NEW TREATMENT REGIMEN FOR DR-TB PATIENTS: BPaL-L

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Chief Director: TB Control & Management
Outline

• The TB situation in SA
• TB Priorities for 2023/24
• Process of revision
• Major guideline changes
• Next steps
**Situational analysis**

1. **TB incidence & mortality**
   - Incidence falling steadily – on track to meet global targets
   - Mortality falling much slower – did not reach WHO milestone

2. **Critical issues across the programme**
   - **Important drivers**
     - **Patient factors**: advanced HIV, late presentation, delayed diagnosis, use of alternative medicine, mobility, stigma, catastrophic costs, misunderstanding of TB, conflicting health beliefs, alcohol and substance use, mental illness,
     - **Health system factors**: access barriers, gaps between levels of the health system, lack of system integration, limited ability of programme staff to track clients moving between facilities, lack of person-centred adherence approach, clinic congestion, health worker uncertainty, difficulty getting samples from young children.

3. **TB Care Cascade, South Africa 2021**
   - [Graph showing TB Burden, Tested, Diagnosed, Notified on treatment, Successfully treated]
     - TB Burden: 304,000
     - Tested: 254,485
     - Diagnosed: 233,270
     - Notified on treatment: 187,735
     - Successfully treated: 138,551

   - [Graph showing Incidence & Mortality]
     - Overall TB incidence
     - TB incidence in PMTCT
     - All TB deaths
     - TB deaths among HIV positive people
TB Recovery Plan – Prioritizing impactful interventions

**Pillar I: Communicate & Advocate**

- **CREATE DEMAND FOR**
  - TB TESTING THROUGH ADVOCACY AND COMMUNICATION

**Pillar II: Find & Link**

- **ACCELERATE IMPLEMENTATION OF TUTT**
  - People with TB are linked to care within one week

**Pillar III: Treat & Retain**

- **ESTABLISH RELIABLE LINKAGE PATHWAYS**
  - People with TB have access to high quality treatment & support

**Pillar IV: Prevent & Prepare**

- **IMPROVE RETENTION IN CARE**
- **STRENGTHEN TB PREVENTION**

**Pillar V: Monitor & Assess**

- **STRENGTHEN TB PROGRAMME IN THE MINES**
- **IMPROVE GOVERNANCE AND ACCOUNTABILITY**

<table>
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<tr>
<th>Costed SBBC plan</th>
<th>3million GXP tests</th>
<th>TB result notification system</th>
<th>Shorter regimens (paeds and DR-TB)</th>
<th>Scale up treatment of latent TB infection</th>
<th>Situational analysis of TB in mines</th>
<th>Streamline and integrate TB data systems</th>
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<td>Communication toolkit</td>
<td>Scale up DCXR</td>
<td>Initiate 224,776 patients on TB treatment</td>
<td>Strengthen adherence counselling</td>
<td>UVGI guidelines</td>
<td>Support examination and Compensation of ex-miners</td>
<td>100 Facilities Nerve Centre Approach Project</td>
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<td>Scale up ULAM</td>
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**Partner coordination**
Revision process

- Following the NEMLC’s ADOLOPMENT (GRADE review), the National Clinical Advisory Committee revised the 2019 RR-TB Clinical Reference guidance
- The 9-month RR-TB regimen has been replaced by a 6-month treatment regimen
- The 6-month regimen is part of the TB Recovery Plan
- The TB Recovery Plan was approved last year by the National Health Council
## DR-TB Patient Journey

### Initial Stages

- Identify people with signs and symptoms of TB disease
- Collect specimens for microbiological testing (refer to NHLS diagnostic algorithm)
- Advise patient that results will follow by SMS and he/she needs to act accordingly

### Laboratory

- Diagnose of RR-TB
- Report sent to requesting facility and SMS to patient within 24 hours of confirmation of diagnosis

### Patients are either hospitalised or initiated on treatment as outpatients

#### Before initiating treatment:
- Patient to be registered in a RR-TB register at appropriate facility (usually at a centralised or decentralised unit); this includes children who are clinically diagnosed and do not have microbiological confirmation of RR-TB
- Counsele the patient and family; obtain consent for RR-TB management; use appropriate DR-TB stationary; conduct psychosocial assessment including history of substance use and mental health; refer for MSF if necessary; refer for further social assessment and support as required

### Patients to start in ambulatory care

<table>
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<th>Indications for hospitalisation of patients with RR-TB</th>
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<tr>
<td>- Respiratory insufficiency</td>
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<tr>
<td>- Haemoglobin &lt;80 g/dL</td>
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<td>- Body Mass Index (BMI) &lt;18 kg/m²</td>
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<td>- Central nervous system (CNS) RR-TB disease</td>
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<tr>
<td>- Clinically unstable</td>
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<tr>
<td>- Unstable social situations that require intensive multi-disciplinary management</td>
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<tr>
<td>- Administration of intravenous therapy</td>
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<tr>
<td>- Unable to attend primary care facility for treatment (e.g., too weak to ambulate)</td>
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<tr>
<td>- Infection control challenges in the patient's home environment</td>
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<tr>
<td>- Recurrent treatment interruption where previous outpatient treatment has been unsuccessful</td>
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<tr>
<td>- Any condition that in opinion of the treating clinician would be better managed in the inpatient setting</td>
</tr>
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<td>- Patient preference for inpatient care</td>
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### On discharge from hospital, site staff/health care providers meet with patient and confirm discharge:

- Ensure all necessary documentation is completed
- Ensure patient has clear understanding of their next steps
- Ensure patient knows how to contact the clinic
- Ensure patient knows how to report any side effects

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### Follow-up care and DR-TB Stabilisation

- All RR-TB units are responsible for providing treatment according to local best practices and for monitoring progress of patients throughout their treatment journey
- RR-TB stationary should be maintained at the facility at which the patient is being managed

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**Note:** The information provided is a summary of the patient journey for DR-TB patients in South Africa, highlighting key stages, indications for hospitalisation, and follow-up care.
The Line Probe assay is phased out

Introduction of GeneXpert XDR (Xpert MTB/XDR) cartridge is used to detect fluoroquinolone and INH resistance, ethionamide and second line injectables (amikacin, kanamycin and capreomycin).

If RR-TB and FLQ resistance

Phenotypic testing for linezolid, bedaquiline and clofazimine

Phenotypic testing for pretomanid at the National TB Reference Laboratory
Two treatment options:

> The Short, all-oral, 6-month regimen (BPaL-L)
> A long-individualized regimen

As the BPaL/L regimen is implemented, the 9–11-month regimen will be phased out gradually.

The treatment regimen for children < 15 yrs has been updated to also include shorter regimens.
Current RR-TB Treatment Regimens & Eligibility

- **Xpert or LPA reported as rifampicin resistant**
- **History of previous treatment with 2nd line drugs > 1/12**
- Complicated EPTB (meningitis, osteoarticular, pericarditis, abdominal)
- Contact with XDR or pre-XDR
- Younger than 6 years
- Extensive disease on CXR
- Both INH mutations (inhA and katG) on LPA

**Legend:**
- Hb: Haemoglobin
- BDQ: Bedaquiline
- LZD: Linezolid
- CFZ: Clofazimine
- INH: Isoniazid
- HDINH: High-dose isoniazid
- Z: Pyrazinamide
- E: Ethambutol
- DST: Drug Susceptibility Test
- LPA: Line Probe Assay
- INH susceptible on LPA and phenotypic
- Resistance to FLQ, injectable, BDQ, LZD or CFZ
- Only one INH mutation (not both) and both FLQ and injectable susceptible
- LPA inconclusive

**None of these:**
- **Send sample for “DR-TB Reflex DST Testing”** (includes smear, culture, first & second line LPA & phenotypic DST)

**One or more of these:**
- Start individualised LONG COURSE

**Hb ≥ 8g/dL at diagnosis or following transfusion:**
- Start SHORT COURSE
  - BDQ, LFX, CFZ, hdINH, Z, E

**Hospitalise:**
- Review LPA and phenotypic DST results

- INH susceptible on LPA and phenotypic

- Both INH mutations

- Resistance to FLQ, injectable, BDQ, LZD or CFZ

- Only one INH mutation (not both) and both FLQ and injectable susceptible

- LPA inconclusive

- Send sample for “DR-TB Reflex DST Testing” (includes smear, culture, first & second line LPA & phenotypic DST)

**Start SHORT COURSE**
- BDQ, LFX, CFZ, hdINH, Z, E

**Reduce INH to normal dose (300mg daily in adults) and continue SHORT COURSE**

**Switch to LONG COURSE**

**Continue SHORT COURSE**

**Send repeat specimen and continue SHORT COURSE**

- Consider switch to LONG COURSE if no clinical improvement

**Standard initial longer regimen is:**
- BDQ, LFX, LZD, TRD and CFZ
  - If FLQ resistance: replace LFX with DLM and another group C drug
  - If age < 6 yrs: to receive individualized injectable—free regimen, including new drugs where possible. Duration dependent on site and severity of disease.
  - If RR-TB meningitis: longer individualized regimen, including DLM, PZA, AND [HDINH OR ETO]
  - Resistance to BDQ, LZD, or CFZ: discuss with NCAC
  - If Hb < 8 g/dL and not in hospital: replace LZD with one or 2 group C drugs, including DLM
# DR-TB Monitoring

<table>
<thead>
<tr>
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<th>Longer register: intensive phase</th>
<th>Longer register: continuation phase</th>
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<td>1</td>
</tr>
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<td><strong>Assess for TB complications</strong></td>
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<td>X</td>
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<tr>
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<td><strong>Height</strong></td>
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<td>Monthly if aged &lt;18 years</td>
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<td><strong>BMI and TDF (≥ 25 or &lt;15)</strong></td>
<td>X</td>
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<tr>
<td><strong>Review family planning</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Frequency tests</strong></td>
<td>X</td>
<td>X</td>
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<td><strong>Sample for smear culture</strong></td>
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### Longer register: continuation phase

**New failure**

- 2: Repeat monthly, or more often as required, until on biannual screening

**Repeat monthly, if on biannual screen, otherwise repeat as required if baseline screen was abnormal, or if patient is difficult to treat through treatment.

**Repeat monthly, if on biannual screen, otherwise repeat as required if baseline screen was abnormal, or if patient is difficult to treat through treatment.

**Repeat every 3 months while on PAP or ETO, or as required if DOT is prolonged.

**Repeat if monitoring, right upper quadrant pain, jaundice, or if patient is in contact with another patient with liver disease.

**Monthly, if on biannual screen, otherwise, as more often as required, while on treatment.

**Drugs:**

- **RBC and PFC and ETO on 1st and 2nd visit**
- **RBC and PFC and ETO on 3rd visit**
- **RBC and PFC and ETO on 4th visit**
- **RBC and PFC and ETO on 5th visit**
1.7. Overall Flow Diagram for people ≥ 15 years of age

Xpert, LPA or culture reported as rifampicin resistant:

Severe extrapulmonary tuberculosis e.g. TB meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease.

Yes

Start individualised LONG REGIMEN

Send sample for "DR-TB Reflex DST Testing (includes smear, culture, first & second line LPA (or Xpert XDR) & phenotypic DST"

No

Hb >8g/dL at diagnosis or following transfusion

Hospitalise

Yes

Resistance to BDQ, LZD or Pretomanid (Pa)

Start SHORT REGIMEN BPaL

Review genotypic and phenotypic DST

One or BOTH INH mutation(s)

SWITCH to individualized LONG Request EDST

Resistance to FLQ

STOP LFQ Continue BPaL

FLQ susceptible injectable susceptible or resistant

Continue SHORT REGIMEN : BPaL

XDR cartridge unsuccessful

Send repeat specimen and continue SHORT REGIMEN (BPaL)

If RR-TB meningitis:
include DLM, FZA, and [INH or ETO]

Resistance to DDQ, LZD, Pa or CFZ: discuss with NCAC.
If Hb < 8g/dL and not in hospital—see section "Management of Haemoglobin < 8g/dL"
Most people with a diagnosis of RR-TB will be eligible to receive the short regimen BPaL-L.

This contains:

- If fluoroquinolone resistance is detected, BPaL can be used without levofloxacin for 6 months.
- Prior use of bedaquiline and linezolid (>1 month) is not a contraindication for BPaL-L.
- **BPaL-L must not be used if there is resistance to bedaquiline or linezolid or pretomanid.**
Summary of changes: Medicines

Old 9-month regimen

- BDQ
- LZD
- LFX
- CFZ
- INH HD
- PZA
- EMB

New 6-month regimen = BPaL-L

- BDQ
- LZD
- LFX
- Pretomanid
- INH HD
- PZA
- EMB
### Inclusion Criteria

- **Individuals with RR-TB**
  Resistance based on initial GXP result, while further awaiting further susceptibility results

- **Non-severe extra-pulmonary RR-TB**, including lymphadenopathy or pleural effusion

- 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

### Exclusion Criteria

- Persons with **severe extra-pulmonary RR-TB**; meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease

- RR-TB with **additional resistance to BDQ or LZD, or pretomanid or delamanid**

- **Children under the age of 15 years** (pretomanid safety is not yet confirmed in this population)

- **Pregnant women** (pretomanid safety is not yet confirmed in this population)
### Significant impact delivered through these interventions

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<th>Pillar II: Find &amp; Link</th>
<th>Pillar III: Treat &amp; Retain</th>
<th>Pillar IV: Prevent &amp; Prepare</th>
<th>Pillar V: Monitor &amp; Assess</th>
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<td>TB is a national priority across sectors</td>
<td>People with TB are linked to care within one week</td>
<td>People with TB have access to high-quality treatment &amp; support</td>
<td>TB prevention is valued as much as treatment</td>
<td>High quality data is used to guide decisions</td>
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**Improved DR-TB Diagnostics**

**Shorter regimen**
- increased efficacy
- Improved retention in care

**MOST IMPACT ON TB INCIDENCE AND MORTALITY**
(Thembisa model)
Guideline dissemination and training in place including a webinar for all provinces on August 30th, 2023.

Meeting held with Affordable Medicines Cluster and Provincial Pharmacy Directors to prepare.

Provincial HODs and TB Managers informed.

The existing 4 BPaL CAP sites will start as soon as possible, not later than 30th September 2023; starting with Jose Pearson Hospital in Gqebera (previously known as Port Elizabeth).

Scale up will be closely monitored from NDOH and Provincial Offices starting from 1st September to 30th November 2023 subject to availability of pretomanid and training roll-out..
Thank you