

Workshop

Joint SEAR-WPR workshop to plan the accelerated implementation of new WHO TB policies

1-4
APRIL
2025

Hanoi,
Viet Nam

Management of adverse events in MDR/RR-TB treatment



Topics to be covered

- Rate of adverse events with BPaL M, BDLLfxC, modified 9-month regimens and 9-month in clinical trials
- Management of adverse events of special interest
 - Myelosuppression
 - Peripheral neuropathy
 - Optic neuropathy
 - Hepatotoxicity
 - Cardiotoxicity

Rate of adverse events on clinical trials

Trial	Grade3- 4	Adverse event related to drug
Zenix	24-31%	17%
PRACTECAL (BPaLM)	23%	
BEAT Tuberculosis	37%	25%
End TB	55-61%	6-18%

Conradie, Bagdasaryan et al. 2022
Nyang'wa, Berry et al. 2024
Guglielmetti, Khan et al. 2025



World Health
Organization



THE
GLOBAL
FUND

KNCV
TB PLUS

Adverse events of special interest

Myelosuppression

- Anemia
- Neutropenia
- Thrombocytopenia

Peripheral neuropathy

Optic neuropathy

Hepatotoxicity

Cardiac toxicity

Myelosuppression

May affect all the cell lines but tends to cause anemia

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/Hb

- If HB is above 8g/dl start L containing regimen 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)

Management of anemia during treatment

Repeat full blood count/Hb 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 than $0.75 \times 10^6 / \text{l}$ or platelet counts is less than $100 \times 10^9 / \text{L}$, repeat in a week or less
 - If persistent, consider interruption of linezolid
Interruption of linezolid and repeat FBC in a week or less
- Reintroduce linezolid at full dose
- Keep dose interruptions to the minimum

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 if 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														
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).																							
3a.	Minimal			Modest				Severe															
	01	02	03	04	05	06	07	08	09	10													
SUBJECT ELICITED SYMPTOMS																							
<ul style="list-style-type: none"> 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' 																							
     																							
<table border="1"> <thead> <tr> <th></th> <th>00</th> <th>02</th> <th>04</th> <th>06</th> <th>08</th> <th>10</th> </tr> </thead> <tbody> <tr> <td></td> <td>Very Happy, No Symptoms</td> <td>Just a little bit</td> <td>A little more</td> <td>Even more</td> <td>A whole lot</td> <td>Worst</td> </tr> </tbody> </table>											00	02	04	06	08	10		Very Happy, No Symptoms	Just a little bit	A little more	Even more	A whole lot	Worst
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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



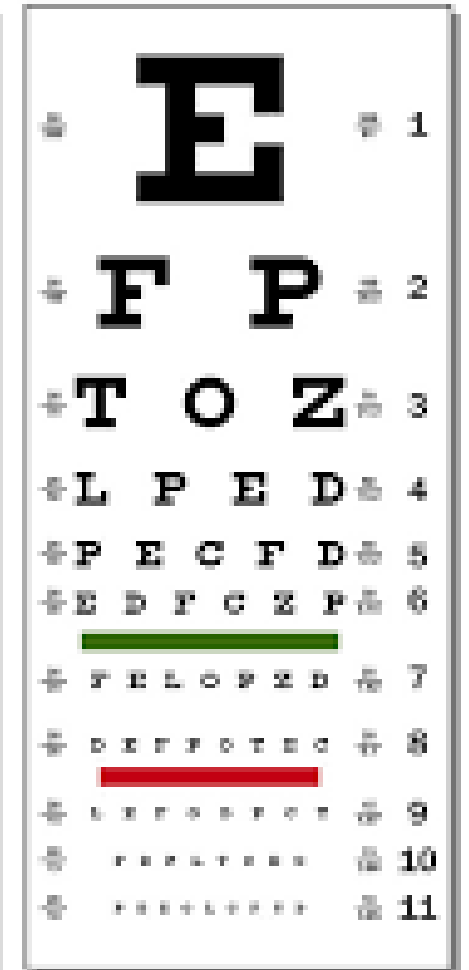
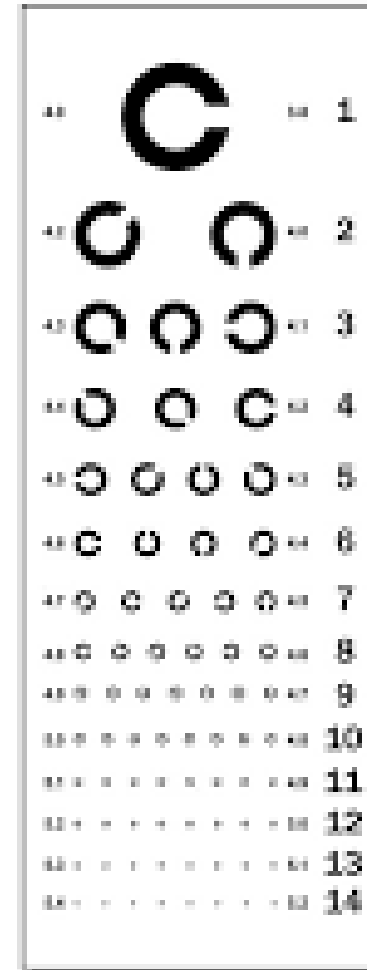
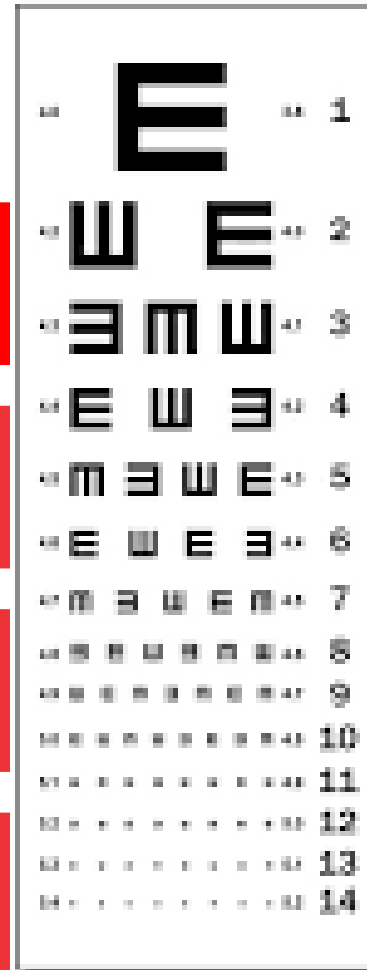
If there is a two-line drop, consider optic neuritis.



If possible, funduscopy or ophthalmology referral



Interrupt linezolid until diagnosis is excluded.



Hepatotoxicity

Competing risks for Hepatotoxicity

- Alcohol
- Viral Hepatitis
- Other toxins

Drug Causes

- PZA
- INH
 - BDQ, Mpm, Amx/Clv, Eto/Pto, Cfz, Trd/Cs, PAS

Often asymptomatic

Monitoring liver function

Monthly transaminase measures (ALT/AST)

Grade 2 $>3.0\text{--}5.0 \times \text{ULN}$ (upper limit of normal)

- Continue the treatment regimen; follow patients until resolution (return to baseline) or stabilization of AST/ALT levels
- Watch for symptoms

Grade 3 $>5.0\text{--}20.0 \times \text{ULN}$

- Grade 3 Stop all drugs, including anti-TB drugs
- repeat LFTs weekly
- Treatment may be reintroduced WITHOUT PZA after toxicity is resolved

Grade 4

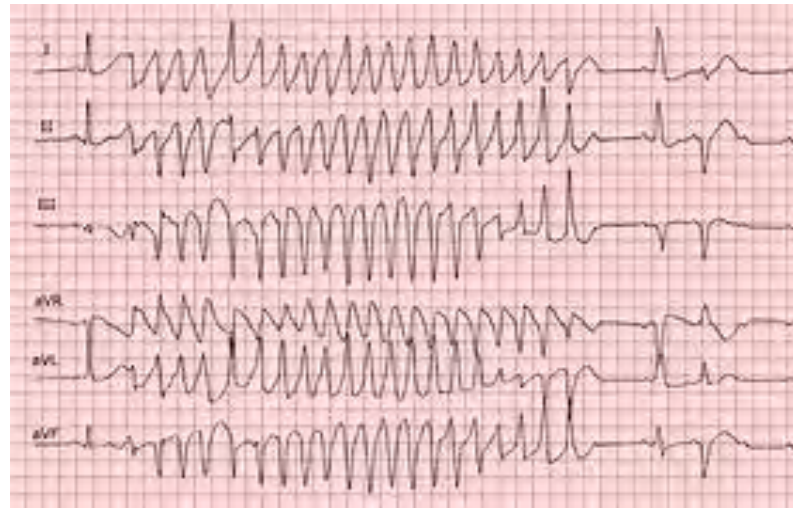
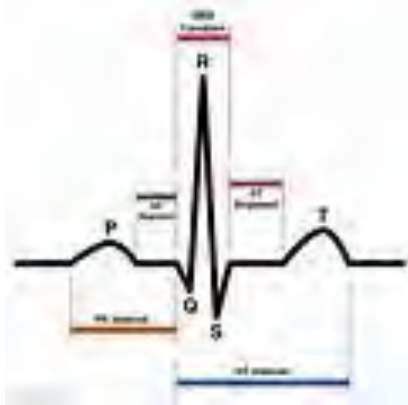
- Stop all drugs, including anti-TB drugs
- repeat LFTs weekly
- treatment may be reintroduced after toxicity is resolved (for the BPAL/BPaLM regimen, see drug modification guidelines for Lzd)

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 causes e.g. electrolytes, hypothyroidism
 - Exclude other QT prolonging drugs
 - If persistent, stop BDQ and moxifloxacin

Cardiotoxicity

- Prolongation of the QT interval
- If QTc F is above 500ms, predisposes to Torsades de Points



Cardiotoxicity

BDQ, Moxi, Clofazimine, DLM

>500 ms without
signs or symptoms
of serious
arrhythmia

- Repeat ECG after allowing the patient to rest for at least 10 min
- Hospitalize if possible and replete electrolytes as necessary
- If QTcF remains >500 ms, stop the regimen and repeat ECG within 2–5 days
- Ensure that the patient is not taking any other QT-prolonging drugs
- Exclude hypothyroidism

>500 ms with signs
or symptoms of
serious arrhythmia

- TdP or polymorphic ventricular tachycardia, or symptoms of serious arrhythmia
- The whole regimen needs to be stopped
- hospitalize and replete electrolytes as necessary
- Ensure that the patient is not taking any other QT-prolonging drugs
- Exclude hypothyroidism

In conclusion

6-9 months of treatment for RR-TB is a breakthrough

The Adverse events are predictable and can be managed mostly at a primary care level.

Safety in pregnancy and children has not yet been established for all drugs