KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

# Management of Drug Resistant Tuberculosis: The New Regimens

Dr S Chotoo
19/10/2023

# Introduction

- DR-TB needs no introduction; it remains a threat to global public health and is one of the leading infectious causes of death globally.
- In 2020, an estimated 10 million people developed TB and 1.5 million died from the disease.
- About 500 000 new cases of multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) are estimated to emerge each year; however, in the latest data (from 2019), only one in three cases were reported to have been treated.

# DR-TB BURDEN: SOUTH AFRICA AND GLOBAL CONTEXTS

| | Global | | South Africa | |
|---|---|---|---|---|
| Incidence | **465,000**<br>RR and MDR-TB estimated in 2019 | | **13,005**<br>RR and MDR-TB diagnosed in 2019 | |
| Treatment | **177,099**<br>RR and MDR-TB initiated during 2019 | **57 %**<br>**2017** RR and MDR-TB success rate | **9,040**<br>RR and MDR-TB initiated in 2019 (incl. 406 XDR-TB) | **65 %**<br>**2018** RR and MDR-TB success rate-**LTR & STR**<br>(n= **8,804**) |
| | **38 %**<br>of MDR-TB cases are initiated on treatment | | **70 %**<br>of DR-TB cases are initiated on treatment in 2019 | |
| XDR | **47 %**<br>Success rate of those started on second-line treatment in 2017 | | **58 %**<br>Success rate of those started on second-line treatment in 2018 (n=**554**) | |

South Africa has one of the **highest DR-TB burdens** in the world but **outperforms the global standard of treatment initiations** almost two-fold

# Definitions

- **Mono-Resistant Tuberculosis**
  Resistant to only one anti-TB drug, without resistance to other drugs.
- **Poly-drug Resistant Tuberculosis**
  Resistance to more than one anti-TB drug, other than both isoniazid and rifampicin.
- **Multidrug- Resistant Tuberculosis (MDR-TB)**
  Resistance to isoniazid and rifampicin with or without resistance to other first line anti-TB drugs.
- **Rifampicin-Resistant Tuberculosis (RR-TB)**
  Resistance to at least rifampicin, with or without resistance to other drugs. This category includes MDR-TB, rifampicin mono-resistant TB, pre-XDR TB and XDR TB.
- **Pre-XDR Tuberculosis**
  Resistance to rifampicin (and may also be resistant to isoniazid), and that is resistant to fluoroquinolones.
- **Extensively drug Resistant Tuberculosis (XDR-TB)**
  Resistance to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levo or moxi), and to at least one additional Group A drug (either bedaquiline or linezolid).

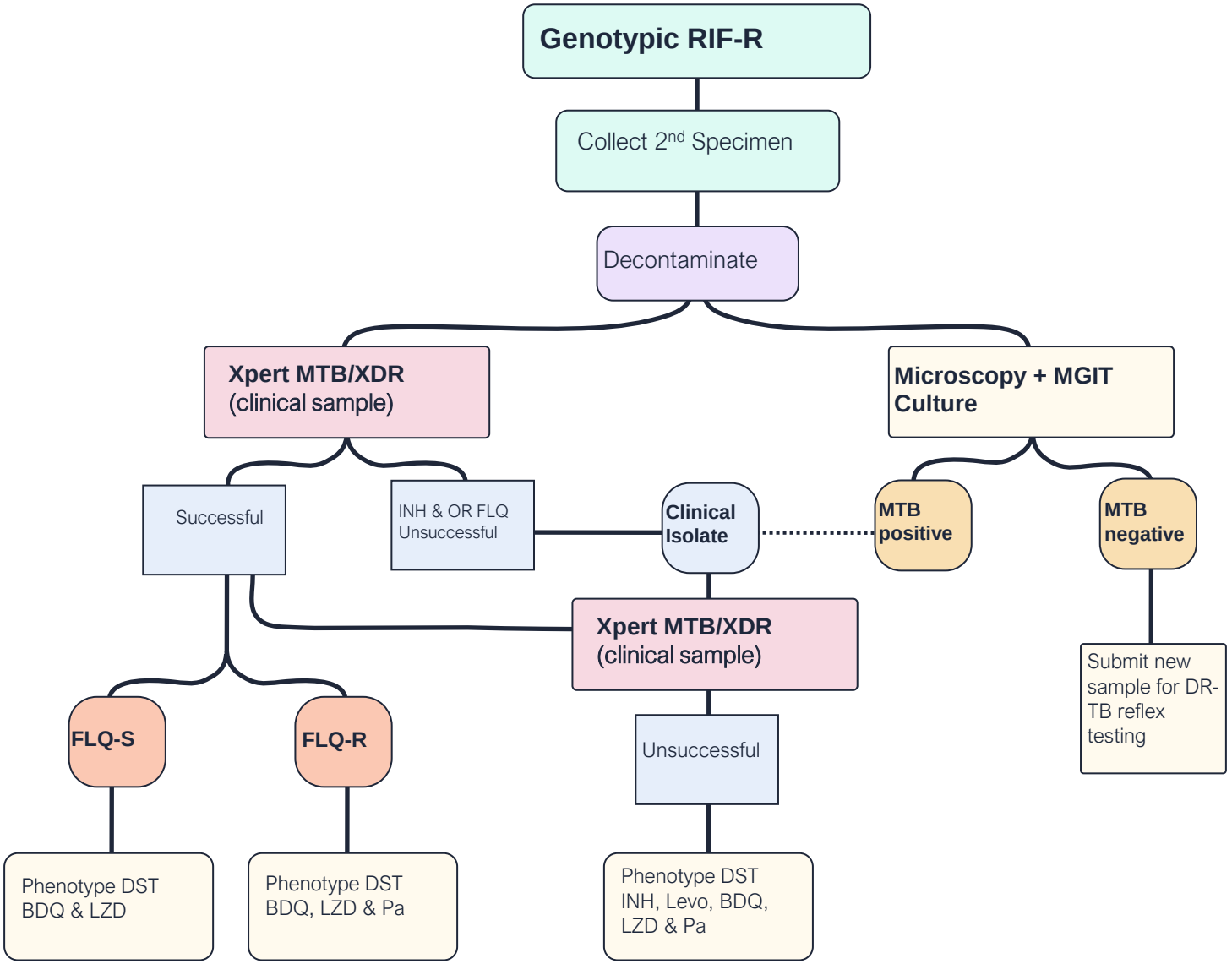
# Diagnosis

- Clinical presentation
  - Symptoms
  - Contact history
  - Previous TB treatment
- Physical examination
- Lab diagnosis
- Radiology
  - CXR
  - Other X-rays
  - Sonography
  - CT scan

# Diagnosis

- Baseline testing for all RR-TB patients is the DR-TB reflex which incudes:
  - smear
  - culture
  - *LPA first line and second line
  - Phenotypic DST based on LPA results
  - * Replaced by the Xpert XDR catridge

# DR-TB Reflex Algorithm




**RSA NDoH: Clinical Management of Rifampicin-Resistant Tuberculosis (2023)**

## MICROBIOLOGY

Specimen received: Sputum
Tests requested: GeneXpert Ultra @, TB cult @, GeneXpert XDR CI @
@ Test referred to another NHLS laboratory

**Real time PCR for M. tuberculosis (Xpert MTB/Rif Ultra):**

| | |
|---|---|
| PCR result | Mycobacterium tuberculosis complex detected |
| Rifampicin (molecular) | Sensitive |

This patient has TB susceptible to rifampicin. Please submit a second specimen for baseline microscopy, if this has not been done already.

**TB Culture:**

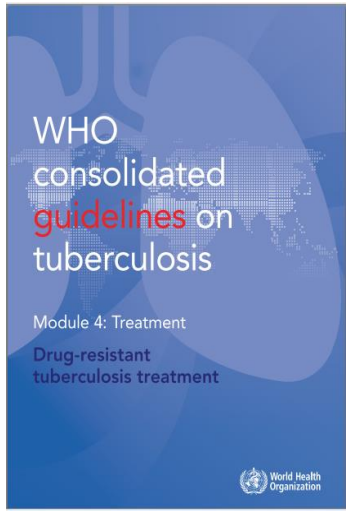
| | |
|---|---|
| Culture result | Culture positive. AFBs observed. |

**Molecular resistance testing for MTB: TB PCR DR-TB (Cultured Isolate):**

| | |
|---|---|
| PCR result | Mycobacterium tuberculosis complex detected |
| Isoniazid, INH (molecular) | Resistant |
| Fluoroquinolones, FLQ (molecular) | Resistant |
| Amikacin, AMK (molecular) | Sensitive |
| Ethionamide, ETH (molecular) | Sensitive |

# Classification of drugs used in DR TB management

| GROUP | MEDICINES | |
|---|---|---|
| Group A | Levofloxacin OR | Lfx |
| | Moxifloxacin | Mfx |
| | Bedaquiline | Bdq |
| | Linezolid | Lzd |
| Group B | Clofazimine | Cfz |
| | Cycloserine OR | Cs |
| | Terizidone | Trd |
| Group C | Ethambutol | E |
| | Delamanid | Dlm |
| | Pyrazinamide | Z |
| | Imipenem-cilastatin OR | Ipm-Cln |
| | Meropenem | Mpm |
| | Amikacin | Am |
| | (OR Streptomycin) | (S) |
| | Ethionamide OR | Eto |
| | Prothionamide | Pto |
| | p-aminosalicylic acid | PAS |




- Drugs in red have paediatric friendly formulations

# Where are we coming from…… ?

# DR-TB Regimens over time – Key facts

| Period | RR/MDR-TB Shorter Regimen | RR/MDR-TB Longer Regimen | XDR-TB Longer Regimen |
|---|---|---|---|
| 2011 – 2016 | • Not applicable | • 18-24 months (at least)<br>• 5 drugs<br>• **180 injections + 7 200 pills** | • 24 months (at least)<br>• 7 drugs<br>• **180 injections + 7 200 pills** |
| 2017 – 2018 (Aug) | • 9 – 11 months<br>• 7 drugs<br>• **Up to 180 injections + approx 2 900 pills** | • 18 – 20 months<br>• 5 drugs | • 18 – 20 months |
| 2018 (Aug) – 2023 | • 9 – 11 months<br>• 7 drugs<br>• All-oral | • 18 – 20 months<br>• 5 drugs<br>• All-oral | • 18 – 20 months |

# SHORTER regimen for adults, adolescents and children ≥ 6 yrs

**4-6 months (Intensive Phase):**

LZD (2 months only)–BDQ (total 6 months)*
–hdINH (4-6 months)–LFX–CFZ–PZA–EMB

**5 months (Continuation Phase):**

LFX–CFZ–PZA–EMB

| | 2 MONTHS | 4 MONTHS | 6 MONTHS | 9 MONTHS |
|---|---|---|---|---|
| Linezolid | | Give for 2 months even if second-line LPA shows injectable and fluoroquinolone susceptibility | | |
| High-dose isoniazid | | | Extend for another 2 months if smear positive at month 4* | |
| Bedaquiline | | | | Continue to 9 months in some patients |
| Levofloxacin | | | | |
| Clofazimine | | | | |
| Pyrazinamide | | | | |
| Ethambutol | | | | |

All patients requiring LZD require FBC monitoring at 2 weeks, 4 weeks and then monthly while on LZD

Pyridoxine should be co-administered with isoniazid to prevent peripheral neuropathy (50 mg/day for adults and adolescents ≥ 12 yrs; and 25 mg/day for children 5 – 12 yrs)

10

# BPaL and BPaL-L: The new regimens

- WHO announced the introduction of BPaL M regimen for RR-TB in May 2022
- The BPaL M regimen will comprise of Bedaquiline, pretomanid, linezolid, with or without moxifloxacin
- In clinical trials, the BPaL M regimen showed up to 90% efficacy
- **TB PRACTECAL and NIX/ZeNIX studies:** The evidence suggest that the 6-month BPaLM regimen – comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin – may be used programmatically in MDR/RR-TB patients in place of the 9-month regimen or the longer (≥18 months) regimen
- Patients taking investigational arms had fewer grade 3 and above AEs and SAEs as compared to SoC at week 72 (BPaLM> BPaL > BPaLC >> SOC)
- NEMLC concluded that levofloxacin will be used in replacement of moxifloxacin in SA

# BPaL and BPaL-L: The new regimens

- The BPaL combination (with 600 mg linezolid) retains sufficient efficacy and allows the regimen to be used without levofloxacin in the case of documented resistance to fluoroquinolones (i.e. in patients with pre-XDR-TB).
- In patients receiving the BPaL combination, where there is a slow response to therapy, an extension of 3 months (bringing the total regimen to 9 months) is possible.
- Individuals who have had more than one month exposure to the second line drugs may be started on BPaL-L, but resistance to BDQ and LZD must be excluded.

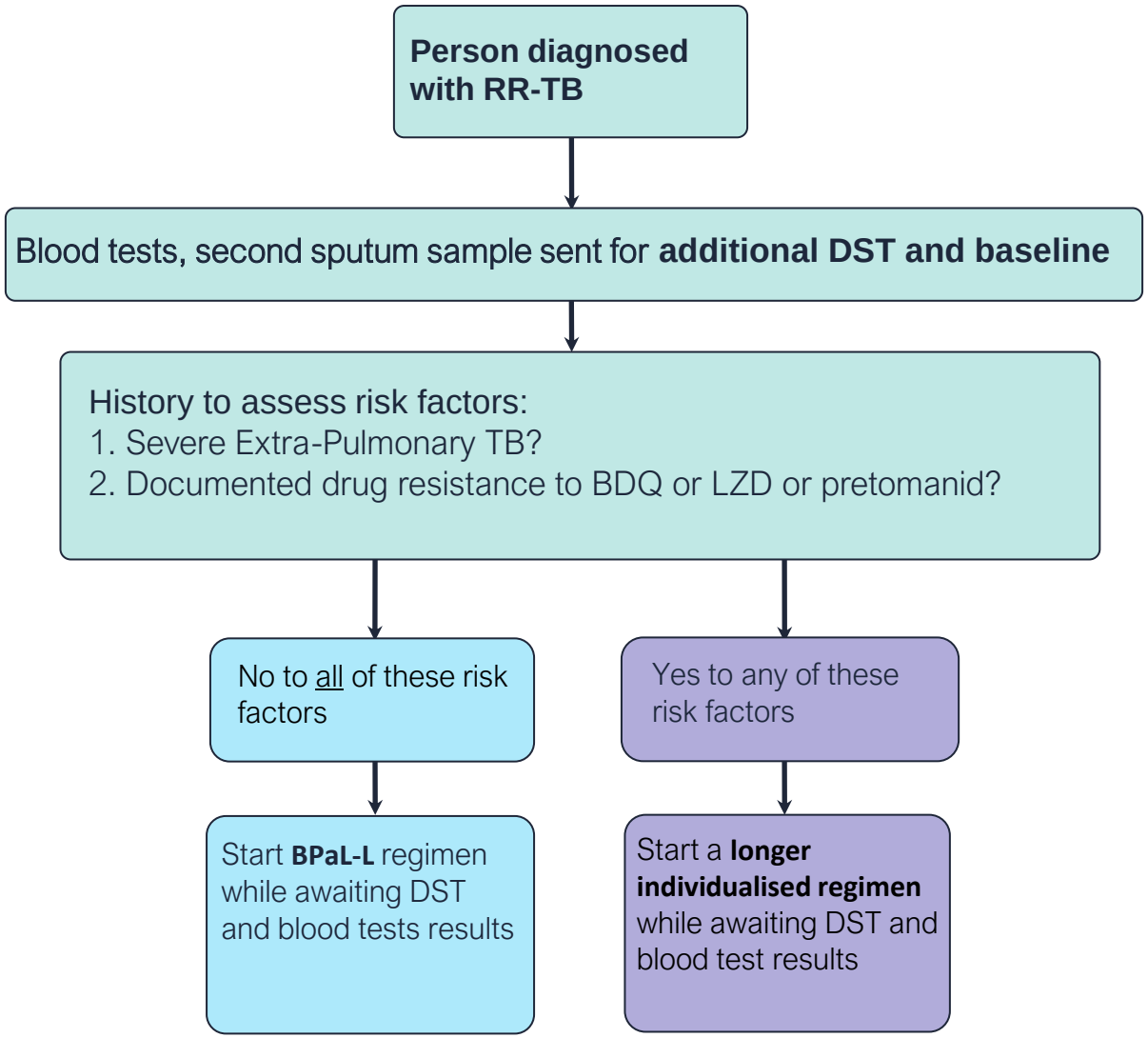
# Criteria for BPaL-L / BPaL

| | **INCLUSION** Criteria | **EXCLUSION** Criteria |
|---|---|---|
| **Resistance Patterns** | • Individuals with RR-TB: resistance based on initial GXP result, while awaiting further susceptibility results | • Documented resistance to Bedaquiline or Linezolid<br>• RR-TB with additional resistance to pretomanid or delamanid<br>• XDR-TB (resistance to fluoroquinolones and resistance to bedaquiline or linezolid) |
| **Clinical Criteria** | • Non-severe extra-pulmonary RR-TB, including lymphadenopathy or pleural effusion<br>• Persons with extensive pulmonary disease (i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in 3 or more lung zones) should have their treatment extended to 9 months | • Persons with severe extra-pulmonary RR-TB: meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease |
| **Specific Populations** | | • Children under the age of 15 years (pretomanid safety is not yet confirmed in this population)<br>• Pregnant women (pretomanid safety is not yet confirmed in this population) |

- There is NO specified intensive phase or continuation phase for these regimens
- All the drugs should be continued throughout treatment, if possible, unless limited by toxicity or intolerance
- The recommended Linezolid dose is 600mg daily, based on efficacy, safety and tolerability evidence-based data.
- The indication for pretomanid is not valid if any of the other two agents cannot be used in the regimen.
- Pyridoxine does not need to be prescribed in patients receiving BPaL-L.

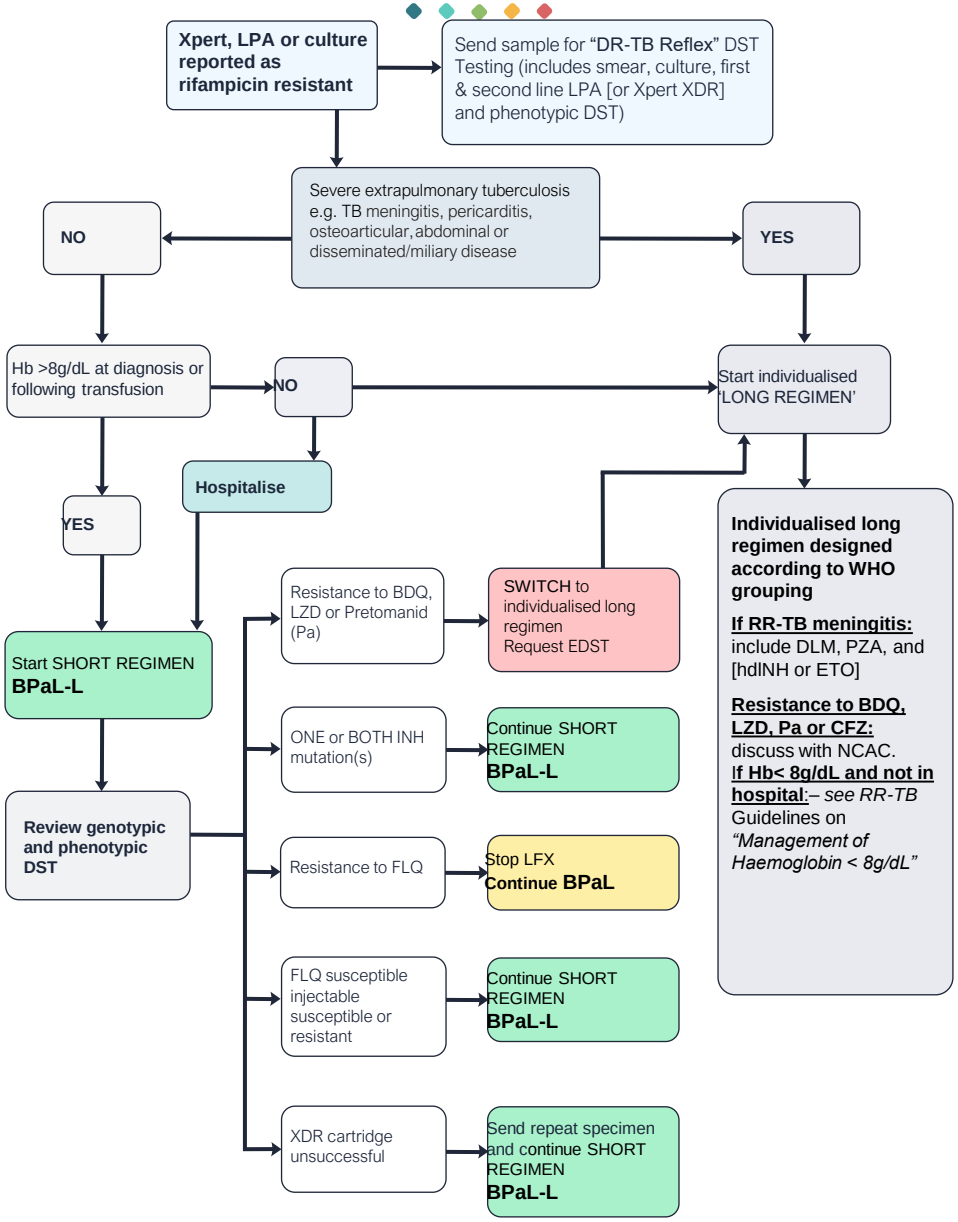
# RR-TB Treatment Regimens in SA

**Initial approach to patients diagnosed with RR-TB**



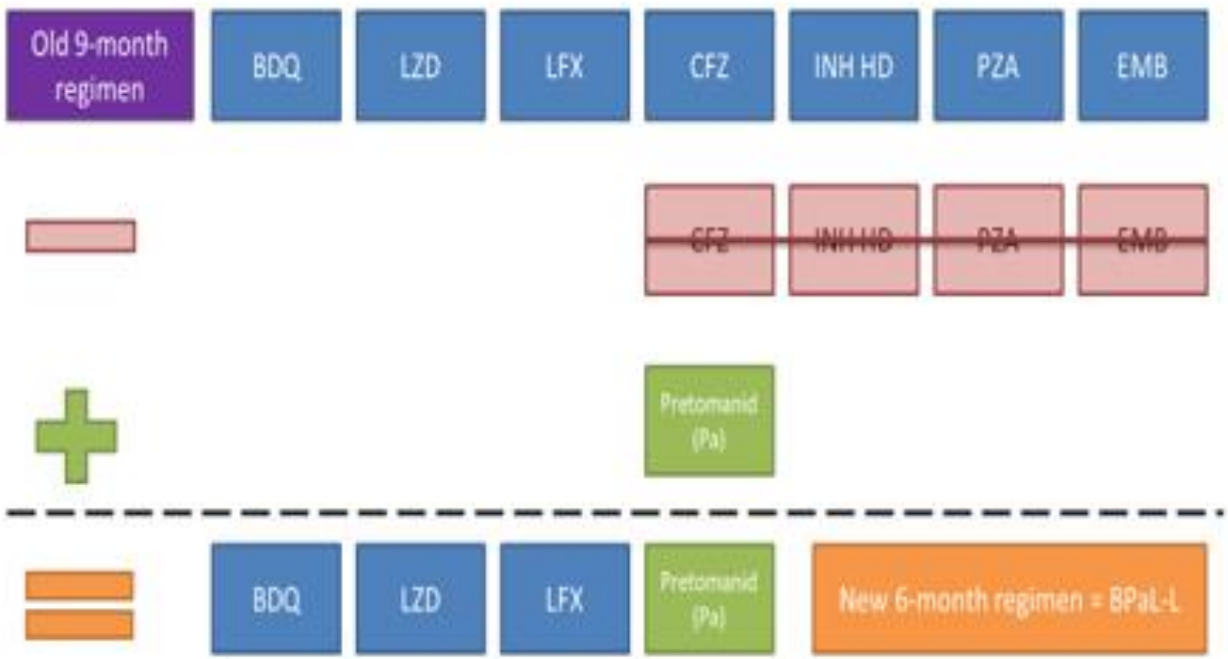

RSA NDoH: Clinical Management of Rifampicin-Resistant Tuberculosis (2023)

# Overall Flow Diagram for people ≥ 15 years of age




**RSA NDoH: Clinical Management of Rifampicin-Resistant Tuberculosis (2023)**

# New Regimen – BPaL-L



# BPaL-L / BPaL Dosing

| Drug | Dose |
|---|---|
| **Bedaquiline** (100mg tablet) | 400mg once daily for 2 weeks, then 200mg 3 times per week afterwards |
| **Pretomanid** (200mg tablet) | 200mg once daily |
| **Linezolid** (600mg tablet) | 600mg once daily |
| **Levofloxacin** (250mg tablet) | 750mg (<46kg) OR 1000mg (≥46kg) once daily |

# Linezolid SE

- Haematological: anaemia, neutropenia, thrombocytopenia
- Optic neuritis
- Peripheral neuropathy
- Lactic Acidosis
- Monitoring is vital

# Switching from BPaL-L/BPaL to Long Individualised regimen

A switch to a long individual regimen should be strongly considered in the following situations:

- **Resistance** to Bedaquiline, pretomanid, clofazimine, delaminid or linezolid is detected
- There is a **positive culture result at month 4** (delayed culture conversion or reconversion back to positive). **Resistance to** bedaquiline, pretomanid, clofazimine, delamanid or linezolid must be excluded.
- Bedaquiline, linezolid or pretomanid is prematurely and permanently **discontinued because of toxicity**
- Delamanid testing is currently not being routinely done, the NTBRL is planning on starting to test for pretomanid. Clofazimine will also not be routinely tested, it will only be tested as part of EDST
- The patient is **clinically deteriorating or has not clinically improved**. Other causes must be excluded in a culture negative patient
- Extended DST is required

# DR TB and HIV

- If ARV-naïve then commence ARV's  2 weeks after DR TB Rx
- If on ARV'S, continue Rx
- TLD is the regimen of choice, provided there is normal renal function
- TBM and CCM require delayed ARV initiation of up to 4- 6 weeks
- Standard guidelines for monitoring
- Cannot use EFV with BDQ
- Cannot use AZT with LZD
- If renal dosing, TDF will need to be adjusted or changed

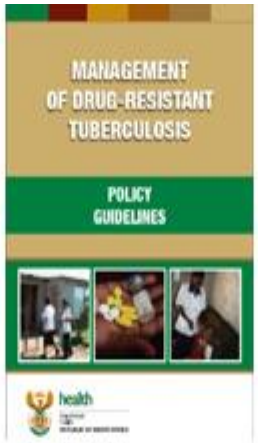
# Referrals to KDHC

- XDR TB
- Complicated cases
- Failing Rx – requiring a Rescue Regimen
- Pediatrics
- Pregnant patients
- OP in KDHC drainage area

# Referrals to KDHC

- Hotline numbers:
  0760768803 / 0714201659 / 0801515155

- Email:
  Nontobeko.Zondi2@kznhealth.gov.za / bookingsmdr2@gmail.com


MANAGEMENT
OF DRUG-RESISTANT
TUBERCULOSIS
POLICY
GUIDELINES
health


health
MANAGEMENT
OF RIFAMPICIN-
RESISTANT
TUBERCULOSIS:


MULTI-DRUG RESISTANT
TUBERCULOSIS
health

# THANK YOU