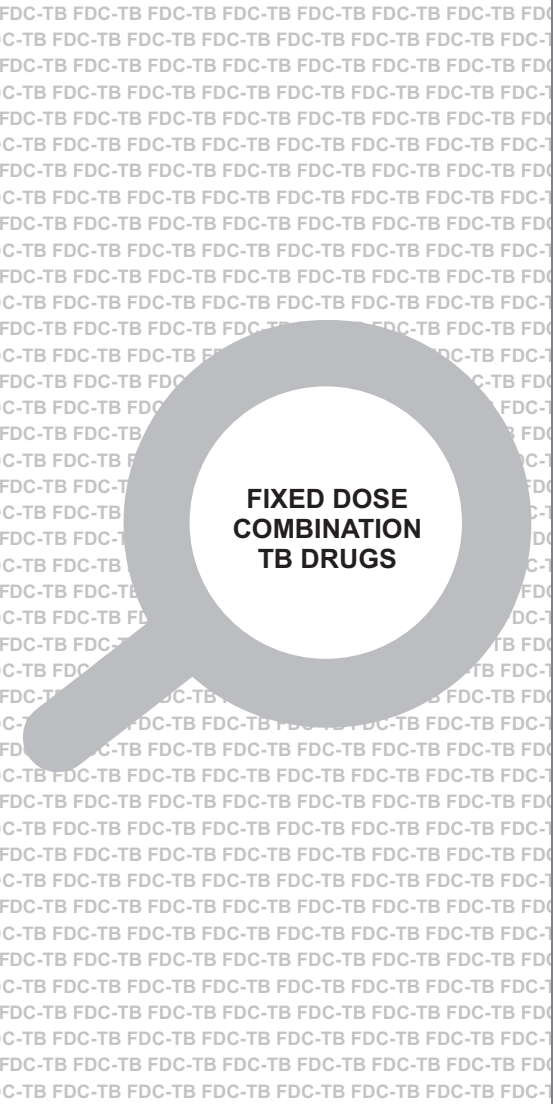
- Clearance of medications metabolised hepatically or in the intestine may be increased including: PIs, NNRTIs, glucocorticosteroids, phenytoin, theophylline, warfarin, sulfonylureas, oral contraceptives, cyclosporin, quinine, quinidine, digoxin, beta blockers, verapamil, midazolam, itraconazole, and ketoconazole. Doses may need to be increased.
- Other hepatotoxic drugs, alcohol: risk of hepatotoxicity increases

Practical Tips:

- Due to discolouration of body fluids, permanent staining of contact lenses may occur
- **Caution** if known hypersensitivity to rifampicin, hepatic dysfunction, alcoholism
- Good CNS penetration
- Contraceptives:
    - Can use oral contraceptive pill containing a higher dose of oestrogen (50mcg), the pill free interval shortened from 7 to 4 days
    - Depo provera 150mg given 8 weekly
    - Nur-Isterate 200mg given 10 weekly
    - Intrauterine contraceptive devices may be recommended
    - Effect of rifampicin may last up to 2 months after treatment has stopped

Storage:

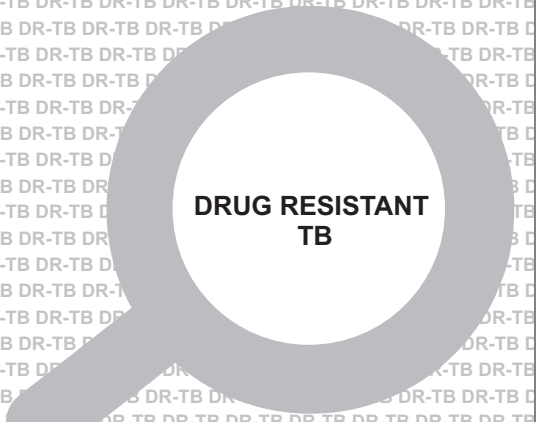
Room temperature, cool, dry and dark place


FIXED DOSE
COMBINATION
TB DRUGS

Fixed Dose Combinations (FDCs) for TB Treatment

Note: It is always preferable to use FDCs for TB treatment. Only use individual drugs in the case of side effects in drug sensitive TB and as per guidelines for Non-tuberculous mycobacteria, mono-, poly-, multi-, and extensively drug resistant TB

FDC	Strength (mg)	Interval
RH	• 150/75 • 300/150	od
RH	• 150/75 • 300/150	od
RHZE	• 150/75/ 400/275	od
RHZE	• 150/75/ 400/275	od
RH	• 60/30 • 60/60	od
RHZ	• 150/75/ 400	od
RHZ	• 60/30/ 150	od


DRUG RESISTANT
TB

MONO- AND POLY-RESISTANT TB REGIMENS

Drug Resistance Pattern	Suggested Regimen	Minimum duration of treatment
INH	RHZE for the full duration of treatment (easier to use fixed-dose combinations in practice)	6-9 months based on symptomatic response to treatment, weight gain and sputum culture results (a minimum of 6 months treatment after culture conversion is adequate)
RIF (± any other 1st line drug other than INH)	Standardised MDR-TB regimen plus INH	18 months treatment after culture conversion required
Poly-resistant TB (two or more 1st line drugs but not including both INH and RIF)	Refer to MDR-TB expert for regimen design based on resistance pattern and history of anti-TB drug use	

MDR-TB REGIMENS

Standardised Regimen for Adults and Children 8 Years And Above

INTENSIVE PHASE:
Duration: add 4 months to date of TB culture conversion (minimum of 6 months; treatment to be taken at least 6 times per week)

Weight(kg)	Drug	Dosage
<33	Kanamycin	15-20mg/kg
	Moxifloxacin	400mg (children: 7.5-10mg/kg)
	Ethionamide	15-20mg/kg
	Terizidone	15-20mg/kg
	Pyrazinamide	30-40mg/kg
33-50	Kanamycin	500-750mg
	Moxifloxacin	400mg
	Ethionamide	500mg
	Terizidone	750mg
	Pyrazinamide	1000-1750mg
51-70	Kanamycin	1000mg
	Moxifloxacin	400mg
	Ethionamide	750mg
	Terizidone	750mg
	Pyrazinamide	1750-2000mg
>70	Kanamycin	1000mg
	Moxifloxacin	400mg
	Ethionamide	750mg-1000mg
	Terizidone	750mg-1000mg
	Pyrazinamide	2000-2500mg

CONTINUATION PHASE
Duration: add 18 months to the date of TB culture conversion (treatment to be taken at least 6 times per week)

Weight (kg)	Drug	Dosage
<33	Moxifloxacin	400mg
	Ethionamide	15-20mg/kg
	Terizidone	15-20mg/kg
	Pyrazinamide	30-40mg/kg
33-50	Moxifloxacin	400mg
	Ethionamide	500mg
	Terizidone	750mg
	Pyrazinamide	1000-1750mg
51-70	Moxifloxacin	400mg
	Ethionamide	750mg
	Terizidone	750mg
	Pyrazinamide	1750-2000mg
>70	Moxifloxacin	400mg
	Ethionamide	750-1000mg
	Terizidone	750-1000mg
	Pyrazinamide	2000-2500mg

- Pyridoxine (Vit B6) 150 mg (maximum 200mg) to be given daily to patients on Terizidone
- Adults who do not tolerate moxifloxacin should be given levofloxacin at the following dosage: 750 mg for patients weighing below 51 kg, and 1000 mg for patients with a weight equal or above 51 kg.

Standardised Regimen for Children Younger than 8 Years

Drug	Dosage
Amikacin	15-22.5mg/kg
Levofloxacin	10-15mg/kg once daily
Ethionamide	15-20mg/kg
Terizidone	15-20mg/kg
Pyrazinamide	30-40mg/kg

Ethambutol may be given at dose of 20-25mg/kg and high dose INH 15-20mg/kg if known inhA mutation

AMIKACIN, Am

Drug properties:
Bactericidal, strong anti-tuberculous activity

Doses:
Adult:
- 15mg/kg/day od, IM
- Usual dose range: 750mg – 1000mg od, IM
- If creatinine clearance <30 ml/min or for patients receiving haemodialysis: 12–15 mg/kg/dose 2-3 x weekly (not daily), IM

Paediatric:
- 15-22.5mg/kg od, IM
- Maximum dose: 1000mg od, IM
- Adjust dose in renal failure (see package insert)

Formulation:
Vials: 100mg/2ml, 250mg/2ml, 500mg/2ml, 1g/4ml

Contraindications:
Hypersensitivity to amikacin/other aminoglycosides

Side-effects:
- Nephrotoxicity: increased creatinine, albuminuria, red and white cells, casts, azotaemia, oliguria reported; usually reversible when drug stopped
- Neurotoxicity
  - can affect 8th cranial nerve causing vestibular and/or cochlear toxicity - deafness, vertigo
  - numbness, skin tingling, muscle twitching, convulsions
- Neuromuscular blockade, respiratory paralysis
- Local pain when given intramuscularly
- Other: skin rash, drug fever, headache, paraesthesia, tremor, nausea, vomiting, eosinophilia, arthralgia, anaemia, hypotension, electrolyte disturbances

Interactions:
Food-Drug:
Ensure adequate hydration

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):

- **Potent diuretics (ethacrynic acid, furosemide): increased toxicity**
- **Other neurotoxic and/or nephrotoxic agents (systemic, oral or topical) including polymyxin B, bacitracin, colistin, amphotericin B, cisplatin, vancomycin, parenteral cephalosporins, other aminoglycosides, tenofovir should be avoided: toxicity may be additive**
- Other neuromuscular blocking agents, anaesthetics: risk of neuromuscular blockade

Practical Tips:

- Cross-resistance with kanamycin and some data suggest cross-resistance with capreomycin
- Contains sodium bisulfite, which may cause allergic or anaphylactic reactions
- Can be given IV (same dose as IM)
- **Monitoring:** renal function, electrolytes & audiometry
  - Current NDoH Guidelines:
    - serum creatinine at baseline and monthly during the injectable phase
    - serum potassium monthly during the injectable phase
    - audiometry at baseline, monthly during the injectable phase and 3 months after cessation of the injectable agent
- Toxicity increased if impaired renal function, high doses, prolonged therapy
- If patient is on TDF, consider switching TDF for the duration of aminoglycoside use. Alternatively, increase monitoring of renal function while on the aminoglycoside and TDF
- High-frequency deafness usually occurs first and can only be detected by audiometry
- **Caution** if neuromuscular disorders such as myasthenia gravis, parkinsonism as muscle weakness may be aggravated
- Risk of congenital deafness if used in pregnancy
- Effective CNS penetration occurs only in presence of meningeal inflammation

Storage:
Store at 20-25^{0}C, cool, dry, dark place

BEDAQUILINE, BDQ

Drug properties:
Bactericidal, inhibits ATP synthesis

Doses:
Adult:
- 400mg once daily for 2 weeks, followed by 200mg 3 times per week

Paediatric:
- Not yet determined

Formulation:
100mg tablets

INDICATIONS
Patients ≥18 years of age;
and
Laboratory-confirmed RR-TB (at least resistance to RIF) by culture-based phenotypic drug sensitivity testing or genotypic line probe assay or PCR testing (Xpert MTB/RIF) from pulmonary and/or extra pulmonary sites;
and
No history or family history of QT prolongation; *and*
Baseline QTcF< 450 msec; *and*
Any one of the following three conditions:
a. Drug resistance in addition to RR TB:
XDR TB;
or
pre XDR TB (resistant to either fluoroquinolone or second line injectable drug);
or
both inhA and katG mutations;
b. Documented / recorded intolerance to 2nd line anti-TB treatment at baseline (prior to treatment initiation) or during RR TB treatment, e.g. hearing loss, renal dysfunction
c. History of, or surgical candidate for pneumonectomy or lobectomy

Patients who meet the above criteria, regardless of HIV infection status or concomitant treatment with ARVs can be considered eligible *for the 6 months of BDQ treatment*.

Patients who meet the above criteria, regardless of the site of TB infection, e.g. inclusive of patients presenting with extra pulmonary TB (EPTB), should be considered eligible for BDQ. Continuation of BDQ beyond 6 months is required to be presented for review by the clinical advisory committee.

1) Patients has already had > 3 months of pre-XDR or XDR treatment prior to BDQ initiation;

OR

2) Patient has fewer than 2 of the following 4 drugs 'counted' to be effective in regimen:

Drug	Count if
Injectable	Only count if no documented resistance to any second line injectable on DST (specimen taken within last 3 months)
Quinolone	Only count if no documented resistance to any fluoroquinolone on DST (specimen taken within last 3 months)
Bedaquiline	Do not count if exposed to clofazimine for more than 3 months previously
Linezolid	Do not count if exposed to linezolid previously for DR TB

Contraindications:

Do not use or discontinue

- Clinically significant ventricular arrhythmia
- A QTcF interval of > 500 ms (confirmed by repeat ECG)
- Severe liver disease
- Abnormal Electrolytes

Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):

- Use with other QT prolonging drugs (eg clofazimine, fluoroquinolones, azole antifungals)
- A history of torsades de pointes
- A history of congenital long QT syndrome
- A history of hypothyroidism and bradyarrhythmias
- A history of uncompensated heart failure
- Serum calcium, Magnesium or potassium levels below the lower limits of normal

Side-effects:

- Common: gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite), joint pain (arthralgia), headache
- Less Common: QT prolongation, hyperuricemia, phospholipidosis, elevated aminotransferases, Possibly an increased risk of pancreatitis

Interactions:

Food-Drug:
None

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):

- Rifampicin, Efavirenz (CYP3A4 inducers) reduces levels of Bedaquiline
- CYP3A4 inhibitors (eg azole anti-fungal drugs, some macrolides, protease inhibitors) can increase the levels of Bedaquiline can be considered for use if the benefits outweighs the risk
- **Delamanid: No safety data on simultaneous use of Bedaquiline and Delamanid – do not use together**
- Avoid use with other drugs that prolong the QT interval as additive QT prolongation will occur (e.g. clofazimine, delamanid, fluoroquinolones, azole anti-fungal drugs)

Practical Tips:

- Indication for use in case of resistance to second-line drugs, ototoxicity or nephrotoxicity
- Recommended for use in individuals aged between 18-65 years
- Monitoring:
- According to Current NDoH Guidelines:
  - Baseline ECG is recommended prior to Bedaquiline initiation, with monthly ECG monitoring while on treatment
  - LFT's should be done monthly

Practical Tips Continued:

- Instruct patients to inform their health care provider if the following occurs:
    - Abdominal pain
    - Yellowing of eyes/skin
    - Palpitations
    - Chest pain
    - Fainting and near fainting events

Storage:

- Room Temperature (15-25˚C)

CAPREOMYCIN, Cm

Drug properties:
Bactericidal, strong anti-tuberculous activity

Doses:
Adult:
- 15-20mg/kg od, IM
- Usual dose range: 750mg - 1000mg od, IM
- Requires dose adjustment if creatinine clearance <30 ml/min or if on haemodialysis: 12–15 mg/kg/dose two or three times per week (not daily), IM

Paediatric:
- 15-30mg/kg od, IM
- Maximum dose: 1g daily

Formulation:
Inject: 1g / vial

Contraindications:
Hypersensitivity to the drug

Side-effects:
- Nephrotoxicity
- Electrolyte disturbances including hypokalaemia, hypomagnesaemia, hypocalcaemia
- Ototoxicity: hearing loss, tinnitus, vertigo
- Hypersensitivity reactions including urticaria, maculopapular rash, fever
- Neuromuscular blockade with high doses or rapid infusions
- Haematological: leukopenia, leucocytosis, eosinophilia
- Liver function abnormalities when used with other TB drugs
- Local pain when given intramuscularly

Interactions:
Food-Drug:
None as drug given IM

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):
- **Other drugs with ototoxic or nephrotoxic potential including other parenteral antituberculous drugs: streptomycin, amikacin, kanamycin, gentamicin,**

neomycin, tobramycin, vancomycin, viomycin, polymyxin A sulfate, colistin sulfate, tenofovir

Practical Tips:

- Usually reserved for XDR TB and aminoglycoside resistant TB
- Some data suggest cross-resistance with amikacin and kanamycin
- **Caution** in patients with renal insufficiency, pre-existing auditory impairment
- **Monitoring**: renal function, electrolytes, audiometry
  - Current NDoH Guidelines:
    - serum creatinine at baseline and monthly during the injectable phase
    - serum potassium monthly during the injectable phase
    - audiometry at baseline, monthly during the injectable phase and 3 months after cessation of the injectable agent
- If patient is on TDF, consider switching TDF for the duration of aminoglycoside use. Alternatively, increase monitoring of renal function while on the aminoglycoside and TDF
- Clinically **monitor** for vestibular effects
- Risk of congenital deafness if used in pregnancy, but is considered the drug of choice if an injectable is required in pregnancy
- Effective CNS penetration only in presence of meningeal inflammation

Storage:

- **Prior to reconstitution:** store at room temperature, cool, dry, dark place
- **After reconstitution:** can be refrigerated for 24 hours

CLOFAZIMINE, Cfz

Drug Properties:

In vitro activity against *M. tuberculosis* without much *in vivo* data

Doses:

Adult:

- <33kg: 3-5mg/kg od, oral
- 33-50kg: 200mg od, oral
- >50 kg: 300mg od, oral

Paediatric:

- Limited data, but doses of 3-5 mg/kg/day, oral have been used

Formulation:

Capsules: 50mg, 100mg

Contraindications:

Hypersensitivity to clofazimine

Side-effects:

- Skin: pigmentation from pink to brownish-black, ichthyosis and dryness, rash and pruritus, photosensitivity
- GIT: abdominal pain, diarrhoea, nausea, vomiting. Splenic infarction, bowel obstruction and GIT bleeding have been reported. Can present as an acute abdomen.
- Ocular: conjunctival and corneal pigmentation, dryness, burning, itching, irritation
- Other: discolouration of urine, faeces, sputum, sweat; elevated glucose; elevated ESR

Interactions:

Food-Drug:

Take with meals (improves absorption and diminishes GIT upset)

Drug-Drug:

- May decrease absorption rate of rifampicin
- Isoniazid increases clofazimine serum and urine concentrations and decreases skin concentrations
- Bedaquiline: Avoid use with Clofazimine as additive QT interval prolongation may occur
- Delamanid: Avoid use with Clofazimine as additive QT interval prolongation may occur

Practical Tips:

- Usually reserved for XDR-TB or pre-XDR TB
- **Caution** in patients with GIT problems, porphyria, hepatic insufficiency (may require dose adjustment in severe hepatic insufficiency)
- Warn patients of discolouration of skin and body fluids
- Skin discolouration is reversible but may take months or years to resolve after cessation of treatment
- Foetal pigmentation has occurred when used in pregnancy and in lactation

Storage:

Store below 30^0C, cool, dry, dark place, airtight containers

DELAMANID, Dlm

Drug Properties

Inhibition of the synthesis of the mycobacterial cell wall

Doses:

Adult:

- 100mg twice daily

Paediatric:

- Not yet determined

Formulation :

Tablets: 50mg film-coated tablets

Indication s:

MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolone or second-line injectable drugs
XDR-TB patients
Adults ≥ 18 years, considered safe to administer in children ages 13 and above

Contraindications:

Do not use or discontinue
Clinically significant ventricular arrhythmia
QTcF interval of > 500 ms (confirmed by repeat ECG)
Severe liver disease
Severely low serum albumin levels (< 2.8g/dL)
Abnormal electrolytes
Use with caution in the following situations
A history of torsade de pointes/ congenital long QT syndrome
Serum calcium, magnesium, or potassium levels below the lower limits of normal
A history of hypothyroidism, bradyarrhythmias
Patients ≥ 65years, diabetes, liver and/or renal dysfunction, malignancies, alcohol and substance use

Side-effects:

- Common: nausea, vomiting, dizziness
- Less common: QT prolongation

Interactions:

Food-Drug:
Food increases absorption, to be taken after a meal
Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- Rifampicin, Carbamazepine (strong CYP3A inducers) reduces delamanid levels
- Lopinavir/ritonavir, Tenofovir, Efavirenz no clinically significant effect on delamanid levels
- Bedaquiline: No safety data on simultaneous use of Bedaquiline and Delamanid- do not use together
- Avoid using with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. clofazimine, fluoroquinolones, bedaquiline, azole anti-fungal drugs, ondansetron)

Practical Tips:

- Should not be introduced into a regimen in which other drugs are known not to be effective – should not be added alone to a failing regimen
- Dose of Delamanid in adults is 100mg twice a day irrespective of body weight for a period of six months
- Cross-resistance with other nitroimidazoles
- ECG Monitoring: Should be done at the following intervals
    - before initiation of treatment,
    - at least 2, 4, 8, 12 and 24 weeks after starting treatment
- Monitor closely for QT prolongation and electrolyte imbalance (especially K^+) which may predispose to cardiotoxicity if the following drugs are used with Delamanid:
    - Fluoroquinolones and clofazimine
    - Azole anti-fungal drugs
- Not safe for use in Pregnant and Breastfeeding women
- Patients should be instructed to inform the health care provider immediately if any of the following occurs:
    - Palpitations
    - Chest pain
    - Fainting and near fainting events

Storage:

Room temperature, cool, dry and dark place

ETHIONAMIDE, Eto

Drug Properties

Bacteriostatic or bactericidal, depending on concentration at infection site. Good CNS penetration

Doses:

See page 81-82 for NDoH weight band dosing tables

Adult:

- 15-20mg/kg od, oral
- Maximum dose: 1g daily
- Usual dose range: 500-750mg daily
- Can divide 250mg mane/ 500mg nocte to minimise GIT side effects
- Creatinine clearance <30ml/min or if patient on haemodialysis: 250-500mg/dose daily

Paediatric:

- 15-20mg/kg od, oral
- Maximum dose: 1g daily
- Can start with 10mg/kg over 1 week then increase to 15-20mg/kg
- Can also be given in 2 divided doses until well-tolerated
- TB meningitis in children: 20 mg/kg od (see page 65 for regimen)

Formulation:

Tablets: 250mg

Contraindications:

Hypersensitivity to ethionamide, severe hepatic disease, porphyria

Side-effects:

- Gastrointestinal intolerance (including metallic taste) most common
- Hepatotoxicity
- Hypothyroidism, especially in HIV-infected patients and if used with PAS
- Diabetes may be difficult to control
- CNS effects including seizures, pellagra type encephalopathy, acute psychosis, anxiety and depression, optic neuritis, peripheral neuropathy

Interactions:

Food-Drug:
Take with food to reduce GIT intolerance

Drug-Drug:
- Neurotoxic agents: increased risk of ocular toxicity
- Diuretics: potentiates effect on serum urate
- PZA: potentiates hepatotoxicity and hyperuricemia
- INH: INH level increased, increased risk of INH toxicity
- Ethambutol: increased risk of adverse events

Practical Tips:
- Vitamin B6 (pyridoxine) 150mg can minimise or prevent peripheral neuropathy
- There may cross resistance between ethionamide and INH mediated via the InhA gene
- Pellagra type encephalopathy responds to niacin treatment
- Avoid the use of ethionamide in first-line treatment if possible as it is an important second-line drug to be preserved for the management of resistant or complicated TB
- Ethionamide has good penetration of blood-brain barrier, so consider using for miliary TB or TB meningitis
- Teratogenic effects observed in animal studies, and significantly worsens nausea associated with pregnancy - **avoid**
- **Monitoring**: thyroid function
    - Current NDoH Guidelines:
        - assess monthly for signs of hypothyroidism, do thyroid stimulating hormone 6 monthly in adults and 2 monthly in children

Storage:
Room temperature, cool, dry and dark place

KANAMYCIN, Km

Drug properties:
Bactericidal, strong anti-tuberculous activity

Doses:
See page 81-82 for NDoH weight band dosing tables

Adult:
- 15mg/kg od, IM
- Usual dose: 750mg-1g od, IM
- If creatinine clearance <30 ml/min or for patients receiving haemodialysis: 12–15 mg/kg/dose 2- 3 times per week (not daily), IM

Paediatric:
- 15-30mg/kg od, IM
- Maximum dose: 1g daily

Formulation:
Inject: 500mg/2ml vial, 1g/3ml vial

Contraindications:
History of hypersensitivity to any aminoglycoside

Side-effects:
- Neurotoxicity:
  - affects 8th cranial nerve causing auditory and vestibular ototoxicity – hearing loss, loss of balance, tinnitus, vertigo
  - numbness, skin tingling, muscle twitching, and convulsions
- Nephrotoxicity: evidenced by urinary cells or casts, oliguria, proteinuria, decreased urine specific gravity, increasing urea and creatinine
- Neuromuscular blockade: acute muscular paralysis and apnoea can occur (rare)
- Other: local irritation following IM injection, skin rash, drug fever, headache, paraesthesia, nausea, vomiting, diarrhoea, malabsorption

Interactions:
Food-Drug:
Ensure adequate hydration to prevent nephrotoxicity

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- Aminoglycosides, some cephalosporins: increased nephrotoxicity
- **Potent diuretics (ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, or mannitol)**: increased ototoxicity, and IV diuretics may enhance aminoglycoside toxicity
- **Other neurotoxic and/or nephrotoxic drugs including polymyxin B, bacitracin, colistin, amphotericin B, cisplatin, vancomycin, TDF, other aminoglycosides**: toxicity may be additive

Practical Tips:

- Resistance to kanamycin induces almost complete cross-resistance to amikacin
- Contains sodium bisulfite, may cause allergic or anaphylactic reactions
- Can be given IV (same dose as IM)
- **Caution** with renal, vestibular, or auditory impairment; patients with intestinal obstructions
- **Caution** if neuromuscular disorders present e.g. myasthenia gravis, parkinsonism - muscle weakness may be aggravated
- Toxicity increased if impaired renal function, high doses, prolonged therapy, elderly, dehydration
- Risk of congenital deafness if used in pregnancy
- **Monitoring:** renal function, electrolytes and audiometry
  - Current NDoH Guidelines: serum creatinine at baseline and monthly during the injectable phase, serum potassium monthly during the injectable phase; audiometry at baseline, monthly during the injectable phase and 3 months after cessation of the injectable
- Penetrates CNS effectively only in presence of meningeal inflammation
- If patient is on TDF, consider switching TDF for the duration of aminoglycoside use. Alternatively, increase monitoring of renal function while on the aminoglycoside and TDF

Storage:

Store at 20-25^{0}C

LEVOFLOXACIN, Lfx

Drug properties:
Bactericidal, strong anti- tuberculous activity

Doses:
See pages 81-82 for NDoH weight band dosing tables

Adult:
- 7.5-10mg/kg/day od, oral
- Usual dose range: 750mg - 1000mg
- If creatinine clearance <30ml/min or if patient receiving haemodialysis: 750-1000mg, 3 x weekly (not daily), oral

Paediatric:
- Children <8 years
  - 10-15mg/kg od, oral
  - Maximum dose: 1g daily, oral

Formulation:
Tablets: 250mg, 500mg, 750mg
IV Infusion: 250mg/50ml, 500mg/100ml

Contraindications:
Known hypersensitivity to levofloxacin or other quinolones

Side-effects:
- **Most common:** nausea, headache, diarrhoea, insomnia, constipation, dizziness
- GIT effects
- Anaphylactic reactions, allergic skin reactions
- Tendonitis, tendon rupture, arthralgia
- Haematological toxicity including agranulocytosis, thrombocytopenia
- Hepatic toxicity
- CNS effects: seizures, confusion, anxiety, depression, insomnia
- Clostridium difficile-associated colitis
- Peripheral neuropathy
- Photosensitivity, phototoxicity
- Blood glucose disturbances: hyper- or hypoglycaemia, usually in diabetics
- Prolonged QT interval, torsade de pointes

- May exacerbate muscle weakness in persons with myasthenia gravis
- Musculoskeletal disorders (arthralgia, gait abnormalities) in children and the elderly

Interactions:

Food-Drug:

- Tablets can be taken with or without food
- Drink plenty of fluids while on levofloxacin to avoid crystalluria

Drug-Drug:

- Multivalent cation-containing products including:
  - antacids containing magnesium/aluminium
  - sucralfate
  - metal cations e.g. iron
  - multivitamins with zinc
- Warfarin effect may be enhanced: monitor prothrombin time, INR
- Antidiabetic agents: monitor glucose
- Non-steroidal anti-inflammatories: CNS stimulation, seizures
- Bedaquiline: Avoid use with fluoroquinolones as additive QT interval prolongation may occur

Practical Tips:

- Cross-resistance with other fluoroquinolones, but data suggests greater activity than ciprofloxacin or ofloxacin
- This is the quinolone of choice in children with MDR-TB
- Used in MDR-TB patients younger than 8 years old and adults who may not tolerate moxifloxacin
- Can be given IV (same dose as IM)
- **Caution** if patient has or is at risk of seizures
- Discontinue treatment if peripheral neuropathy occurs to prevent irreversibility
- Delamanid: Avoid use with fluoroquinolones as additive QT interval prolongation may occur

Practical Tips Continued:

- Discontinue if pain or inflammation in a tendon occurs
- **Avoid** in patients with known QT prolongation, hypokalemia, myasthenia gravis, and avoid use with other drugs that prolong the QT interval
- Rapid or bolus IV infusion can cause hypotension, levofloxacin should be infused IV slowly over 60 – 90 minutes
- Additives or other medications should not be added to or infused simultaneously with IV levofloxacin in the same intravenous line
- **Caution** in pregnancy (arthropathy in animal studies)
- **Avoid** prolonged sunlight exposure during treatment

Storage:
Oral forms, IV solution stored at room temperature, cool, dry, dark place

LINEZOLID, Lzd

Drug Properties:

Linezolid is an oxazolidinone antibacterial. It has *in vitro* bactericidal activity, little clinical experience

Doses:

Adult:

- 600 mg od, oral

Paediatric:

- 10-12 mg/kg/day divided bd, oral

Formulation:

Film-coated tablets: 600mg
IV infusion: 2mg/ml (200mg/100ml infusion bag, 600mg/300ml infusion bag)
Oral solution: 20mg/ml

Contraindications:

Known hypersensitivity to the drug

Side-effects:

- **Most common:** diarrhoea, headache, nausea, monoliasis, metallic taste
- Myelosuppression including anaemia, leukopenia, pancytopenia, thrombocytopenia
- Clostridium difficile associated diarrhoea
- Hypoglycaemia in diabetic patients on insulin or hypoglycaemics
- Lactic acidosis
- Serotonin syndrome with co-administration of serotonergic drugs
- Peripheral and optic neuropathy
- Convulsions

Interactions:

Food-Drug:

- May be taken with or without food
- Avoid food and drinks that contain tyramine including aged cheeses, dried meats, sauerkraut, soy sauce, tap beers, red wines

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):

- **Monoamine oxidase inhibitors:** do not use linezolid within 2 weeks of taking a drug which inhibits monoamine oxidase A or B
- Serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor antagonists, meperidine, buspirone: risk of serotonin syndrome, avoid unless carefully observed
- Adrenergic agents including sympathomimetics (e.g. pseudoephedrine), vasopressive agents (e.g. adrenaline, noradrenaline), dopaminergic agents (e.g. dopamine, dobutamine): enhancement of pressor response; avoid unless BP carefully monitored; reduce initial doses and titrate

Practical Tips:

- Reserved for XDR-TB or Pre-XDR TB
- Category 5 drug
- No cross-resistance with other antibiotics
- Can be given IV (same dose as oral)
- All patients should receive pyridoxine while receiving linezolid
- **Caution** in patients with uncontrolled hypertension – monitor BP carefully
- **Monitoring:** monitor FBC and visual function

Storage:

- **Tablets:** store at room temperature, protect from light and moisture
- **Reconstituted oral solution:** may be stored at room temperature for 21 days
- **Parenteral preparation:** store at room temperature, protect from light and do not freeze

MOXIFLOXACIN, Mfx

Drug properties:
Weakly bactericidal

Doses:
See pages 81-82 for NDoH weight band dosing tables

Adult:
- 400mg od, oral

Paediatric:
Children >8 years:
- 7.5-10mg/kg od, oral
- Maximum dose: 400mg daily

Formulation:
Tablets: 400 mg
IV infusion: 400mg in 250ml 0.8% sodium chloride solution

Contraindications:
Known hypersensitivity to moxifloxacin or other quinolones, known history of myasthenia gravis

Side-effects:
- **Most common:** nausea, diarrhoea, headache, dizziness
- Tendonitis, tendon rupture, arthralgia
- Exacerbation of myasthenia gravis
- QT interval prolongation, torsade de pointes
- Hypersensitivity reactions
- Other serious reactions include: hepatitis, interstitial nephritis, haematological effects, vasculitis, severe dermatological reactions
- CNS effects: dizziness, confusion, hallucinations, depression, seizures, insomnia, anxiety, tremor, pseudo tumour cerebri, nightmares; CNS effects worse in older patients
- Clostridium difficile-associated diarrhoea
- Peripheral neuropathy
- Photosensitivity/phototoxicity

Interactions:
Food-Drug:
- Tablets may be taken with or without food

- Drink fluids liberally

Drug-Drug:
(In bold: Co-administration is not recommended or C/I):

- Products containing magnesium, aluminium, iron or zinc including antacids, sucralfate, multivitamins tablets: moxifloxacin absorption decreased, tablets to be taken 4 hours before or 8 hours after these products
- Warfarin: enhanced anticoagulation, monitor INR, prothrombin time
- **Class 1A (including quinidine, procainamide) and Class III (including amiodarone, sotalol) antiarrhythmics: enhanced proarrhythmic effect**
- Other drugs that prolong the QT interval including erythromycin, cisapride, antipsychotics, tricyclic antidepressants: exercise caution
- NSAIDs: CNS stimulation, convulsions
- Bedaquiline: Avoid use with fluoroquinolones as additive QT interval prolongation may occur

Practical Tips:

- A preferred drug in MDR-TB and XDR-TB
- Can be given IV (same dose oral)
- Limited evidence that strains resistant to ofloxacin may be susceptible to moxifloxacin
- Discontinue if pain or inflammation in a tendon occurs, or if skin rash, jaundice, other signs of hypersensitivity occur (drug can be replaced with another)
- **Caution** in patients with known QT prolongation, hypokalaemia, other drugs that prolong the QT interval, other proarrythmic conditions
- **Caution** in patients with CNS disease or at risk of seizures
- **Caution** in hepatic insufficiency - risk of QT prolongation
- **Avoid** rapid or bolus IV administration, give as slow infusion over 60 minutes. Do not mix with other medications in IV bag or line

Storage:
Oral and IV: Room temperature, cool, dry dark place

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- Multivalent cation-containing products including:
  - antacids containing magnesium/aluminium
  - sucralfate
  - metal cations e.g. iron
  - multivitamins with zinc
- Oral hypoglycaemics, insulin: potentiation of hypoglycaemic effect
- **Class 1A (quinidine, procainamide) and Class III (amiodarone, sotalol) antiarrhythmics: risk of prolongation of QT interval**
- Cimetidine: increased quinolone levels
- Warfarin, theophylline, cyclosporin levels may increase: monitor
- NSAIDs: increased CNS stimulation, seizures
- Probenecid: affects tubular secretion and may increase ofloxacin levels
- Bedaquiline: Avoid use with fluoroquinolones as additive QT interval prolongation may occur

Practical Tips:

- Use recommended in patients< 8 years old and adults who may not tolerate moxifloxacin
- Cross-resistance with other quinolones
- Data suggest less activity and less favourable outcomes than with levofloxacin or moxifloxacin
- **Caution** if at risk for seizures, hepatic/renal impairment
- **Caution** in pregnancy (arthropathy in animal studies)
- **Avoid** in patients with known QT prolongation, untreated hypokalaemia
- Delamanid: Avoid use with fluoroquinolones as additive QT interval prolongation may occur

Storage:

Room temperature, cool dry dark place

OFLOXACIN, Ofx

Drug Properties:
Bactericidal

Doses:
Adult:
- 400mg bd, oral
- If creatinine clearance <30 ml/min or for patients receiving haemodialysis: 600 – 800 mg per dose three times per week (not daily), oral

Paediatric:
- 15-20 mg/kg od, oral (safety not established)
- Maximum dose: 800mg daily

Formulation:
Tablets: 200 mg, 400 mg
Infusion: 200mg/100ml

Contraindications:
Hypersensitivity to ofloxacin or other quinolones

Side-effects:
- Generally well tolerated
- **Most common**: nausea, insomnia, headache, dizziness, diarrhoea, vomiting, rash, pruritus, external genital pruritus in women, vaginitis, dysgeusia
- **Other**: CNS effects including seizures, toxic psychosis, raised intracranial pressure, malaise, insomnia, restlessness, dizziness, tendinitis and tendon rupture, arthralgia (can usually be treated symptomatically), increased LFTs, photosensitivity, hypersensitivity reactions, QT_c prolongation, peripheral neuropathy, Clostridium difficile diarrhoea

Interactions:
Food-Drug:
- Take with or without meals
- Drink plenty of fluids
- Avoid concurrent intake of multivitamins and/or dairy products

PARA-AMINOSALICYLIC ACID, PAS

Drug properties:

Bacteriostatic, valuable in preventing resistance to other drugs

Doses:

Adult:

- 150mg/kg/day
- Usual dose range 8-12g/day in 2-3 divided doses, oral
- Creatinine clearance <30mL/min or patients receiving haemodialysis: 4g/dose bd

Paediatric:

- 200-300mg/kg/day 2-4 times per day, oral
- Maximum dose: 12g/day

Formulation:

Delayed-release granules: 4g/packet

Contraindications:

Severe renal disease

Side-effects:

- Side effects are **common,** this is generally a poorly tolerated drug
- GIT effects: anorexia, diarrhoea, nausea, vomiting, abdominal pain
- Hypothyroidism, goitre
- Hepatitis: usually in first 3 months, may be accompanied by rash, fever, GIT disturbance, lymphadenopathy, eosinophilia, leucocytosis
- Hypersensitivity reaction: includes rashes, fever, leukopenia, agranulocytosis, thrombocytopenia, Coomb positive haemolytic anaemia, jaundice, hepatitis, pericarditis, hypoglycaemia, optic neuritis, encephalopathy, hyper eosinophilia syndrome, vasculitis, reduced prothrombin
- Malabsorption syndrome
- Prolonged prothrombin time
- Crystalluria

Interactions:

Food-Drug:

Take with food without chewing by sprinkling on an acidic food (e.g. apple sauce or yogurt) or swirl with juice (e.g. apple, orange, tomato, grape).

Drug-Drug:

- Isoniazid acetylation reduced
- Rifampicin absorption may be reduced
- Vitamin B12 absorption decreased
- Digoxin levels may be reduced

Practical Tips:

- Currently only recommended for Extensively Drug Resistant (XDR) TB and pre-XDR TB
- **Monitoring:** thyroid function
  - Current NDoH Guidelines**:**
    - monitor monthly for signs of hypothyroidism, do thyroid stimulating hormone 6 monthly in adults and 2 monthly in children
- If on treatment for more than 1month consider vitamin B supplementation
- Use with **caution** in hepatic disease
- Shells of the granules may be seen in stool
- Do not use if packets are swollen or granules have lost their tan colour and are purple or dark brown
- Discontinue if signs of hypersensitivity develop
- Poor CNS penetration

Storage:

Store below 15^0C, keep in a refrigerator or freezer

TERIZIDONE, Trd

Drug Properties:
Bacteriostatic

Doses:
See page 81-82 for NDoH weight band dosing tables

Adult:
- 15-20mg/kg, oral, can be given in 2 divided doses
- Usual dose range: 500 -750mg daily (can go up to 1g if weight >70 kg)
- Extend dose interval in renal failure

Paediatric:
- (Off-label)
- 10-20mg/kg od, oral
- Maximum dose: 1g

Formulation:
Capsules: 250mg

Contraindications:
Avoid if history of alcoholism, epilepsy, mental illness including depression, psychosis, severe anxiety; porphyria, severe renal impairment

Side-effects:
- CNS effects (dose-related): dizziness, slurred speech, convulsions, headache, vertigo, drowsiness, tremor, paraesthesia, coma, insomnia, confusion, depression, anxiety suicidality, psychosis, confusion, aggression, irritability, paranoia, peripheral neuropathy
- Changes in liver function tests, hepatitis
- Hypersensitivity, allergic dermatitis
- Photosensitivity
- Megaloblastic anaemia
- Heart failure at high doses

Interactions:
Food-Drug:
Administer with meals if GIT upset occurs

Drug-Drug:

- Ethionamide: potentiates neurotoxic side effects
- Alcohol: increased risk of seizures
- Isoniazid: increased CNS effects, may need dose adjustment

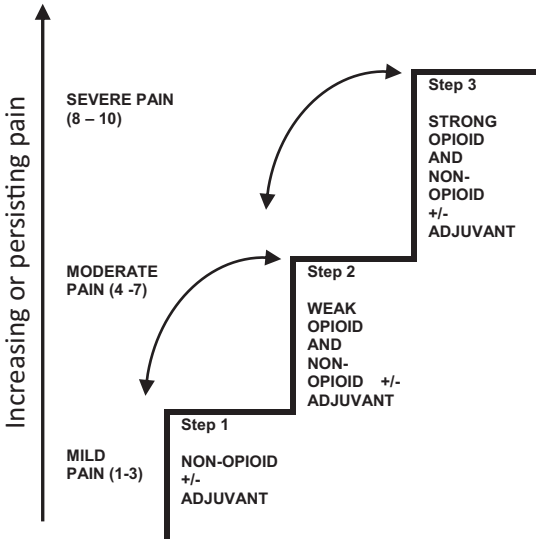
Practical Tips:

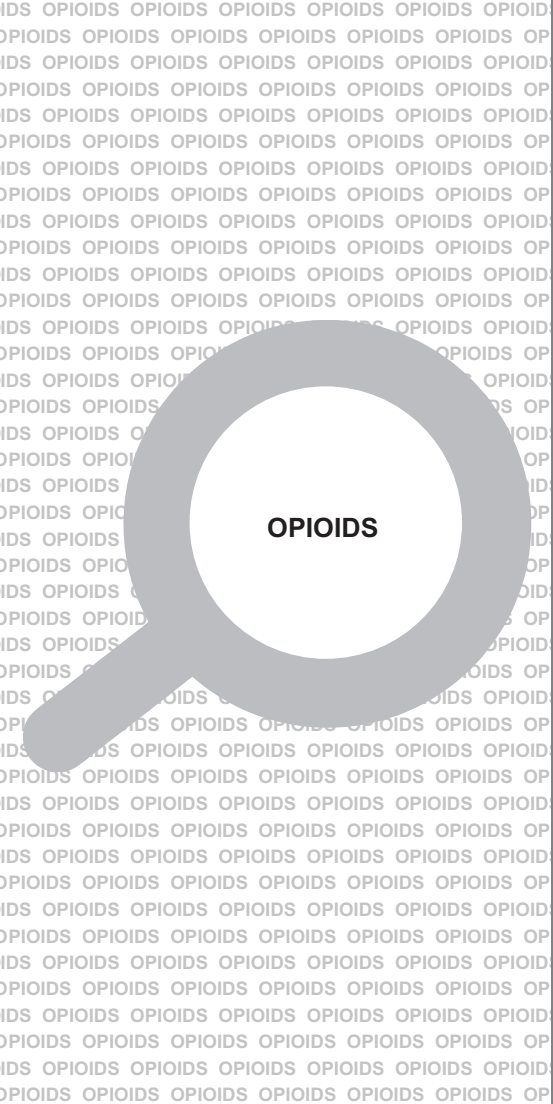
- Terizidone is a dimer of cycloserine
- Both are valuable as they do not have cross-resistance with other active TB drugs
- Pyridoxine 150mg should be given together with terizidone to prevent neurological side effects. May be increased to 300 mg/day when adverse effects are experienced.
- **Caution** in renal failure
- Side effects more common at high doses, with renal failure and with alcohol or drug dependence
- **Monitoring**: CNS effects - reduce dose or discontinue if CNS toxicity occurs
- Advise patients / family members to report depression or personality changes immediately
- Monitor closely if used in psychiatric patients
- **Avoid** in patients with uncontrolled seizures. However, if no option, it may be given and the treatment for seizures adjusted to control them

Storage:
Room temperature, in airtight container


ANALGESIA

THE WHO PAIN LADDER:




OPIOIDS

TILIDINE
Weak Opioid

Use:
- Severe pain
- Post procedural analgesia

Doses:
Adult:
- 50mg 3-4 times daily, oral
- Higher initial doses may be used for severe pain

Paediatric: see package insert for dosing table
- 1mg/kg/dose qid, oral (1 drop per 2.5kg)
- 1mg/kg/dose should not be exceeded

Formulation:
Capsules: 50mg
Drops: 100mg/ml

Contraindications:
Head injuries or raised intracranial pressure, asthma, respiratory depression, cardiac failure

Side-effects:
- Dry mouth, sweating, flushing, constipation
- Hypersensitivity
- CNS effects: dizziness, confusion, drowsiness
- Bradycardia, palpitations
- Over dosage in children may cause convulsions

Interactions:
Food-Drug:
Take with or without food

Drug-Drug:
- Do not use with or within14 days after use of monoamine oxidase inhibitors
- CNS depressants: effects of tilidine enhanced

Practical Tips:

- Drops are used undiluted perilingually or sublingually; may be taken with sugar
- 20 drops = 0.5ml = 50mg
- 1 drop = 2.5mg
- **Caution** in infants less than 6 months

Storage:

Room temperature, cool, dry and dark place

CODEINE PHOSPHATE

Weak Opioid

Use:

- Mild to moderate pain
- Marked diarrhoea
- Cough suppressant

Doses:

Adult:

- **Analgesia:** 15-60mg 4-6 hourly as required, oral
- **Antitussive:** 10-20mg 4 - 6hourly, oral
- **Antidiarrheal:** 30mg up to 4 times per day, oral
- **Renal impairment:**
  - GFR 10-50mL/min: 75% of dose
  - GFR <1mL/min: 50% of dose
- Lower doses required in elderly

Paediatric:

Weight range (kg)	Dosage
Analgesia	
Neonate	**Oral/rectal/SC/IM**: 0.5 -1mg/kg/dose every 4-6 hours
1 month - 12 years	**Oral/rectal/SC/IM**: 0.5-1mg/kg/dose every 4-6hours Maximum 240mg daily
12 - 18years	**Oral/rectal/SC/IM**: 30-60mg every 4-6 hours Maximum 240mg daily
Cough suppressant in form of pholcodine linctus/syrup	
6 – 12 years	2.5mg 3-4 times daily
12 – 18 years	5-10mg 3-4 times daily

- See SAMF for dose adjustments in renal impairment

Formulation:

Tablets: 30mg
Oral solution: 25mg/5ml

Contraindications:
Hypersensitivity to codeine sulphate, respiratory depression in the absence of resuscitative equipment, acute or severe asthma or hypercarbia, paralytic ileus, head injury

Side-effects:
- Similar to other opioids, but produces less sedation, euphoria and addiction
- **Most common**: dizziness, excitation, drowsiness, light headedness, sedation, shortness of breath, nausea, vomiting, sweating, constipation, respiratory depression
- Hypotension, elevation of intracranial pressure, slowed gastric emptying and biliary spasm

Interactions:
Food-Drug:
Can be taken with or without food

Drug-Drug:
- As for morphine

Practical Tips:
- **Caution** in elderly or debilitated patients, severe hepatic / renal impairment, hypothyroidism, Addison's disease, prostatic hypertrophy / urethral stricture, CNS depression, acute alcoholism, delirium tremens
- All opioids may aggravate convulsions in patients with convulsive disorders
- Pharmacologically, codeine is no different from morphine except that it is weaker and less consistently effective. This has led the WHO to recommend that it is better replaced by low doses of morphine.
- 5-34% of the population have an enzyme deficiency that prevents activation of codeine to active metabolite, and so it is ineffective in this group
- Must not be given IV

Storage:
Room temperature, cool, dry and dark place

TRAMADOL
Weak Opioid

Use:
- Moderate to severe pain

Doses:
Adult:
- **Oral:** 50-100mg 4-6 hourly; maximum 400mg/day
- **Rectal:** 100mg up to 4 times daily
- **IV:** over 2-3 minutes or by infusion, 50-100mg 4-6 hourly; maximum 400mg/day
- Hepatic or renal impairment: increase dose interval to 12 hourly
- Elderly: reduce dose or extend dosing interval

Paediatric:
- Not licensed for use in children less than 12 years

Formulation:
Capsules: 50mg
Tablets: 50mg
Slow release tablets: 100mg, 150mg, 200mg
Inject: 50mg/ml, 100mg/2ml
Suppositories: 100mg

Contraindications:
Respiratory depression

Side-effects:
- Similar to morphine but less potential for abuse, respiratory depression, constipation

Interactions:
Food-Drug:
Take with or without food

Drug-Drug:
- Carbamazepine: enhances metabolism of tramadol therefore may require increased tramadol dose
- CNS depressants: potentiates CNS effects
- Monoamine oxidase inhibitors: do not use with or within 14 days after use of MAOIs

Practical Tips:

- By mouth about 1/10 as potent as morphine
- Onset of action after oral dose is 30 to 60 minutes. Duration of action is 4-9 hours.
- **Caution** in hepatic and renal impairment (may require decreased dose and increased dosing interval in liver and renal impairment, see doses)

Storage:
Room temperature, cool, dry and dark place

MORPHINE
Strong Opioid

Use:

- Severe Pain
- Dyspnoea
- Cough suppressant as Morphine linctus

Doses:

Adult:

- **Oral:** Initially 5-10mg every 4 hours adjusted to response
- **IV injection**: initially 2.5mg every 4 hours adjusted to response
- **IV infusion**: 20ug/kg/hour (maximum 20mg/24hours) titrated upwards against pain
- **Controlled release tablets, long acting ORAL morphine (MST):** After pain is controlled with 4 hourly short acting morphine, it can be converted to sustained release long acting morphine (MST) that is given 12 hourly for greater convenience. Determine the dose of MST as follows: add up all the doses given in 24 hours and divide by 2

Paediatric:

Age	Dosage
Neonate	**Oral**: 0.05mg/kg 4 hourly **IV injection**: Initially 0.025mg/kg - 0.1mg/kg every 6 hours adjusted to response **IV infusion**: 5ug/kg/hour adjusted according to response
1 – 3 months	**Oral**: 0.05mg/kg 4 hourly **IV injection**: 0.025mg/kg/dose 6 hourly adjusted to response **IV infusion**: 5ug/kg/hour adjusted according to response
3 -6 months	**Oral**: 0.1mg/kg/dose 4 hourly **IV injection**: 0.05mg/kg/dose 6 hourly adjusted to response **IV infusion**: 5ug/kg/hour adjusted according to response
6 - 12 months	**Oral:** Initially 0.1mg/kg/dose every 4 hours adjusted to response

	IV injection: 0.05-0.1mg/kg/dose 6 hourly adjusted according to response **IV infusion**: 10ug/kg/hour adjusted according to response
>12 months	**Oral:** 0.2 - 0.4mg/kg/dose 4 hourly **IV injection:** 0.1 – 0.2mg/kg/dose 4 hourly **IV infusion**: 10 – 50ug/kg/hour adjusted according to response
12 - 18years	**Oral:** Initially 5 - 10mg every 4 hours adjusted to response **IV injection**: initially 2.5mg every 4 hours adjusted to response **IV infusion**: 20ugkg/hour (max 20mg/24hours) adjusted according to response

Formulation:
Inject: 10mg/ml, 15mg/ml
Controlled release tablets: 10mg, 30mg, 60mg, 100mg
Oral Solution: 5mg/5ml, 10mg/5ml, 20mg/5ml, 100mg/5ml

Contraindications:
Known hypersensitivity to morphine, respiratory depression in the absence of resuscitative equipment, acute or severe asthma or hypercarbia, paralytic ileus, head injury/other intracranial lesions

Side-effects:
- Sedation (resolves within 2-3 days), nausea and vomiting, sweating, dizziness, light headedness, constipation, pruritus, urinary retention (uncommon), euphoria, dysphoria, miosis
- Respiratory depression (may occur at therapeutic doses if pre-existing pulmonary disease), circulatory depression
- Orthostatic hypotension, syncope, hypotensive effect increased if compromised ability to maintain blood pressure
- Tolerance and dependence may occur in prolonged use (adults)
- Allergic reactions
- Slowed gastric emptying and biliary spasm (increased smooth muscle tone and reduced peristalsis)
- Elevation of intracranial pressure: may be markedly exaggerated in the presence of head injury, other intracranial lesions

Interactions:

Food-Drug:

Take with or without food

Drug-Drug:

- CNS depressants including alcohol, sedatives, antipsychotics, antidepressants, antihistamines: depressant effects potentiated
- Antidiarrheal: increased constipation
- Anticholinergics: constipation, urinary retention, CNS effects potentiated
- Cimetidine: decreased elimination of morphine, increased toxicity
- Metoclopramide: antagonism of metoclopramide effects
- Muscle relaxants: neuromuscular blocking action of skeletal muscle relaxants enhanced, increased respiratory depression
- Monoamine oxidase inhibitors: generally regarded as safe but monitor for adverse response

Practical Tips:

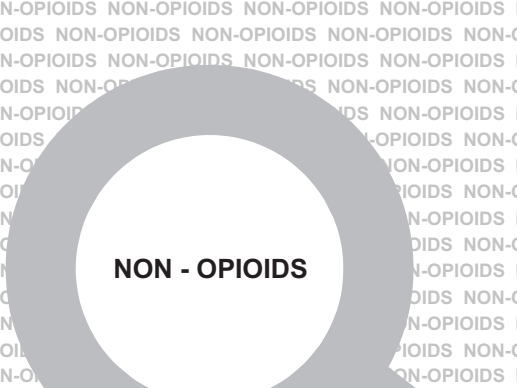
- Use with **caution** and in reduced dosages in patients with severe renal or hepatic impairment, Addison's disease, hypothyroidism, prostatic hypertrophy/urethral stricture, the elderly, CNS depression, toxic psychosis, acute alcoholism, delirium tremens, hypotension, decreased pulmonary reserve
- All opioids may aggravate convulsions in patients with convulsive disorders
- There are 2 ways to increase morphine as required for pain:
  1. Increase the regular dose by 30 – 50% of the previous dose if pain is not controlled.
  2. Add up all breakthrough doses given in 24 hours and 4 hourly regular doses then divide this by 6. Remember also to increase the breakthrough dose as the regular dose is being increased
     - Breakthrough dose is 50-100% of regular dose. It should not be given within 30 minutes of regular dose
- Procedural pain: needs to be given 60 minutes before the procedure (takes 30 – 90 minutes to reach peak levels)

Practical Tips Continued:

- Dyspnoea doses of morphine are 30-50% of the regular dose used for pain control
- Always wean morphine (decrease by 1/3 every 3 days) if it has been given for > 10 - 14 days to prevent withdrawal symptoms
- Tolerance develops in a few days to most side effects except constipation. Constipation can be prevented with the prophylactic use of laxatives (lactulose, senna)
- Haloperidol 1 - 4mg/day po in 2 - 3 divided doses or Metoclopramide 0.15 – 0.3mg/kg qid PO/IV/SC/PR are good drug choices for opioid associated nausea and vomiting
- Patients with urinary retention may need to be catheterized
- Pruritus is **not** related to histamine release and is best treated with ultra-low dose naloxone (0.25ug/kg/hr) or opioid switch
- Prolonged use in pregnancy may cause dependence and withdrawal in the neonate

Storage:

Room temperature, cool, dry and dark place


NON - OPIOIDS

DICLOFENAC SODIUM

Use:

- Mild to moderate pain and inflammation, particularly musculoskeletal disorders

Doses:

Adult:

- **Oral:** 25 -50mg 3 times daily, the lower dosage range (75-100mg/day) is indicated for long term therapy but patients with arthritic disorders may need up to 150mg/day
- **Rectal:** usually 100mg at night
- Maximum total combined dose (oral and rectal) should not exceed 150mg/day

Paediatric:

Age	Dosage
>2 years	**Oral/Rectal**: Initial dose of 0.3mg/kg 3 times daily increasing if necessary to a maximum of 1 - 3mg/kg 3 times daily (maximum 50mg single dose)

Formulation:

Tablets: 25mg, 50mg, 75mg
Tablets, sustained release: 75mg, 100mg
Dispersible tablets: 50mg
Capsules (SR): 100mg
Drops (oral): 15mg/ml
Inject: 75mg/3ml
Suppositories: 12.5mg, 25mg, 100mg
Powder for oral solution: 50mg

Contraindications:

Hypersensitivity to aspirin or NSAIDs, active peptic ulceration, duct dependent congenital cardiac disease (will cause closure of ductus arteriosus)

Side-effects:

- Gastritis, hypersensitivity, renal toxicity, hepatic dysfunction, inhibition of platelet aggregation

Interactions:

Food-Drug:

Administer with food (proton pump inhibitor can be prescribed in prolonged use)

Drug-Drug:

- Oral anticoagulants: increased risk of bleeding
- Steroids: enhanced toxicity of both agents
- Lithium: increased lithium levels
- Methotrexate levels increased: monitor for toxicity
- Digoxin: altered response to digoxin
- Antihypertensives, diuretics, angina and cardiac failure therapy: effect of these drugs attenuated
- Probenecid: NSAID excretion inhibited

Practical Tips:

- Not licensed for children <1 year old
- **Caution** in renal and hepatic impairment, compromised cardiac function, hypertension, bleeding disorders, elderly
- Suppositories not licensed for children <6 years old except in juvenile idiopathic arthritis
- Smallest dose that can be given rectally is 3.125mg by cutting a 12.5mg suppository into quarter
- Proton pump inhibitor or H_2 – receptor antagonist may be given with diclofenac for gastric protection

Storage:

Room temperature, cool, dry and dark place

IBUPROFEN

Use:

- Mild to moderate pain
- Pyrexia
- Adjuvant for musculoskeletal pain

Doses:

Adult:

- 600mg - 1200mg/day in divided doses

Paediatric:

Age	Dosage
Neonate	5mg/kg/dose every 12 hours
1 – 3 months	5mg/kg 3-4 times daily
3 – 6 months	50mg 3 times daily Severe conditions: up to 30mg/kg daily in 3-4 divided doses
6 months – 1 year	50mg 3 times daily Severe conditions: up to 30mg/kg daily in 3-4 divided doses
1 – 4 years	100mg 3 times daily Severe conditions: up to 30mg/kg daily in 3-4 divided doses Maximum daily dose: 2.4g
4 – 7 years	150mg 3 times daily Severe conditions: up to 30mg/kg daily in 3-4 divided doses Maximum daily dose: 2.4g
7 – 10 years	200mg 3 times daily Severe conditions: up to 30mg/kg daily in 3-4 divided doses Maximum daily dose: 2.4g
10 – 12 years	300mg 3 times daily Severe conditions: up to 30mg/kg daily in 3-4 divided doses Maximum daily dose: 2.4g
12 – 18 years	300-400mg 3-4 times daily Severe conditions: 2.4g/day

Rheumatic diseases / Idiopathic Juvenile arthritis

40-60mg/kg in 4 – 6 divided doses. Maximum of 2.4g/day

Formulation:
Oral solution: 100mg/5ml
Tablets: 200mg, 400mg, 600mg
Capsules: 200mg
Long-acting tablets: 800mg
Inject: 10mg/2ml

Contraindications:
Hypersensitivity to NSAIDs, duct dependent congenital cardiac disease (will cause closure of ductus arteriosus), active peptic ulcer disease

Side-effects:
- **Most common**: abnormal renal function, anaemia, dizziness, oedema, elevated liver enzymes, fluid retention, gastrointestinal effects, headaches, increased bleeding time, nervousness, pruritus, rashes and tinnitus
- GIT effects include gastritis, bleeding, ulceration, perforation
- Hypersensitivity
- Hepatic dysfunction: abnormal liver functions may be transient or may progress, severe hepatic reactions rare
- Increased risk of serious cardiovascular thrombotic events, myocardial infarction, stroke, new onset or worsening of existing hypertension, congestive cardiac failure
- Rashes including maculopapular, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis
- Aseptic meningitis rare

Interactions:
Food-Drug:
Should be taken with or after food

Drug-Drug:
- Oral anticoagulants: increased gastro-intestinal bleeding
- Methotrexate toxicity may be increased
- Lithium levels increased
- Diuretics: monitor for renal failure, diuretic efficacy
- ACE-inhibitors: effect may be diminished
- Aspirin: increased adverse effects

Practical Tips:

- Gastric protection should be taken when using NSAIDs for a prolonged period (proton pump inhibitor can be used)
- **Caution** with asthma, atopy, nasal polyps, bleeding disorder, low platelets, history of peptic ulcer disease, atherosclerosis, angina, cardiac, renal or hepatic dysfunction, geriatrics
- **Avoid** in late pregnancy: may cause premature closure of the ductus arteriosus

Storage:

Room temperature, cool, dry and dark place

PARACETAMOL

Use:

- Mild to moderate pain
- Pyrexia

Doses:

Adult:

- **Oral**: 0.5–1.0g 4-6 hourly as required
- **Rectal**: 1g 4 - 6 hourly as necessary
- **IV**: as infusion over 15 minutes, 1g every 4 - 6 hours
- Maximum: 4g in 24 hours
- Adjust dose in renal and liver impairment: decrease dose and increase dosing interval to 8hourly

Paediatric:

- Adjust dose in renal and liver impairment

Age	Dosage
<32weeks gestation	**Oral**: 20mg/kg as a single dose then 10 - 15mg/kg every 8 - 12 hours as necessary **Rectal**: 20mg/kg as single dose then 15mg/kg every 12 hours. Maximum (oral and rectal): 30mg/kg/day in divided doses
>32 weeks gestation	**Oral**: 20mg/kg as a single dose then 10 – 15mg/kg every 6 - 8 hours as necessary **Rectal**: 30mg/kg as a single dose then 20mg/kg every 8 hours as necessary Maximum (oral and rectal): 60mg/kg/day in divided doses **IV**: (as infusion over 15 minutes) 7.5mg/kg every 8 hours (maximum 25mg/kg/day)
1 - 3 months	**Oral**: 20 -30mg/kg as a single dose then 15-20 mg/kg every 4-6 hours as necessary **Rectal**: 30mg/kg as a single dose, then 15-20mg/kg every 4-6hours; Maximum (oral and rectal): 90mg/kg/day in divided doses **IV**: (as infusion over 15 minutes) 10mg/kg every 4-6 hours (maximum 30mg/kg/day)
3 months – 6 years	**Oral**: 20 -30mg/kg as a single dose then 15-20 mg/kg every 4-6 hours as necessary

	Rectal: 30mg/kg as a single dose (maximum 1g) then 15-20 mg/kg every 4-6 hours as necessary Maximum (oral and rectal): 90mg/kg/day in divided doses **IV**: (as infusion over 15 minutes) <50kg: 15mg/kg every 4-6 hours (maximum 60mg/kg/day)
6 -12 years	**Oral**: 20-30mg/kg (maximum 1g) as a single dose then 15-20mg/kg every 4-6 hours as necessary **Rectal**: 30mg/kg as a single dose (maximum 1g) then 15-20mg/kg every 4 -6 hours as necessary Maximum (oral and rectal): 90mg/kg/day or 4g/day in divided doses **IV**: (as infusion over 15 minutes) <50kg: 15mg/kg every 4-6 hours (maximum 60mg/kg/day) >50kg: 1g every 4-6 hours (maximum 4g/day)
> 12 years	**Oral**: 1g every 4-6 hours as necessary **Rectal**: 1g every 4-6 hours as necessary Maximum (oral and rectal): 4g/day in divided doses **IV**: (as infusion over 15 minutes) <50kg: 15mg/kg every 4-6 hours (maximum 60mg/kg/day) >50kg: 1g every 4-6hours (maximum 4g/day)

Formulation:
Infant drops: 60mg/0.6ml
Oral Solution: 120mg/5ml
Tablets: 500mg
Effervescent tablets: 500mg
Capsules: 500mg
Extended-relief caplets: 650mg
Suppositories: 125mg, 250mg
IV infusion: 500mg/50ml, 1g/100ml

Contraindications:
Severe hepatic or renal disease

Side-effects:
Hepatotoxic in overdose or prolonged high doses

Interactions:
Food-Drug:
Take with or without food

Drug-Drug:
Low potential to cause drug interactions

Practical Tips:

- Onset of action 15-30 minutes orally, 5-10 minutes IV (analgesia), 30 minutes IV (antipyretic)
- Duration of action 4-6hours orally and IV
- Oral bioavailability 60-90%. Rectal bioavailability about 2/3 of oral

Storage:
Room temperature, cool, dry and dark place


DRUGS USED IN
PROPHYLAXIS

COTRIMOXAZOLE, CTX

Doses:

Adult:

- Prophylaxis of *Pneumocystis jirovecii* pneumonia, toxoplasmosis, *Isospora belli* diarrhoea in HIV-infected patients: 160mg/800mg od, oral
- If creatinine clearance 10-50ml/min: 75% of dose
- If creatinine clearance <10ml/min: 50% of dose

Paediatric:

- Prophylaxis in HIV infection:

Weight range (kg)	Dose
3 - 4.9	2.5ml od
5 - 13.9	5ml od
14 - 29.9	10ml od **OR** 1 tab od
≥30	2 tabs od

Formulation:

Oral Solution: 40/200mg/5ml
Tablets: 80/400mg, 160/800mg
IV infusion: 80/400mg/5ml

Contraindications:

Known hypersensitivity to trimethoprim or sulphonamides, infants <2 months, porphyria, G6PD deficiency

Side-effects:

- **Most common**: GIT effects, allergic skin reactions
- Risk of sulphonamide hypersensitivity reaction
- Rashes: erythematous, maculopapular, morbilliform and pruritic rashes most common, usually occurs 7-14 days after starting treatment. Hypersensitivity reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis less common
- GIT effects: nausea, vomiting, abdominal pain, diarrhoea, anorexia, glossitis, Clostridium difficile diarrhoea, pancreatitis
- Haematological effects include:

- aplastic anaemia, agranulocytosis, leukopenia, megaloblastic anaemia, thrombocytopenia (thrombocytopenia immune mediated, usually resolves 1 week after stopping CTX)
- methaemoglobinaemia and haemolysis in G6PD deficiency

- Neurological: includes ataxia, headache, aseptic meningitis, vertigo, tinnitus, seizures
- Increased transaminases, occasionally hepatitis (may be cholestasis), fulminant hepatic necrosis rare
- Hyperkalaemia (reversible), hyponatraemia, hypoglycaemia in non-diabetic patients
- Interstitial nephritis, renal failure, crystalluria with azotaemia, urolithiasis, oliguria
- Fever, myalgia, depression, hallucinations

Interactions:

Food-Drug:

- Take with or without food
- Ensure high fluid intake to prevent crystalluria

Drug-Drug:

- Increased levels of:
  - Phenytoin
  - Digoxin
- Diuretics, primarily thiazides: increased risk of thrombocytopenia
- Oral contraceptives: effect may be reduced, additional contraception advised
- Rifampicin: CTX levels reduced
- Warfarin and sulfonylureas: effect potentiated
- AZT: increased haematological toxicity
- Phenytoin, phenobarbital and pyrimethamine: increased risk of megaloblastic anaemia
- Cyclosporin levels reduced, nephrotoxicity reported
- Tricyclic antidepressant effect decreased
- ACE inhibitors: hyperkalaemia

Practical Tips:

- **Caution** in folic acid deficiency, renal or hepatic impairment, serious haematological disorders, thyroid dysfunction, severe allergies

Practical Tips Continued:

- Prophylaxis in HIV protects against *Pneumocystis* pneumonia, toxoplasmosis, isosporiasis, bacterial pneumonia
- Prophylaxis may be continued if mild rash, or may be interrupted and then reintroduced. Treatment should not be continued if fever, hepatitis or mucous membrane lesions.
- If hypersensitivity reaction occurs, use dapsone for prophylaxis but not for the treatment of *Pneumocystis* pneumonia
- Do not start cotrimoxazole and ART together as rash may occur with either:
  - if patient not on CTX already, it should ideally be started during the ART preparation phase
  - CTX initiation should never delay ART, can usually be deferred until ART is established
- Prescribe folate if folic acid deficiency occurs
- Those at risk of folate deficiency include the elderly, alcoholics, malnourished, debilitated patients
- Risk of teratogenicity with 1st trimester use and hyperbilirubinaemia/ kernicterus with 3rd trimester exposure but use for HIV prophylaxis recommended in pregnancy
- Monitor blood counts in prolonged therapy

Storage:

Room temperature, cool, dry and dark place

DAPSONE

Doses:

Adult:

- *Pneumocystis* pneumonia prophylaxis (alternative regimen): 100mg od, oral
- *Pneumocystis* pneumonia and toxoplasmosis prophylaxis: 50mg od, oral with pyrimethamine 50mg weekly, oral and folinic acid 15-25 mg weekly, oral

Paediatric:

- *Pneumocystis* pneumonia prophylaxis (alternative regimen): 2 mg/kg od or 4mg/kg/week, oral
- Maximum dose: 100mg od, oral

Formulation:

Tablets: 100mg

Contraindications:

Hypersensitivity to dapsone, severe anaemia, porphyria

Side-effects:

- Haematological effects:
  - haemolysis and methaemoglobinaemia - dose-related, rare with 100mg od unless G6PD deficiency
  - agranulocytosis, aplastic anaemia, neutropenia, leukopenia
- Rash, pruritus common
- Serious cutaneous reactions such as exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis less common but serious
- GIT effects: nausea, vomiting, anorexia
- Toxic hepatitis and cholestasis jaundice reported early in therapy. Hyperbilirubinemia occurs more often in G6PD deficient patients
- Peripheral neuropathy (predominantly motor loss)
- Sulfone syndrome: hypersensitivity reaction with fever, malaise, exfoliative dermatitis, hepatic necrosis, lymphadenopathy, anaemia with methaemoglobinaemia, occurring after 1-4 weeks
- Other: headache, psychosis, insomnia, nephrotic syndrome

Interactions:

Food-Drug:

Can be taken with meals to reduce GIT side effects

Drug-Drug:

- Rifampicin: dapsone levels reduced significantly
- Trimethoprim: levels of both drugs increased, monitor for methaemoglobinaemia
- Folic acid antagonists including pyrimethamine: increased marrow toxicity, monitor FBC
- Probenecid: increased dapsone levels

Practical Tips:

- Use dapsone in patients who have had a mild reaction to cotrimoxazole, should not be used after severe reactions, as there may be cross-reactivity
- Provides protection against *Pneumocystis* pneumonia and limited protection against toxoplasmosis
- **Caution** in G6PD deficiency (increased risk of haemolysis), severe cardio-pulmonary disease (haemolysis, methaemoglobinaemia may be poorly tolerated)
- **Monitor** FBC in long-term treatment; stop dapsone if a significant reduction in leucocytes, platelets or haemopoiesis occurs
- Can be used for *Pneumocystis* pneumonia prophylaxis in pregnant women, but consider risk of neonatal haemolysis and methaemoglobinaemia if used in 3rd trimester; haemolytic anaemia reported in nursing infants

Storage:

Store below 25^0 C

FLUCONAZOLE

Doses:

Adult:

- Cryptococcal meningitis:
- 1200mg stat when Cryptococcal Antigen test is positive and symptoms of cryptococcal meningitis are suspected before the patient is referred to hospital for LP.
- 800mg daily for 2 weeks in the induction phase,
- 400mg daily for 2 months in the consolidation phase
- 200mg daily for a minimum of 12 in total and discontinue when patient has had 2 CD4 counts >200 Cells/µl taken at least 6 months apart as secondary prophylaxis.

Paediatric:

- Cryptococcal meningitis secondary prophylaxis:
  - 6 – 10 mg/kg/day, oral

Dose adjustment required in renal impairment:

- GFR 10-50mL/min : reduce dose by up to 50%
- GFR <10mL/min: give 25% of dose

Formulation:

Capsules: 50mg, 150mg, 200mg
Tablets: 200mg
Infusion: 2mg/ml
Oral solution: 50mg/5ml, 200mg/5ml

Contraindications:

Hypersensitivity to the drug

Side-effects:

- **Most common in adults**: nausea, vomiting, abdominal pain, diarrhoea, headache, rash, mild transient increase in liver transaminases
- **Most common in children**: vomiting, abdominal pain, nausea, diarrhoea, elevated transaminases or alkaline phosphatase
- Reversible alopecia occurs occasionally
- Hepatic toxicity: serious cases rare, more common in patients with serious underlying medical conditions or if co-prescribed with NVP
- Angioedema, anaphylactic reactions rare

- Exfoliative skin disorders including Stevens-Johnson syndrome rare
- QT prolongation and torsade de pointes
- Others: thrombocytopenia, hypokalaemia

Interactions:

Food-Drug:

Can be taken with or without food

Drug-Drug:

(In bold: Co-administration is not recommended or C/I):

- Levels of the following drugs may be increased:
  - Cyclosporin, oral tacrolimus, sirolimus: monitor levels and renal function
  - **Cisapride, terfenadine when 400mg or more of fluconazole is used, astemizole, pimozide quinidine, erythromycin, voriconazole**: avoid, risk of cardiotoxicity
  - Oral midazolam, triazolam: monitor and consider decreasing dose
  - Nevirapine: monitor closely
  - Phenytoin , carbamazepine: monitor levels
  - Sulphonylureas: can cause hypoglycaemia
  - Theophylline: monitor levels
  - Warfarin: monitor INR, consider reduced dose
  - Zidovudine: monitor for adverse effects
  - Rifabutin: monitor carefully, reports of uveitis
  - Calcium channel blockers including nifedipine, isradipine, amlodipine, and felodipine: monitor for adverse events
  - NSAID's incl. celecoxib, ibuprofen: may need to adjust dose, monitor for adverse effects
  - Halofantrine levels increased
  - Vinca Alkaloids including vincristine and vinblastine: may lead to neurotoxicity
  - Alfentanil: may require dose adjustment
- Amitriptyline, nortriptyline: fluconazole increases effect, may need dose adjustment
- Cyclophosphamide: increased bilirubin, creatinine
- Rifampicin: fluconazole levels decreased
- HMG-CoA reductase inhibitors including fluvastatin, atorvastatin, simvastatin: myopathy, rhabdomyolysis, monitor CK and for symptoms

- Losartan: effect reduced, monitor BP
- Hydrochlorothiazide: increased fluconazole levels
- Bedaquiline: Avoid use with azole antifungals as additive QT interval prolongation may occur

Practical Tips:

- **Caution** in patients with renal and hepatic impairment, hypersensitivity to other azoles, porphyria
- **Caution** if structural heart disease, electrolyte abnormalities, concomitant medications that could be proarrythmic - risk of arrythmias
- Teratogenicity with continuous high doses in 1st trimester reported

Storage:

Room temperature, cool, dry, dark place

ISONIAZID, H, INH

Drug Properties:
Bactericidal, high potency

Doses:
See pages 60-65 for NDoH weight band dosing tables

Adult:
- TB Treatment:
  - 5 (4-6) mg/kg od, oral
  - Maximum dose: 300mg od, oral
  - Dose may be increased to overcome resistance
- TB prophylaxis:
  - 300 mg od, oral (duration based on result of tuberculin skin test – see NDOH guidelines)
  - Maximum dose: 300mg od, oral

Paediatric:
- TB Treatment: 10 (10-15) mg/kg od, oral
- Maximum dose: 300mg od, oral
- TB meningitis in children: 20mg/kg od (see page 65 for regimen)
- TB prophylaxis: 10 (10-15) mg/kg od, oral (max 300mg) for 6 months
  - Weight band dosage recommendations for INH preventive therapy in children

Body weight	Daily INH 100mg tablet
2 - 3.4kg	¼ tablet
3.5 - 6.9kg	½ tablet
7 - 9.9kg	1 tablet
10 - 14.9kg	1 ¼ tablets
15 - 19.9kg	1 ½ tablets
20 - 24.9kg	2 tablets
25 - 29.9kg	2 ½ tablets
≥30kg	3 tablets

Formulation:
Tablets: 100mg
Oral Solution: 50mg/5ml

Contraindications:
Severe hypersensitivity reaction to INH, acute hepatic disease

Side-effects:

- **Most common**: neurological effects, hepatotoxicity
- Hepatotoxicity: transient increase in transaminases in 10-20%, hepatitis in <2%
- Neurotoxicity: peripheral neuropathy, seizures, psychosis, optic neuritis, encephalopathy; neurotoxicity can be reversed with pyridoxine
- Haematological effects: agranulocytosis, haemolytic anaemia, sideroblastic anaemia, aplastic anaemia, thrombocytopenia, eosinophilia
- Drug-induced lupus erythematosus
- Rash: acne-form eruptions common, pellagra-type dermatitis in malnourished patients which responds to niacin
- GIT effects: nausea, vomiting, epigastric distress
- Other: hypersensitivity reactions, fever, interstitial nephritis rare, arthralgia

Interactions:

Food-Drug:

Absorption is better on an empty stomach. However, this is not always practical and patients may experience fewer GIT effects if taken after food.

Drug-Drug*: (inhibits cytochrome P450)*

- Anticonvulsant (e.g. phenytoin, carbamazepine, valproate) levels increased: anticonvulsant dosages may need reduction
- Warfarin levels increased: may need dose adjustment
- Rifampicin: increased hepatotoxicity but combination recommended
- Theophylline levels may increase
- Alcohol, corticosteroids: increased INH metabolism
- Disulfiram: increased psychosis
- Alcohol and paracetamol: increased hepatotoxicity
- Aluminium containing antacids: decreased INH absorption, should be given $\geq$2 hours apart

Practical Tips:

- Pyridoxine must be given with INH (for TB treatment and IPT) to prevent neurotoxicity
  - Adult dose: 10-50 mg/ day (may increase to 100mg/day for treatment)
  - Children: 12.5mg od
- **Caution** in patients with epilepsy, porphyria, peripheral neuropathy; if possible **monitor** transaminases in patients with pre-existing liver disease
- Safe during pregnancy and breastfeeding
- Advise patients that alcohol may increase risk of hepatotoxicity
- Appropriate proportion of INH tablet can crushed, dissolved in water or multi-vitamin syrup and given to children
- Good CNS penetration

Storage:
Room temperature, cool, dry and dark place


WHO
STAGING

- Extra-pulmonary tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extra-pulmonary cryptococcosis (including meningitis)
- Disseminated non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated mycosis (coccidiomycosis or histoplasmosis)
- Recurrent non-typhoidal salmonella bacteraemia
- Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV- associated tumours
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or symptomatic
- HIV-associated cardiomyopathy

ADULTS & ADOLESCENTS

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy

CLINICAL STAGE 2 - Mild Symptoms

- Moderate unexplained weight loss (< 10% of presumed or measured body weight)
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

CLINICAL STAGE 3 - Moderate Severity

- Severe unexplained weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for > 1 month
- Unexplained persistent fever (above 37.6^0C intermittent or constant, for longer than one month)
- Persistent oral candidiasis
- Oral hairy leucoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (<8g/ dl), neutropenia, (<0.5x 10^9 per litre) or chronic thrombocytopenia (<50x 10^9 per litre)

CLINICAL STAGE 4 - Severe

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (HSV) (orolabial, genital or anorectal) of more than 1 month's duration or visceral at any site
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

INFANTS & CHILDREN

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy

CLINICAL STAGE 2 - Mild Symptoms

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Angular cheilitis
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis

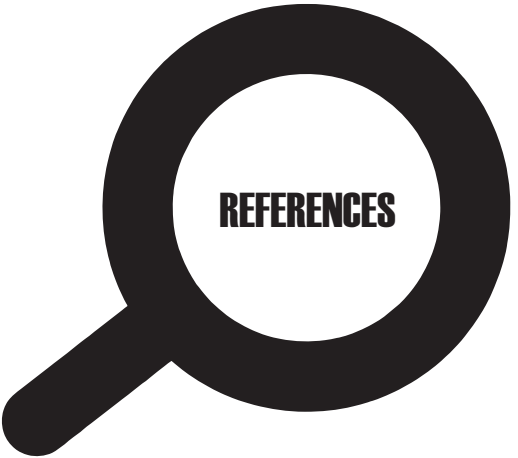
CLINICAL STAGE 3 - Moderate Severity

- Unexplained moderate malnutrition or wasting not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after 6-8 weeks of life)
- Oral hairy leucoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV associated lung disease including bronchiectasis
- Unexplained anaemia (<8g/ dl), neutropenia, (<0.5x 10^9 per litre) and or chronic thrombocytopenia (<50x 10^9 per litre)

CLINICAL STAGE 4 - Severe

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia

- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extra-pulmonary tuberculosis
- Kaposi's sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV-encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month.
- Extra-pulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B-cell non Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy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