Treatment of RR-TB in South Africa

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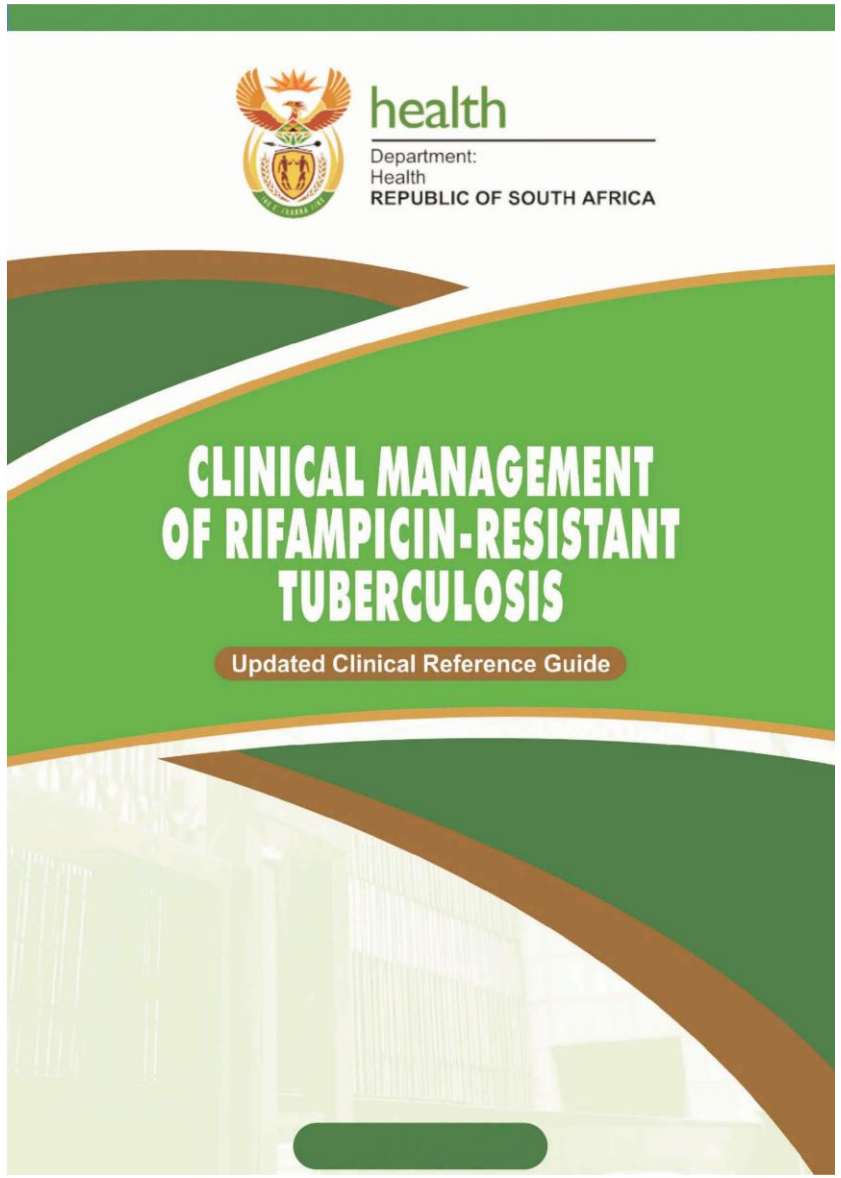

1. The success rate of treatment of MDR-TB in a person living with HIV using the newest regimen BPaL L
    1. Less than 50%
    2. Between 50 and 75%
    3. Between 75% and 85%
    4. **More than 85%**

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Topics to be covered

- Quick overview of definitions
- Two regimens available in South Africa
  - BPaL L
  - Individualized long regimen
- Adverse events
- Special populations

Definitions of RR-TB

RR-TB is rifampicin resistant TB

MDR-TB is RR-TB + INH resistance

preXDR is RR-TB/MDR-TB + fluoroquinolone resistant

XDR-TB is preXDR +resistance to BDQ or LNZ

Two options for the treatment of RR-TB

BPaL L regimen (in preXDR TB: BPaL)

Given for 6 months with option to extend to 9 months

Individualized longer regimen

What is the BPaL L regimen?

It is an all-oral treatment regimen

It consists of 4 medications

Bedaquiline
Pretomanid
Linezolid
Levofloxacin

It can be used in most people who have RR TB.

Who is eligible for BPaL L?

Non-pregnant patients (aged ≥15 years)

Not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).

Individuals who had more than 1 month exposure of second line drugs will be started on BPaL-L, but resistance to bedaquiline and linezolid must be excluded. Treatment initiation must not be delayed pending

This regimen may be used without levofloxacin (BPaL) in the case of documented resistance to fluoroquinolones.

BPaL L for the treatment of MDR TB can be given to the following patients.

1. A child aged 10.
2. **A person living with HIV with a CD4+ of 500.**
3. **A person living with HIV with a CD4+ of 50.**
4. **A person who has extensive disease on CXR**
5. A woman who is 32 weeks pregnant

BPaL side effects

In clinical trials

Adverse events rates are driven by linezolid

- Zenix 13%-38%
- Practecal 23%

Can be immediately life threatening thus require rapid detection and follow up

Myelosuppression or suppression of the bone marrow

May affect all the cells lines but tends to cause anaemia

Tends to occur in the first 8 weeks.

Anaemia is common co-morbidity with TB

- Undernutrition
- Anemia of chronic disorder
- HIV co-infection
- Blood loss due to hemoptysis

Detection and management of anemia (1)

- Management of anemia when starting treatment
  - Baseline full blood count
  - If HB is above 8g/dl start BPaL L and repeat in 2 weeks
  - If Hb is below 8g/dl
    - Consider admission
    - Consider transfusion
    - If starting treatment, repeat in 1 week
    - Warn patient about symptoms of anemia and how to get help

There is no place for starting the regimen without linezolid

Detection and management of anemia (2)

- Repeat full blood count at 2 weeks and then every month while on linezolid
  - If HB is above 8g/l continue at full dose (600mg)
  - If Hb is below 8g/l
    - Consider admission
    - Consider transfusion
    - Assess for symptoms of anemia
    - Interruption of linezolid and repeat FBC in a week or less
    - Reintroduced linezolid at 600mg or 300mg
    - Warn patient about symptoms of anemia and how to get help
    - Keep dose interruptions to the minimum

Detection and management of neutropenia and thrombocytopenia

- Full blood count at initiation, 2 weeks and then every month while on linezolid
- If absolute neutrophil counts is less that 0.75 10^6 /l or platelet counts is less that 100 10^9/L, repeat in a week or less
  - If persistent, consider interruption of linezolid Interruption of linezolid and repeat FBC in a week or less
  - Reintroduced linezolid at full dose
  - Keep dose interruptions to the minimum

What are the side effects of linezolid?

1. Increase in the QTc interval.
2. **Optic neuritis**
3. Skin darkening
4. **Anaemia**
5. **Peripheral neuropathy**

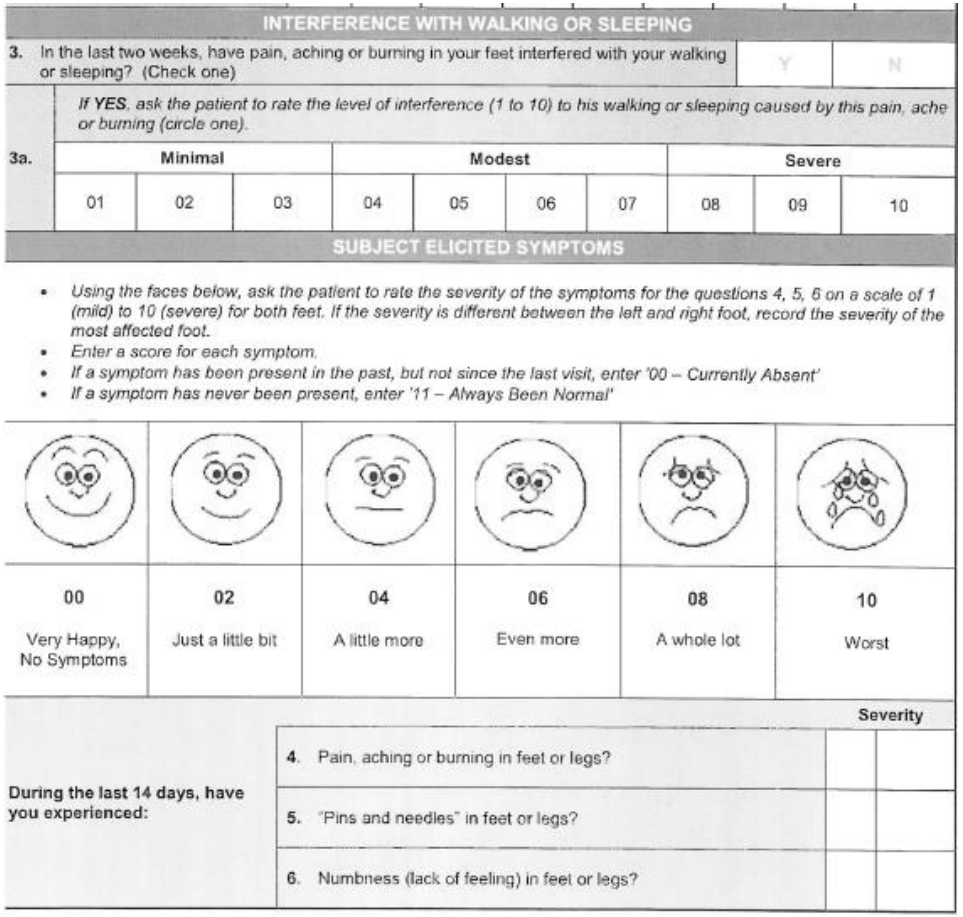
Detection and management of peripheral neuropathy

- Requires clinician and patient awareness
- Other common causes of peripheral neuropathy
  - Diabetes
  - HIV infection
  - Alcohol
  - Other medications e.g., INH
- Tends to occur later in treatment (from 16 weeks)
- Check at every visit of there is pain, pins and needles, loss of sensation or paresthesia

Detection and management of peripheral neuropathy

Difficult to grade severity

Ask patient about interruptions of daily life esp. sleep



INTERFERENCE WITH WALKING OR SLEEPING

3. In the last two weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one) — Y / N

3a. *If YES, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one).*

Minimal			Modest				Severe		
01	02	03	04	05	06	07	08	09	10

SUBJECT ELICITED SYMPTOMS

- *Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.*
- *Enter a score for each symptom.*
- *If a symptom has been present in the past, but not since the last visit, enter '00 – Currently Absent'*
- *If a symptom has never been present, enter '11 – Always Been Normal'*

00	02	04	06	08	10
Very Happy, No Symptoms	Just a little bit	A little more	Even more	A whole lot	Worst

During the last 14 days, have you experienced:		Severity
	4. Pain, aching or burning in feet or legs?	
	5. "Pins and needles" in feet or legs?	
	6. Numbness (lack of feeling) in feet or legs?	

Detection and management of peripheral neuropathy

If occurs early in treatment prior to clinical and microbiological response

Interrupt	• Interrupt linezolid only
Monitor	• Monitor for resolution of symptoms
Re-introduce	• When symptoms are manageable at a lower dose
Permanently discontinue if recurs	

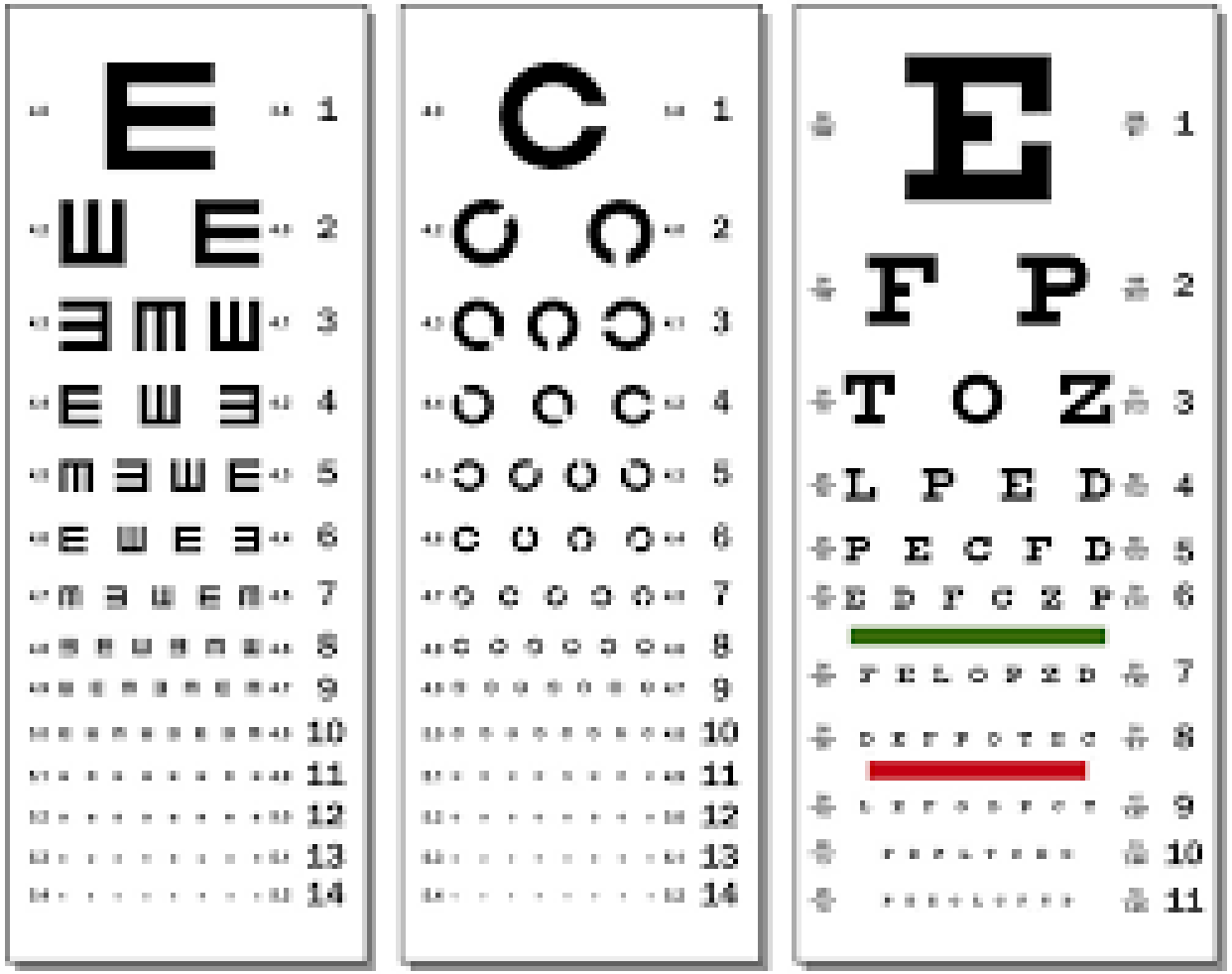
If occurs later in treatment after to clinical and microbiological response

Interrupt	• Interrupt linezolid only
Monitor	• Monitor for resolution of symptoms
Consider	• Consider permanent discontinuation of 16 weeks of treatment have been completed

Detection and management of optic neuritis

Routine visual screening

- Done at initiation and at every visit while of linezolid
- If there is a two-line drop, consider optic neuritis.
- If possible, fundoscopy or ophthalmology referral
- Interrupt linezolid until diagnosis is excluded.



Adverse events to bedaquiline

Prolongation of the QT interval

- Consider QTc F above 500 ms
- In STREAM 2 , small proportion of participants (3–6%) did the QTcF interval reach 500 ms or higher, the threshold at which the risk of serious arrhythmia starts to increase
- If QTcF above 500
  - Check for reversible courses e.g. electrolytes, hypothyroidism
  - Exclude other QT prolonging drugs
  - If persistent, stop BDQ

Adverse event to Bedaquiline (1)

Hepatotoxicity

- AST, ALT and bilirubin done while on treatment
- Symptoms of Hepatotoxicity:
  - Nausea
  - Vomiting
  - Right upper quadrant pain
  - Jaundice

Adverse event to Bedaquiline (2)

- ALT/AST increase to 5 times upper limit of normal (with/out symptoms) or to 3 times upper limit of normal with symptoms
  - Stop whole regimen
  - Look for other causes e.g.
    - Viral Hepatitis
    - Alcohol
    - Other hepatoxic drugs
  - Re-start regimen when ALT/AST less than 5 times upper limit of normal

Adverse events to pretomanid

- Newest drug
- Low AE profile
- For hepatoxicity see previous slides

Patients follow up: mycobacterial

- Smear and culture to be done prior to starting treatment
- At 2 weeks
- At month 1 and every month thereafter until treatment is completed
- Follow up at 6 months and 12 months
- Culture conversion usually occurs by the end of month 2
- If month 3 culture is still positive, this should prompt action.
- Seek advice of the NCAC if needed

To monitor the response to treatment in a person with MDR TB, sputum culture is done

1. At the start of treatment and at the end of treatment
2. **Every month while the person is on treatment.**
3. After 3 months of treatment
4. Never, we do sputum smears to monitor the response.

What to do when you get DSTs back

Genotypic/ Phenotypic results	Action
INH resistant (InhA or KatG)	Continue BPaL L
INH susceptible	Continue BPaL L
Fluroquinolone susceptible	Continue BPaL L
Fluroquinolone resistant	Continue BPaL
Second-line injectable susceptible/resistant	Continue BPaL L
Ethionamide susceptible/resistant	Continue BPaL L

Individualized long regimen
Must be referred to a DR TB centre

Documented resistance to pretomanid and/or BDQ and/or LZD.

Extended DST will be done on request

Individualized long regimen the composition of the regimen will depend on the drug resistance pattern, prior drug exposure and toxicity.

Complicated extrapulmonary disease

Special populations: Pregnant women

01

Family planning as part of care

02

Safety of pretomanid has not been established in pregnancy

03

Consider bedaquiline, delamanid, linezolid and levofloxacin. (BDLL)

The duration of treatment of a person with active MDR TB disease using BPaL Lis

1. 4 months
2. **6 months**
3. 9 months
4. 18 months
5. Individualized on a case-by-case basis

In conclusion

What are the risks of this approach

Short regimen needs excellent adherence

Increased resistance to bedaquiline

Adverse event related to linezolid

In conclusion

What are the benefits?

Shorter regimen with lower pill burden to increase adherence

Higher rate of success outcomes

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