LIFTB
Leveraging Innovation for Faster Treatment of Tuberculosis

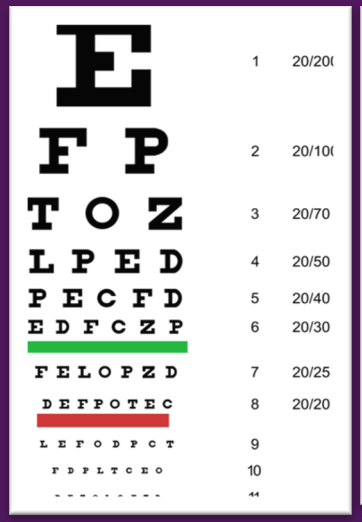
International Tuberculosis Research Center

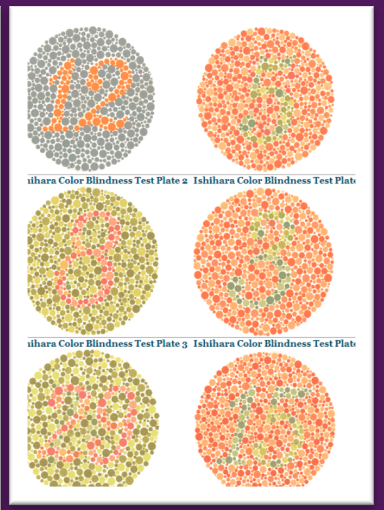
KNCV TUBERCULOSIS FOUNDATION

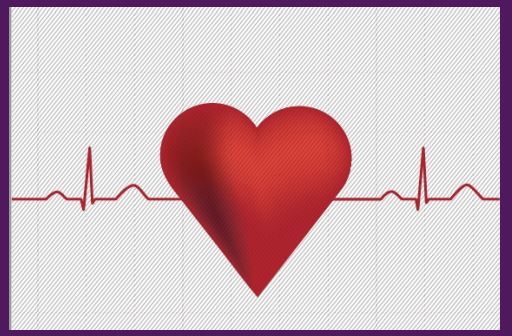
TB Alliance

aDSM application: Clinical management of adverse events in BPaL

Training of Trainers for the BPaL Operational Research
Philippines, 19-21 May 2021







Mansa Mbenga
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Outline

Adverse events of special interest in this OR

1. Peripheral neuropathy
2. Optic neuritis
3. Myelosuppression
4. QT prolongation
5. Hepatotoxicity

Reporting of AEs in the BPaL OR

Adverse event types that need reporting (AE Form for BPaL):

1. AE leading to treatment discontinuation or change in drug dosage
2. AE of special interest
3. Serious adverse event (SAE)

Central component of MDR-TB treatment

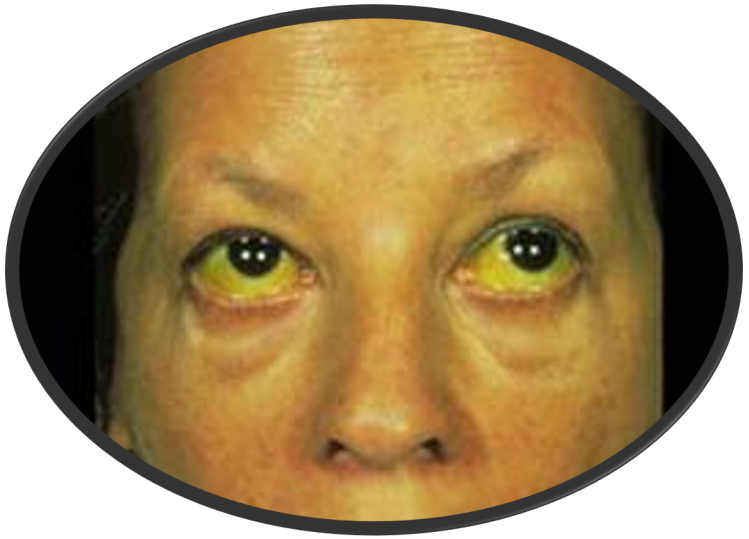
- Effective management of AEs :

  a) Starts with a rapid identification (through clinical and laboratory monitoring)

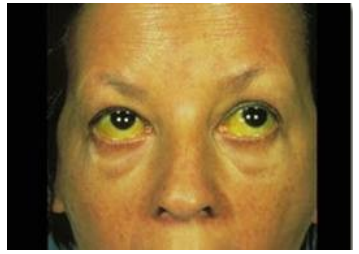
  b) Includes proper and aggressive management

    - AE management should be aggressive; response to treatment closely monitored
    - Aggressive management should not be considered a contraindication to treatment
    - Poorly managed AEs can lead to inadequate or irregular treatment or abandonment of treatment, permanent disability and death

Hepatotoxicity



Hepatitis or elevated liver enzymes



- Patients may present with:
  - poor appetite
  - nausea and vomiting
  - fatigue
  - jaundice (yellowing of skin, mucous membranes, and conjunctiva)
  - darkening of urine
  - pruritus
  - Epigastric/abdominal pain

Possible drug causes
Z, H, B, Pa, Pto,
PAS, Dlm, Bdq

- Patients may have no symptoms, only increased liver enzymes
  - Increase liver enzymes (ALT and AST , hyperbilirubinaemia)

Management of hepatitis or elevated liver enzymes

- Severity grading scale for hepatotoxicity

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT /AST	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	**Stop full BPaL regimen**, including other non-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved, (LFTs returned to Grade 1)	**Stop full BPaL regimen**, including other non-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved, LFTs returned to Grade 1)

EndTB Severity Grading Scale for Adverse Events, version 5.0. Available from: http://endtb.org/resources/pharmacovigilance

Management of hepatitis or elevated liver enzymes

- Consider **medical conditions** which may cause elevated liver enzymes, viral hepatitis (A, B, C), alcohol, HIV In HIV coinfection

- Consider present **medicines**: TB or non-TB medicinces
- Consider **drug-drug interactions**
- In case of jaundice, stop all anti-TB drugs until resolution
  - Check ALT/AST/bilirubin. Stop if severity is grade 3.
  - Reintroduce full BPaL regimen once liver enzymes return to at least grade 1 and monitor AST/ALT/bilirubin weekly for the first month and then monthly
  - If unable to restart the full BPaL regimen with 35 days, refer to Expert TB Committee to construct a new treatment regimen

Hepatotoxicity in the Nix-TB Study

- Most hepatic disorder AEs in the Nix-study were grade 1 or grade 2

- The BPaL regimen was interrupted for hepatotoxicity in 8 patients (7%); the events resolved in all patients and the BPaL was restarted, resulting in full completion of the intended length of therapy

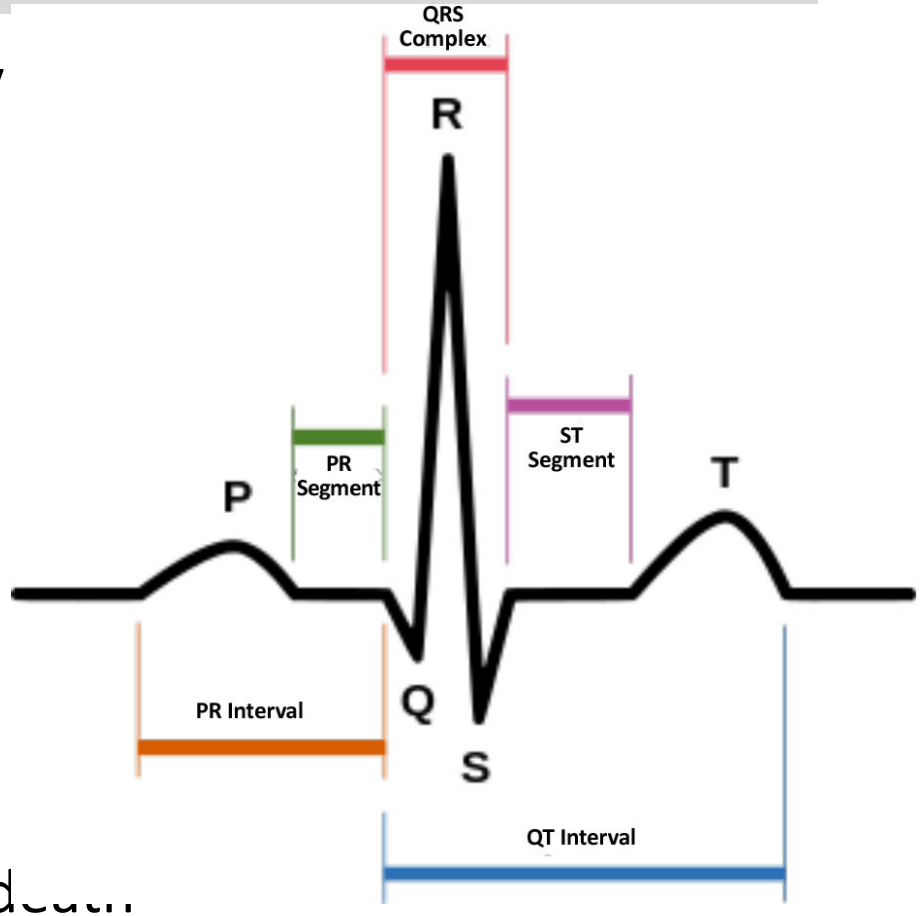
Always consider and rule out other causes other than the BPaL regimen

Mild elevation of liver enzymes, especially at baseline, may be related to TB disease rather than an AE of treatment

Cardiac disorders (QTcF prolongation)

Cardiac disorders

- QT Prolongation - cardiac dysrhythmia characterized by abnormal (long) corrected QT interval (QTc)
- Causes:
  - Congenital conditions
  - Acquired conditions
  - Antiarrhythmics
  - Electrolyte abnormalities (Hypokalemia, Hypocalcemia, Hypomagnesaemia)
  - Ischemia
  - Hypothyroidism
  - DRUGS:
- Consequences: lead to syncope, cardiac arrest/sudden death

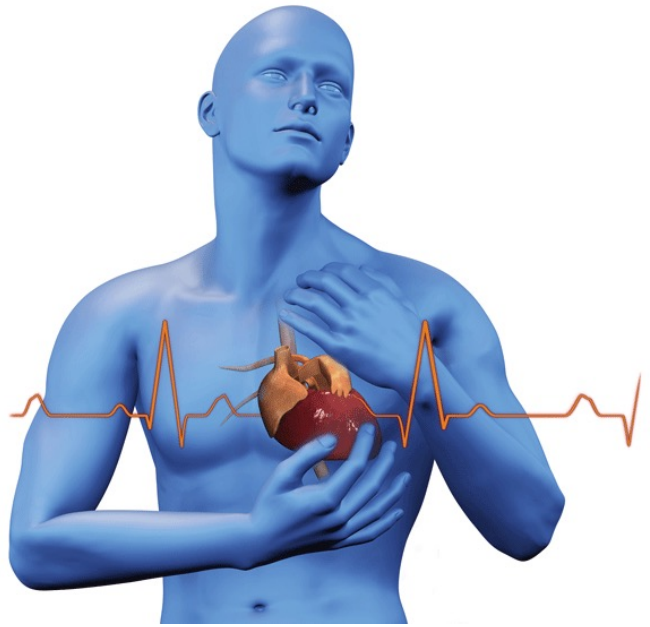


Risk factors for QT prolongation (1)

1. Congenital disorders
2. Age: (linearly increased after 60 years)
3. Gender: female
4. Cardiac abnormalities: low left ventricular ejection fraction, LV hypertrophy, ischemia, slow heart rate
5. Electrolyte abnormalities: hypokalemia, hypomagnesemia
6. Medicines and drug interaction: Fluoroquinolones, Bedaquiline, Clofazimine, Delamanid
   Complete list in *https://www.crediblemeds.org*
7. Renal and hepatic disease causing impaired elimination of medicines
8. Hypothyroidism
9. Starvation and obesity

TB drugs causing QT prolongation

- Signs and symptoms:
  - Usually patients are asymptomatic
  - Symptomatic patients may complain
    - Palpitations, tachycardia
    - Dizziness
    - Chest pain
    - Syncope



Management of QT prolongation

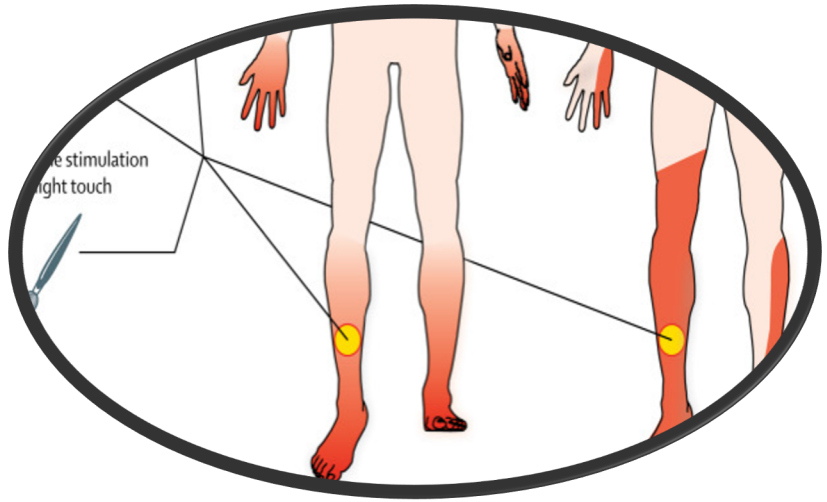
Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
Prolongation of QTcF	QTcF 450 – 480 ms.	QTcF interval 481 – 500 ms.	QTcF >= 501 ms without signs/symptoms of serious arrhythmia	QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the BPaL regimen and other suspected causative drugs, including non-TB drugs Hospitalize and replete electrolytes as necessary.	Stop the BPaL regimen and all other suspected causative drug(s), including non-TB drugs. Hospitalize and replete electrolytes as necessary.

Modified from End TB Clinical and Programmatic Guide for patient management with new TB drugs, version 4.0, January 2018

Management of cardiac disorders

- Perform a thorough history and a full clinical examination to R/O palpitations, presyncope or syncope and any systemic factors
- Withhold all medication(s) at Severity Grade 3 especially the QT prolonging agents (TB and non-TB
- Check electrolytes (especially K, Mg, Ca) and replace if needed.
- Check other factors: TSH, Hgb
- Consider cardiologist consultation/using national clinical guideline
- Consider continuous cardiac monitoring based on the severity of the QT prolongation

Peripheral neuropathy



Peripheral neuropathy

Associated drugs: Lzd, H_{HD}, Cs/Trd, Pto/Eto, E, d4T, ddI, alcohol, diabetes, HIV

Diagnosis: Combination of a subjective neuropathy in the BPNS and at least one bilateral objective finding (vibration perception or deep tendon ankle reflex).

Prevention: pyridoxine 50 -200 mg for all patients on INH, Cs/Tzd, alcoholism,

** Insufficient evidence of pyridoxine for Lzd-induced peripheral neuropathy*

Management of Peripheral neuropathy

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Neurosensory alteration	Mild discomfort; no treatment required; and/or BPNS subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic analgesia
Action	Stop or reduce dose of Lzd. If symptoms improve, consider restarting Lzd at a lower dose 600 mg or 300 mg	Stop Lzd, provide symptomatic, If symptoms improve, consider restarting Lzd at a lower dose 600 mg or 300 mg. Stop Lzd permanently if symptoms reappear .	Stop Lzd, do not restart. Provide symptomatic relieve.	Stop Lzd, do not restart. Provide symptomatic relieve.

Modified EndTB Severity Grading Scale for Adverse Events, version 4.0. Available at: http://endtb.org/resources/pharmacovigilance or https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf

Symptomatic relief of peripheral neuropathy

- NSAIDs or acetaminophen may help alleviate symptoms
- Gabapentin start 300 mg OD increase to 300 -600 mg TID
- Pregabalin 50 to 75 mg per day in 2 divided doses, up to 150 - 300 mg BID
- ~~[Tricyclic antidepressant: start amitriptyline 25 mg at bedtime; max dose 150 mg~~ daily for refractory symptom]
  - **Not** with Bdq or Dlm (QT prolongation); **not** with Lzd (serotonin)
- ~~Carbamazepine 100-400 mg BID; **not** with Bdq or Dlm (reduced levels); **not** with Lzd~~ (serotonin)

Spellberg B, Yoo T, Bayer AS. J Antimicrob Chemother 2004; 54(4): 832-5

Ancillary medicines

Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

DEPARTMENT MEMORANDUM
No. 2015 - 0228

TO: **ALL DEPARTMENT OF HEALTH REGIONAL OFFICE DIRECTORS, SECRETARY OF HEALTH AUTONOMOUS REGION IN MUSLIM MINDANAO, AND DIRECTORS OF HOSPITALS WITH PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS (PMDT) TREATMENT FACILITIES.**

SUBJECT: **EXPANDED LIST OF PMDT ANCILLARY DRUGS**

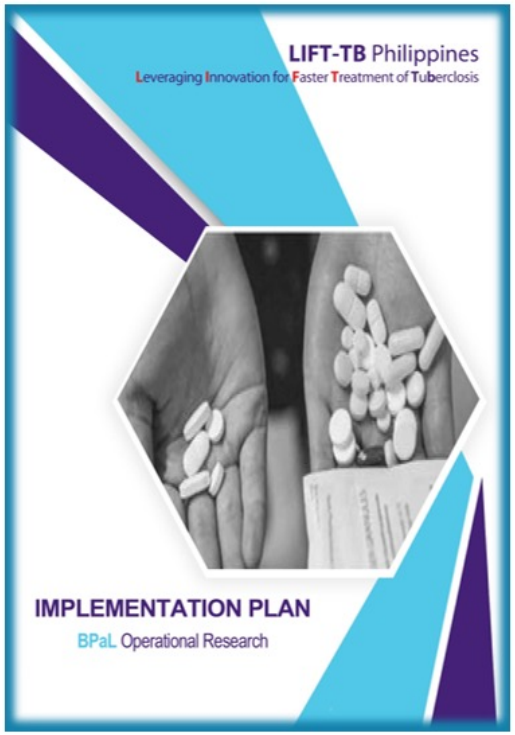
DATE: **JULY 1, 2015**

To better address the management of Adverse Drug Reactions of patients taking Second-Line Drugs, the National Tuberculosis Control Program conferred with the following partners to evaluate the use of additional ancillary drugs, WHO, SIAPS-MSH and the Pharmaceutical Division of the Department of Health.

In view thereof, the National Tuberculosis Program is now releasing the expanded list of the ancillary medicines for the Programmatic Management of Drug-Resistant Tuberculosis.

For information.

ANTI-VERTIGO • Betahistine HCl 8mg tablet • Cinnarizine 75mg capsule
ANTIPYRETICS • Paracetamol 500mg tablet
NON-OPIOID ANALGESICS • Mefenamic Acid 500mg tablet • Indomethacin 25mg tablet • Celecoxib 100mg tablet
SPASMOLYTIC • Baclofen 10mg tablet
FOR NEUROPATHIC PAIN • Gabapentin 100mg capsule
ANXIOLYTIC • Bromazepam 1.5mg tablet • Clonazepam 2mg tablet
ANTIPSYCHOTIC • Haloperidol 5mg tablet • Quetiapine Fumarate 25mg tablet
ANTIDEPRESSANT • Sertraline HCl 50mg tablet
HYPNOTIC • Zolpidem 10mg tablet
ANTIGOUT • Allopurinol 100mg tablet • Colchicine 500mcg tablet
ANTIBACTERIAL • Clarithromycin 500mg tablet • Clindamycin HCl 300mg capsule • Co-amoxiclav 1g tablet • Cefuroxime 500mg capsule
RESPIRATORY MEDICINE (Reliever,Controller) • Salbutamol SulfateTab 2mg



Visual disturbances

Causes of optic neuritis

- Drugs (mainly referred to as Toxic neuropathy – TON)
  - Anti-TB drugs: Ethambutol and Lzd
  - Antibiotics: chloramphenicol, cimetidine, vincristine, and cyclosporine
- Autoimmune conditions often are associated with optic neuritis:
  - Multiple sclerosis
  - Neuromyelitis optica
- **Infections**:
  - Bacterial infections (Lyme disease, meningitis, syphilis, etc)
  - Viruses (measles, mumps, toxoplasmosis, herpes, etc)
  - Other diseases such as sarcoidosis and lupus
- **Risk factors**
  - Age (20 to 40 years)
  - Tobacco and alcohol
  - Radiation
  - Vitamin B deficiency

Management of optic neuritis

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Optic nerve disorder	Asymptomatic or mild symptoms; clinical or diagnostic observations only or unable to read 4 or more plates in color vision test	Symptomatic; moderate decrease in visual acuity (20/40 [6/12] or better) or drop of 2 lines on VA (Snellen) chart or unable to read 4 or more plates in color vision test.	Limiting vision in the affected eye; visual acuity worse than 20/40 [6/12] but better than 20/200 [6/60]) or drop of more than 2 lines (Snellen chart) or unable to read 4 or more plate (color vision test)	Blindness (20/200 [6/60] or worse) in the affected eye.
	Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist.	Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist. **Do not restart** unless there is an alternative diagnosis.	Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist. **Do not restart** if diagnose confirmed.	Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist**. Do not restart** if diagnose confirmed.

Always capture baseline test result to compare test to establish a change in (color) vision or VA

NOTE: Due to frequent testing, patients can memorize the plates and respond by memory.

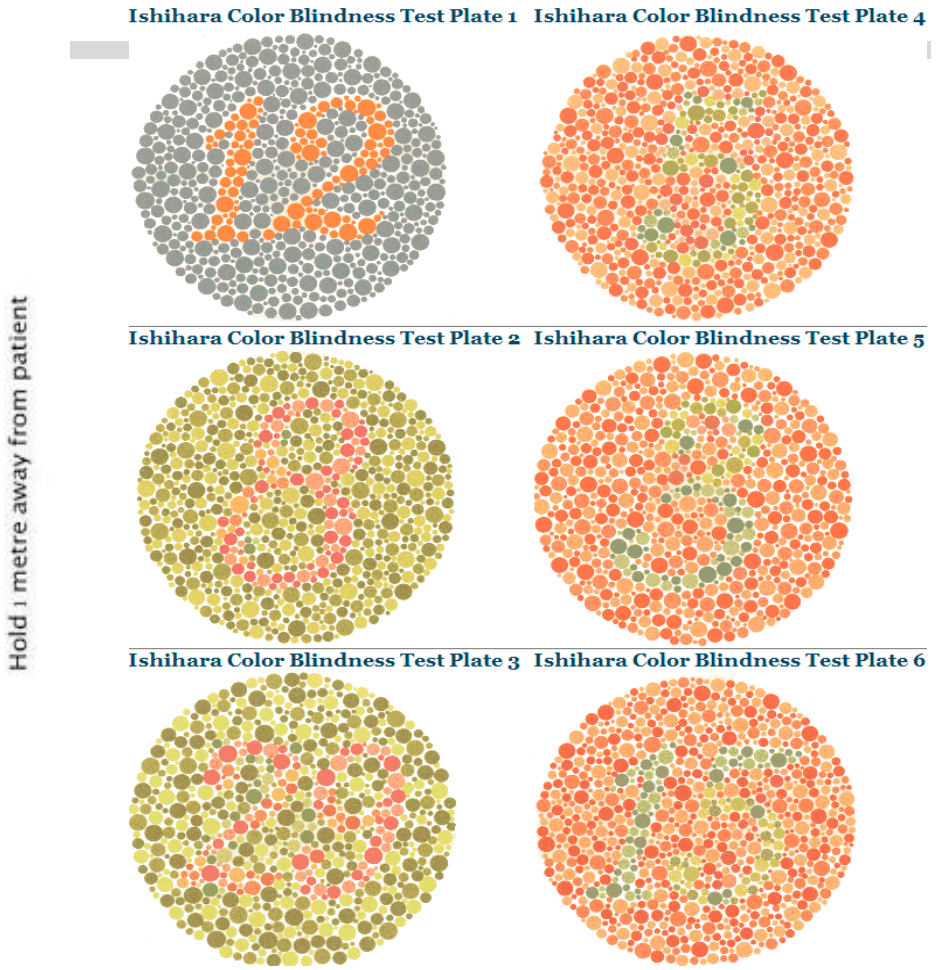
Modified EndTB Severity Grading Scale for Adverse Events, version 4.0. Available at: http://endtb.org/resources/pharmacovigilance or https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf

Management of optic neuritis

- Stop medication (Lzd, E) at the earliest suspicion

Example: Patients with limited visual acuity (less than 20/40 or 6/12) or an abnormal color vision test on follow up visits should be referred to the ophthalmologist for an assessment.

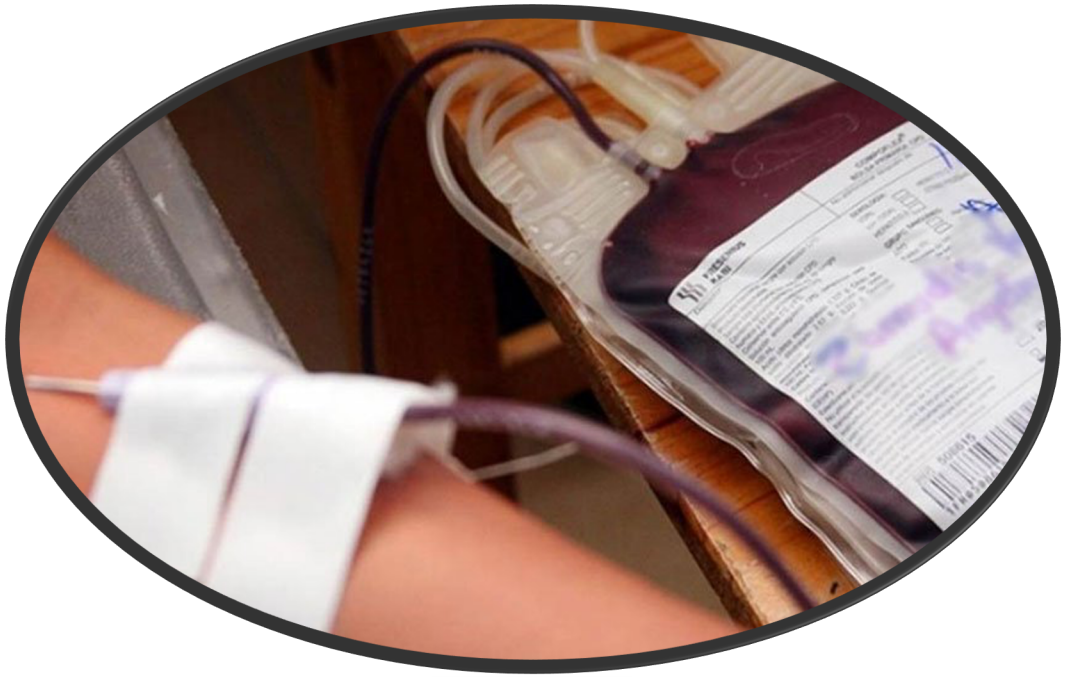
Visual acuity test



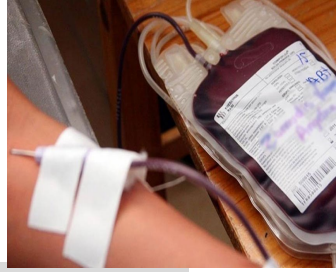
Ishihara color test

Myelosuppression

- Anemia
- Neutropenia
- Thrombocytopenia

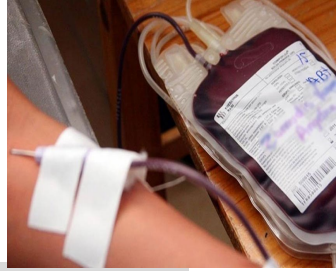


Myelosuppression



- Experienced by 47% of the patients in the Nix-TB study (anemia)
- Generally occurred within the first 3 months of treatment and could be managed with Lzd dose reduction or interruption
- There is some evidence that adding pyridoxine to the BPaL regimen will prevent myelosuppression
- Check for other causes of anemia (TB, iron-deficiency, occult GI bleeding etc.), although these are less likely to occur in the middle of treatment, especially if the patient is clinically improving.

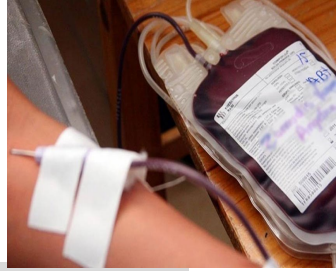
Severity grading and management of myelosuppression



Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Hemoglobin	10.5 - 9.5 g/dL	9.4 – 8.0 g/dL	7.9 – 6.5 g/dL	< 6.5 g/dL
Platelets	99,999- 75,000/mm^3	74,999- 50,000/mm^3	49,999- 20,000/mm^3	< 20,000/mm^3
While blood cells	<LLN - 3,000/mm^3	<3,000 - 2,000/mm^3	<2,000 - 1,000/mm^3	< 1,000 /mm^3
Absolute neutrophil count	1500 - 1000/mm^3	999 - 750/mm^3	749 - 500/mm^3	<500/mm^3

EndTB Severity Grading Scale for Adverse Events, version 5.0.
Available from: http://endtb.org/resources/pharmacovigilance

Management of myelosuppression

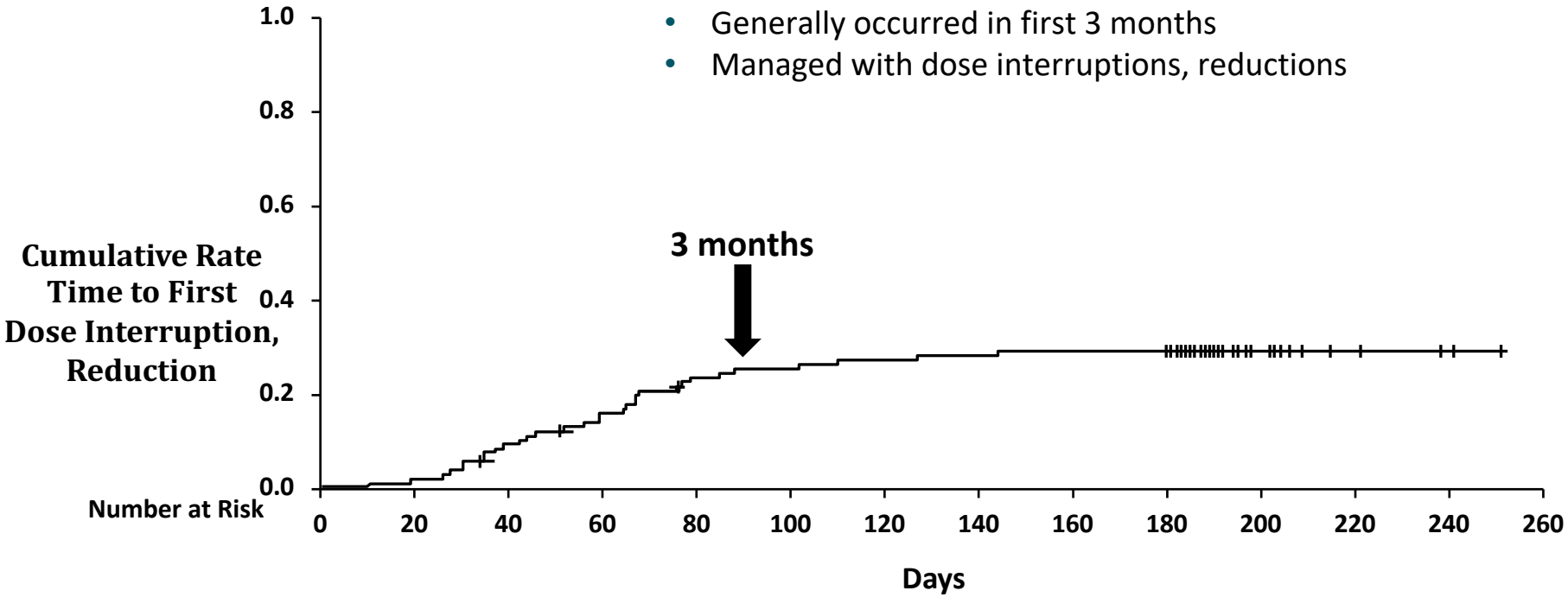


	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Action	Monitor carefully, do weekly FBC and **consider reduction** of Lzd dose to 600 mg or 300 mg daily.	Monitor carefully, do weekly FBC and **consider reduction** of Lzd dose to 600 mg or 300 mg daily. In case of **Grade 2 neutropenia, stop Lzd . Restart** at reduced dose once toxicity has decreased to Grade 1.	**Stop Lzd immediately. In case of Grade 3 anemia**, consider EPO. **Restart** at reduced dose once toxicity has decreased to Grade 1 or consider to stop Lzd permanently	**Stop Lzd immediately.** Hospitalize patient and consider blood transfusion or EPO. **Restart** at reduced dose once toxicity has decreased to Grade 1 or consider to stop Lzd permanently.

EndTB Severity Grading Scale for Adverse Events, version 4.0. Available from: http://endtb.org/resources/pharmacovigilance

Onset of myelosuppression during Nix-TB study

- Generally occurred in first 3 months
- Managed with dose interruptions, reductions



Source: Dr. F. Conradie: NiX-TB trial experience: safety reporting and recommendations for programmatic implementation of the regimen. The 50th Union World Conference on Lung Health; 2019 Nov 1; Hyderabad India.

Summary

- Importance of vigilant monitoring and prompt aggressive management of AEs in DR-TB treatment
- Standard severity grading scales can help find the appropriate management option
- Health care providers need to be equipped with knowledge to manage expected AEs

Thank you

ACKNOWLEDGEMENTS

Agnes Gebhard, Mamel Quelapio, Inge Koppelaar, Fraser Wares, Ieva Leimane, Mansa Mbenga

This presentation was developed by KNCV TB Foundation with support of the TB Alliance, and uses elements from new WHO policies guidance on the use of new drugs for the treatment of DR-TB

www.kncvtbc.org

Funding for LIFT-TB

Leveraging Innovation for Faster Treatment of Tuberculosis

KOICA
Korea International Cooperation Agency

Ministry of Foreign Affairs

TB Alliance