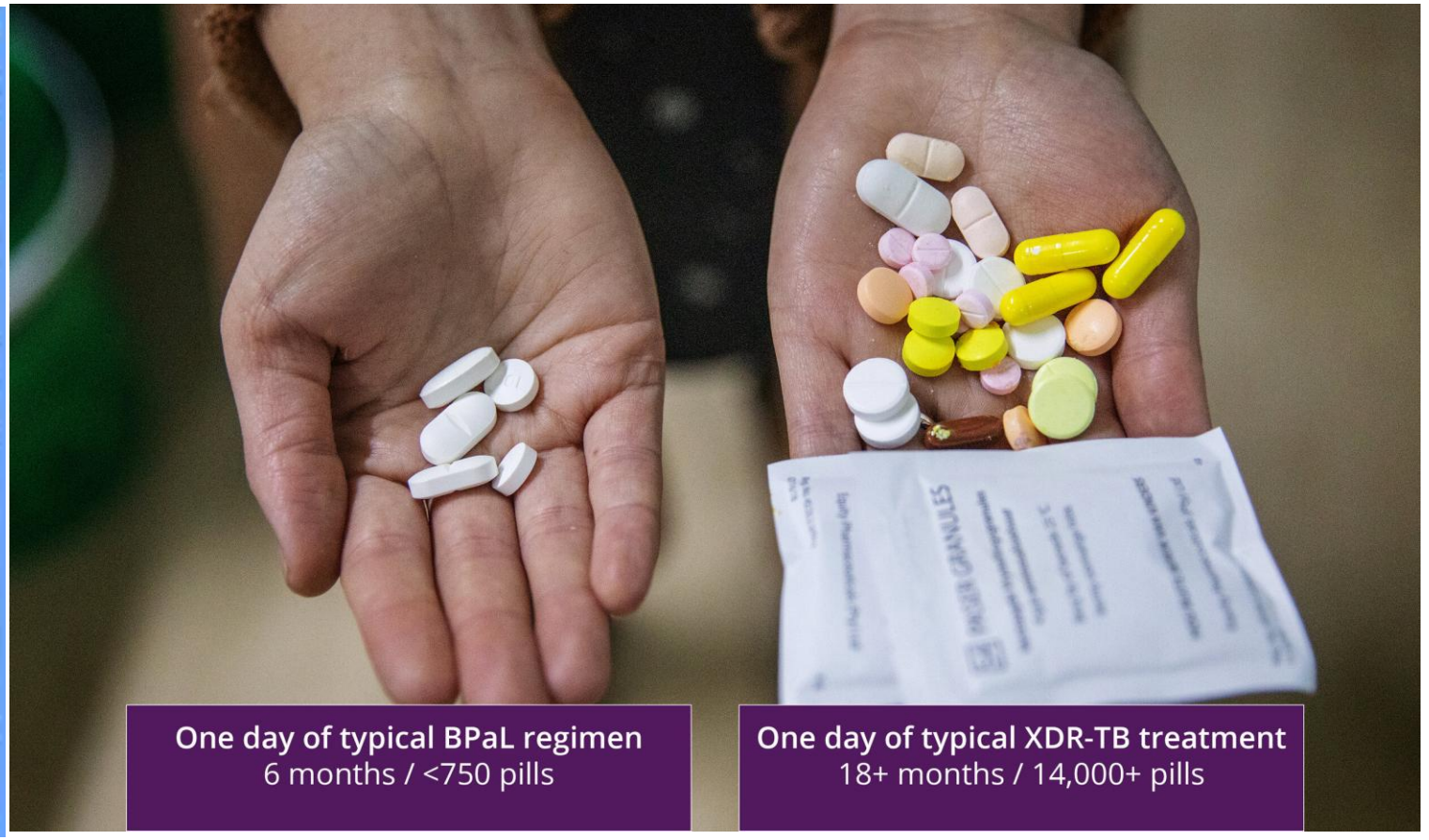
# Adverse events & aDSM framework.

**NTEP**

# *Outline*

- Brief review and major publications
- Severity of AEs and attributable criteria
- AEs of drugs in various trials using BDQ and Pretomanid
- Various ADRs and their management
- aDSM framework
- Conclusions

# *The new era!*



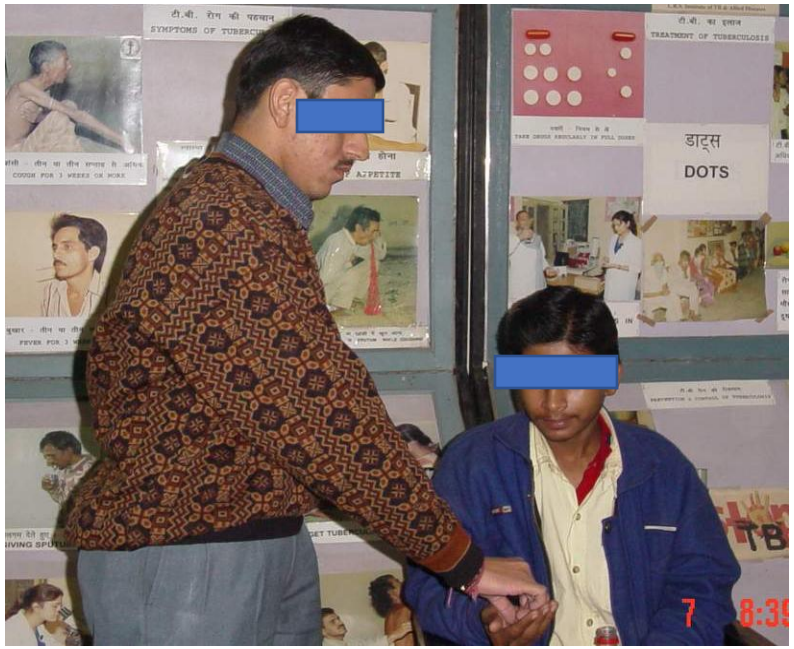

HRZE / HRE – 6 months

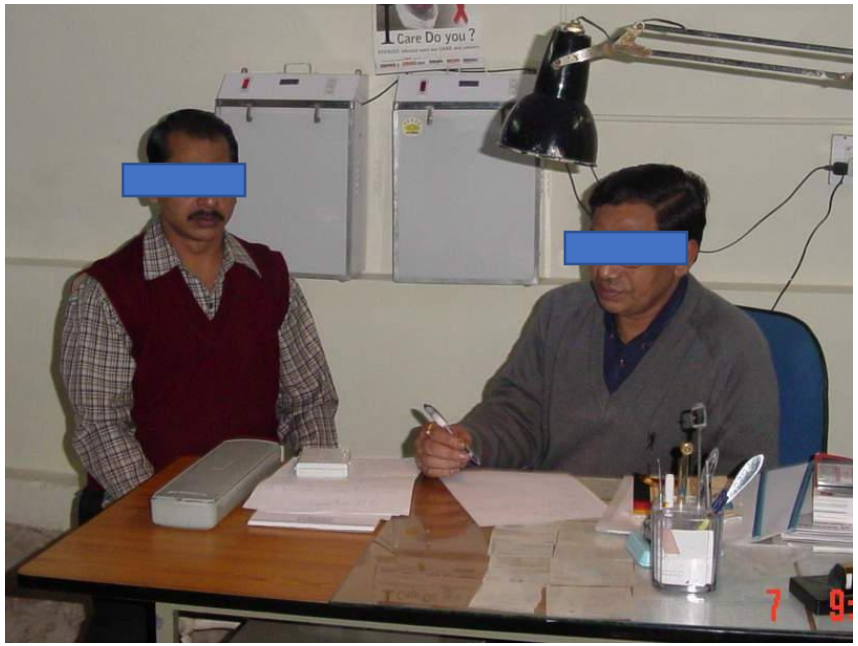
BPaLM – 6 months

XDR-TB: 18m

# *Coordination between patients and Providers*

Good coordination between patient and PMDT system can solve many problems



# European Respiratory Society Monograph 2018

Chapter 12

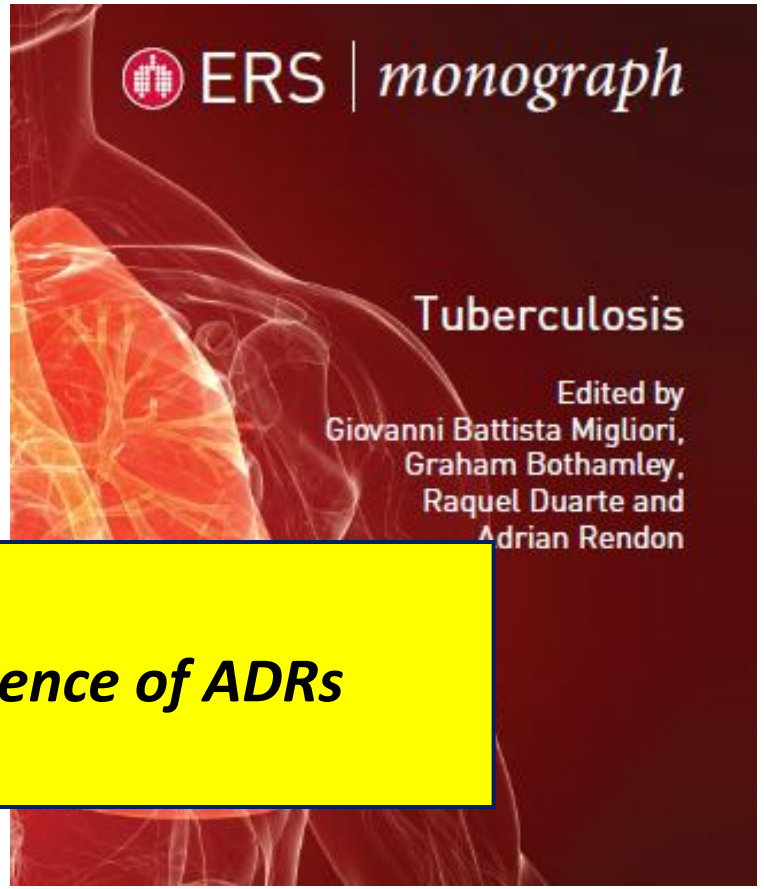
## Adverse anti-tuberculosis drug events and their management

José A. Caminero[1,2], Paula Lasserra[3,4], Alberto Piubello[2,5] and Rupak Singla[6]

It is currently possible to cure TB, but multiple drugs are required over a long term, and both of these factors produce adverse drug reactions (ADRs). ADRs can be caused by all anti-TB drugs but are much more frequent with second-line drugs. Fortunately, most

most adequate management in each situation are outlined.

**Cite as:** Caminero JA, Lasserra P, Piubello A, *et al.* Adverse anti-tuberculosis drug events and their management. *In:* Migliori GB, Bothamley G, Duarte R, *et al.*, eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society, 2018: pp. 205–227 [https://doi.org/10.1183/2312508X.10021617].




- ***Articles on ADR with ATT drugs***
  - ***11-70% ADR are observed - vide variations in occurrence of ADRs with SL drugs.***

# *Lancet Respir Med 2020;8(4):383-94*

## Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis

***-IPD of 9178 pts among 35 (out of 50) studies across globe (largest ever cohort analysed)***

**-Drugs with lowest incidence of ADRs leading to stoppage of drug**

**Fluoroquinolones, Clofazimine & Bedaquiline**

**-Drugs with higher incidence of ADRs leading to stoppage of drug**

**Linezolid, Second line injectables & PAS**

***Table for toxicity is in the subsequent slide.***

pir Med 2020
Online
March 16, 2020
https://doi.org/10.1016/
S2213-2600(20)30047-3
See Online/Comment

deafness, and in some instances can lead to death. Our aim was to estimate the absolute and relative frequency of adverse events associated with different tuberculosis drugs to provide useful information for clinicians and tuberculosis programmes in selecting optimal treatment regimens.

# *WHO guidelines 2020: SAEs leading to permanent discontinuation or grade 3-5 severity*

| **Medicine** | **Absolute risk of AE** | |
|---|---|---|
| | **Median %** | **95% credible interval** |
| Bedaquiline | 2.4% | [0.7,7.6] |
| Moxifloxacin | 2.9% | [1.4,5.6] |
| *Amoxycillin-Clavulanic acid* | 3.0% | [1.5,5.8] |
| Clofazimine | 3.6% | [1.3,8.6] |
| Ethambutol | 4.0% | [2.4,6.8] |
| Levofloxacin | 4.1% | [1.9,8.8] |
| Streptomycin | 4.5% | [2.3,8.8] |
| Cycloserine / terizidone | 7.8% | [5.8, 10.9] |
| *Capreomycin* | 8.4% | [5.7, 12.2] |
| Pyrazinamide | 8.8% | [5.6, 13.2] |
| Ethionamide / prothionamide | 9.5% | [6.5, 14.5] |
| Amikacin | 10.3% | [6.6, 17.0] |
| *Kanamycin* | 10.8% | [7.2, 16.1] |
| *p*-aminosalicylic acid | 14.3% | [10.1,20.7] |
| *Thiacetazone* | 14.6% | [4.9, 37.6] |
| Linezolid | 17.2% | [10.1,27.0] |

# Severity criteria of AEs

**Mild**

Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Moderate**

Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

**Severe**

Sufficient discomfort is present to cause interference with normal activity.

- The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject, e.g. laboratory abnormalities.
- Safety assessment measure is the proportion of patients experiencing a Grade 3 or greater adverse event, as defined by DAIDS (Division of AIDS) criteria during treatment and follow-up.

Ref for DAIDS criteria: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

# Serious adverse event

- Any untoward medical occurrence that at any dose:
  - **results in death**;
  - is **life-threatening** (subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe);
  - requires **inpatient hospitalization** or prolongation of existing hospitalization;
  - results in persistent or significant **disability/incapacity**;
  - is a **congenital anomaly/birth defect**;
  - is a **suspected transmission of any infectious agent via a medicinal product**; and
  - is **medically important**. (require intervention to prevent one of other outcomes listed in the definition above. These is usually considered serious.)

# Attribution definitions

| | |
|---|---|
| **Not related** | • AE that is not related to the use of the drug. |
| **Doubtful** | • AE for which an **alternative explanation is more likely**, e.g. concomitant drug(s), concomitant disease(s) or the relationship in time suggests that a causal relationship is unlikely. |
| **Possible** | • AE that might be **due to the use of the drug**. An alternative explanation, e.g. concomitant drug (s) or concomitant disease (s) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded. |
| **Probable** | • AE that **might be due to use of the drug**. The **relationship in time is suggestive**, e.g. confirmed by de-challenge. An alternative explanation is less likely, e.g. concomitant drug (s), concomitant disease (s). |
| **Certain (very likely)** | • AE that is listed as a **possible adverse reaction and cannot be reasonably explained by an alternative explanation**, e.g. concomitant drug (s), concomitant disease (s). The relationship in time is suggestive, e.g. confirmed by dechallenge and rechallenge. |

# *Adverse drug reactions to drugs used in DR-TB*

| Adverse Drug Events | Drugs |
|---|---|
| • QT prolongation | **Bdq, FQ, Cfz, Dlm, Pa** |
| • Rash, allergic reaction and anaphylaxis | **Any drug** |
| • Gastrointestinal symptoms | **Eto, PAS, Z, E, Bdq, Cfz, Lzd, FQs** |
| • Diarrhoea and/or flatulence | **PAS, Eto** |
| • Hepatitis | **Z, Eto, PAS, Bdq** |
| • Giddiness | **Am, Eto, FQ and/or Z** |
| • Haematological abnormalities | **Lzd** |
| • Hypothyroidism | **Eto, PAS** |
| • Arthralgia | **Z, FQ, Bdq** |
| • Peripheral neuropathy | **Lzd, Cs, Am, FQ, rarely Eto, E** |
| • Headache | **Bdq, Cs** |
| • Depression | **Cs, FQ, Eto** |
| • Psychotic symptoms | **Cs, H, FQ,** |
| • Suicidal ideation | **Cs, Eto** |
| • Seizures | **Cs, H, FQ** |

| Adverse Drug Events | Drugs |
|---|---|
| • Tendonitis and tendon rupture | **FQ** |
| • Nephrotoxicity (renal toxicity) | **Am** |
| • Vestibular toxicity (tinnitus and dizziness) | **Am, Cs, FQs, Eto, Lzd** |
| • Hearing loss | **Am** |
| • Optic neuritis | **E, Lzd, Eto, Cfz,** |
| • Metallic taste | **Eto, FQs** |
| • Electrolyte disturbances (Hypokalaemia and Hypomagnesaemia) | **Am** |
| • Gynaecomastia | **Eto** |
| • Alopecia | **Eto** |
| • Superficial fungal infection and thrush | **FQ** |
| • Lactic acidosis | **Lzd** |
| • Dysglycaemia and Hyperglycaemia | **Eto** |

# Pretomanid (with Linezolid)

- The Pretomanid (Pa) has not been given alone. The ADRs for Pa have been observed along with Lzd only.
- **Most Common ADRs:**
  - **Peripheral Neuropathy**
  - **Haematological Abnormalities**
  - **Visual Impairment (**especially when used with Linezolid (Lzd)
  - **QT interval prolongation**
- **Other ADRs:**
  - Acne, Nausea, Vomiting, Headache, Increased transaminases, Dyspepsia, Rash, Pruritus, Abdominal pain, Pleuritic pain, Increased gamma-glutamyl transferase, Lower respiratory tract infection, Hyperamylasemia, Hemoptysis, Back pain, Cough, Hypoglycemia, Abnormal loss of weight, and Diarrhoea

# *Linezolid*

- **Peripheral neuropathy**
- **Myelosuppression**
- **Anemia**
- **Optic neuritis**
- *Lactic acidosis*
- *Serotonin syndrome*
- Convulsions
- Anaphylaxis
- Arrhythmia
- Pseudomembranous colitis

# *Bedaquiline*

## Bedaquiline

- **QTc prolongation**
- Acneiform skin lesions
- Liver enzymes elevation
- Gastritis and vomiting
- Psychiatry  & Neurological complaints
- Auditory and vision problems
- Haemoptysis

# *Moxifloxacin*

Quinolones

- GI symptoms- diarrhoea, vomiting
- Dizziness, convulsions
- Phototoxicity, photosensitivity
- Tendinitis
- Skin rash
- Arthralgia
- **QT prolongation:** more with moxifloxacin, less with Levofloxacin

# *Cardiotoxicity*

# *QT interval prolongation*

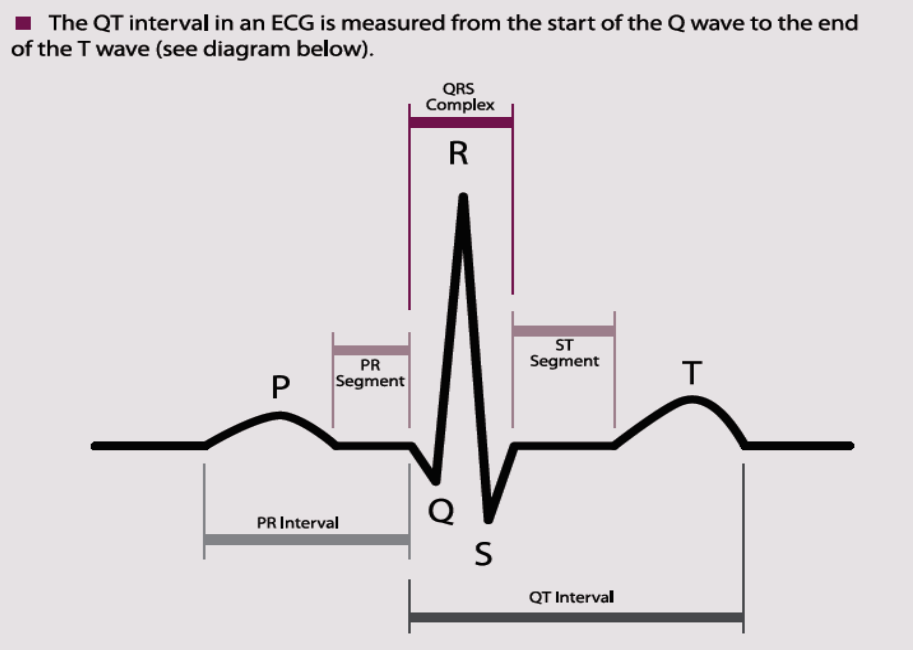
- Suspected agent(s): Bdq, FQ, Dlm, Pa, Cfz

-QT interval is measured from the start of the QRS complex to the end of the T wave

-QT intervals need to be corrected for heart rate

-Various formulas to calculate corrected QTc:

1. **Bazzet's formula ($QTcB=QT/RR^{1/2}$)**
2. **Fridericia's formula ($QTcFri=QT/RR^{1/3}$)**
3. Framingham formula ($QTcFra=QT+0.154\ (1-RR)$)




**Values above QTc fridericia correction (QTcF) 450ms in male and 470ms in female are referred to as prolonged** & they are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening.

**-Most of ECG machines give reading as per Bazzet's formula**
**-Usually QTc by Bazzet's formula gives higher Reading than Fridericia formula-**

# *QT prolongation*

## Suspected agent(s): **Bdq, FQ, Cfz, Dlm, Pa**

- **FQ may cause prolong**ation of the QTcF
  - Mfx and Gfx cause the greatest QTcF prolongation
  - Lfx and Ofx have a lower risk
- QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and sudden death. Monitoring of ECG is essential during course of treatment

- **High risk factors for QTc prolongation:** dyselectrolyemia (Low serum levels of potassium, calcium and magnesium), renal failure, hepatic failure, malnutrition, diabetes, thyroid dysfunction, underlying heart diseases etc.
- **If no risk factor at baseline & QtcF <450 in males & <470 in females: No need to admit the patient and just perform ECG at baseline, at 2 weeks, then monthly intervals**

***450 for males and 470 for females is the cut-off to start any regimen.***
***For QTcF prolongation 450 is the cut off for both males and females.***

# *Management of QT prolongation*

| Normal Value | Grade 1 (Mild) | Grade 2 (Moderate) | Grade 3 (Severe) | Grade 4 (Life threatening) |
|---|---|---|---|---|
| **QTcF (M: <450, F < 470)** | **M: 450-480 ms F: 470-480** | **481-500 ms** | **> 500 ms on two separate ECGs** | **> 500 ms and life-threatening consequences** |
| Condition | Asymptomatic | Asymptomatic, transient rhythm abnormality | Recurrent, persistent, symptomatic arrhythmia | Unstable dysrhythmia |
| Action | Check electrolytes and correct it, as necessary<br>Monitor ECG more closely.<br>Cont. drugs | Check electrolytes.<br>a. If abnormal, hold all QTcF prolonging drugs and correct the electrolytes before restarting them. Monitor ECG<br>b. If normal, cont. drugs, monitor ECG | Consider hospitalization, hold QTcF prolonging drugs and correct electrolytes as necessary<br>Repeat ECG after 24 hours and reintroduce the drugs if QTcF remains below 500 ms | -Hospitalize and replete electrolytes as necessary<br>-Stop the offending drug<br>-Repeat ECG after 24 hours |

# *Management of prolonged QTcF during treatment with shorter/longer oral/BPaLM MDR-TB regimen*

**Instruction applying for the whole algorithm if QTcF is 450 ms or above**

- Check serum K, Mg, Ca corrected for albumin;
- Evaluate the patient for factors like malnutrition, LFT, RFT, diabetes, Hypothyroidism etc. prior to taking decision
- When QTcF does not return to 470 ms even after discontinuation of the QTcF prolonging drugs or increased after re-introduction, decision to discontinue the suspected drugs or regimen is in the purview of the DR-TBC committee.

# Management of prolonged QTcF during treatment with BPaLM/ Shorter/ Longer oral MDR- TB regimen

Instruction applying for the whole algorithm if **QTcF** is **450** or above

1. Check S. Potassium (K), Calcium (Ca), Magnesium (Mg) corrected for albumin
2. Consider abnormalities for thyroid function
3. When QTcF does not remain to 470ms even after discontinuation of the QTcF prolonging drugs or increased after re-introduction, decision to continue the suspected drug or regimen is in the purview of DR- TB committee. Evaluate the patient for malnutrition, diabetes, LFT, RFT, etc prior to taking decision.

If **QTcF 480- 500ms**, repeat ECG daily (atleast twice a week and check S. electrolytes daily (K, Mg, Ca)

If **QTcF ≥500ms** irrespective of electrolytes

Electrolytes WNL and QTcF <500ms

low electrolytes

Continue with drugs and repeat ECG twice a week

Withhold Cfz, FQ, DLM/ Pa and BDQ. Correct Electrolytes, monitor QTcF daily

**Electrolytes WNL and QTcF < 470ms (2 consecutive ECG's 24hrs apart), restart BDQ and repeat ECG daily**

**Electrolytes WNL and QTcF < 470ms (2 consecutive ECG's 24hrs apart), restart FQ and repeat ECG daily**

**Electrolytes WNL and QTcF < 470ms (2 consecutive ECG's 24hrs apart), restart Cfz and repeat ECG daily**

**Electrolytes WNL and QTcF < 470ms (2 consecutive ECG's 24hrs apart), restart DLM/Pa and repeat ECG daily for 1 week**

Serial addition of drugs should be done every 3- 4 days with regular monitoring

# Management of prolonged QTcF during treatment with BPaLM/ Shorter/ Longer oral MDR- TB regimen

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Electrolytes WNL and QTcF <500ms

low electrolytes

**Sequence of reintroduction of drugs (to be done every 3-4 days)**
**- Bedaquiline**
**- Fluoroquinolone**
**- Clofazimine**
**- Pa / Delamanid**

Continue with drugs and r… ECG twice a week

…Pa and BDQ. Correct Electrolytes,

**Electrolytes WNL and QTcF < 470ms** …ily

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Serial addition of drugs should be done every 3- 4 days with regular monitoring

# *Hepatotoxicity*

## Hepatitis

Suspect agent(s): Z, H, R, Eto, PAS, Bdq, Pa

- ***High risk factors for hepatitis include:***
  - Old age
  - Malnutrition
  - Alcoholism
  - Pre-existing liver diseases
  - Pregnancy
  - Concomitant use of 2/3 hepatotoxic drugs
- **BPaLM can be administered to patients with mild to moderate hepatic impairment**, but should be avoided in patients with severe hepatic impairment

# *Hepatitis*

Suspect agent(s): Z, H, R, Eto, PAS, Bdq, Pa

- In cases where **patient is very sick** eg., meningitis, extensive diseases; one can stop all ATT drugs. Give at least three non-hepatotoxic medications (e.g. injectable agent, FQ and Cs). **Don't give this regimen for very long**
- Where **patient is not seriously ill** and one can wait, hold all anti-TB drugs
- Once **enzyme level improves**, reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing enzymes every three days
- **Eliminate other potential causes of hepatitis** (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that are identified

# Management of hepato-toxicity during treatment with BPaLM/shorter/ longer oral MDR/RR-TB regimen.

Enquire other medications as well as alcohol intake. Investigate for other causes of hepatitis. If symptoms or transaminase are abnormal or don't resolve, refer to nodal DR TB Centre. Consider if FQ is also causing liver function abnormality.

AST or ALT elevation< 5x ULN, with normal bilirubin with asymptomatic patient.

Continue with all drugs, monitor clinical symptoms, ALT/AST and bilirubin levels every 2 weeks till resolution.

Continue with all the drugs

AST or ALT elevation ≥ 5x ULN, with normal bilirubin OR
AST or ALT elevation ≥3x ULN accompanied by bilirubin ≥2x ULN, OR
Symptomatic patient.

1. Withhold BPaLM regimen.
2. Withhold $H^h$ , Z & Eto* in case of shorter oral MDR/RR-TB regimen.
3. Withhold Bdq, Z* , Eto * and PAS * in case of longer oral M/XDR- TB regimen.

Monitor clinical symptoms, AST, ALT and bilirubin once a week

**Improvement**

If AST and ALT decreases to ≤2x ULN, restart full doses of withheld drugs in the allocated regimen gradually in the following order:
1. Lzd+ Mfx, Bdq Pa in case of BPaLM regimen.
2. $H^h$ , Z in case of shorter oral MDR/ RR-TB regimen.
3. BDQ, Z *, Eto * and PAS * in case of longer M/XDR-TB regimen

Monitor AST and ALT every 3 days after each reintroduction to ensure no deterioration before re-introducing the next drug.

**If used Introduction can be tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms*

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Monitor clinical symptoms, AST, ALT and bilirubin once a week

**No Improvement**

**Deterioration**

Shift the patient to the longer oral M/XDR-TB regimen if any drug needs to be permanently stopped in BPaLM/ shorter oral MDR/RR-TB regimen. Also, if the patient is no longer M/XDR regimen, modify regimen from replacement sequence if any drug is to be permanently stopped.

**If used Introduction can be tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms*

# Management of hepato-toxicity during treatment with BPaLM/shorter/ longer oral MDR/RR-TB regimen.

Enquire other medications as well as alcohol intake. Investigate for other causes of hepatitis. If symptoms or transaminase are abnormal or don't resolve, refer to nodal DR TB Centre. Consider if FQ is also causing liver function abnormality.

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1. Withhold BPaLM regimen

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***Shorter Oral RR/MDR-TB Regimen***

Reintroduction sequence:

Bdq, $H^h$, Z, Eto

If not tolerated, shift to oral longer regimen

***Longer Oral M/XDR-TB Regimen***

Reintroduction sequence:

Bdq, *Z, *Eto, *PAS

(*if patient is on these drugs)

***BPaLM Regimen***

Reintroduction sequence:

Lnz, Mfx, BDQ/Pa

If AS
in the
1. Lz
2. H
3. B

Monitor AST and ALT every 3 days after each reintroduction to ensure no deterioration before re-introducing the next drug.

XDR-

ter
e

modify regimen from replacement sequence if any drug is to be permanently stopped.

**If used Introduction can be tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms*

# *Haematological Toxicity*

# *Heamatological abnormalities*

## Suspect agent(s):Lzd, Rifampicin

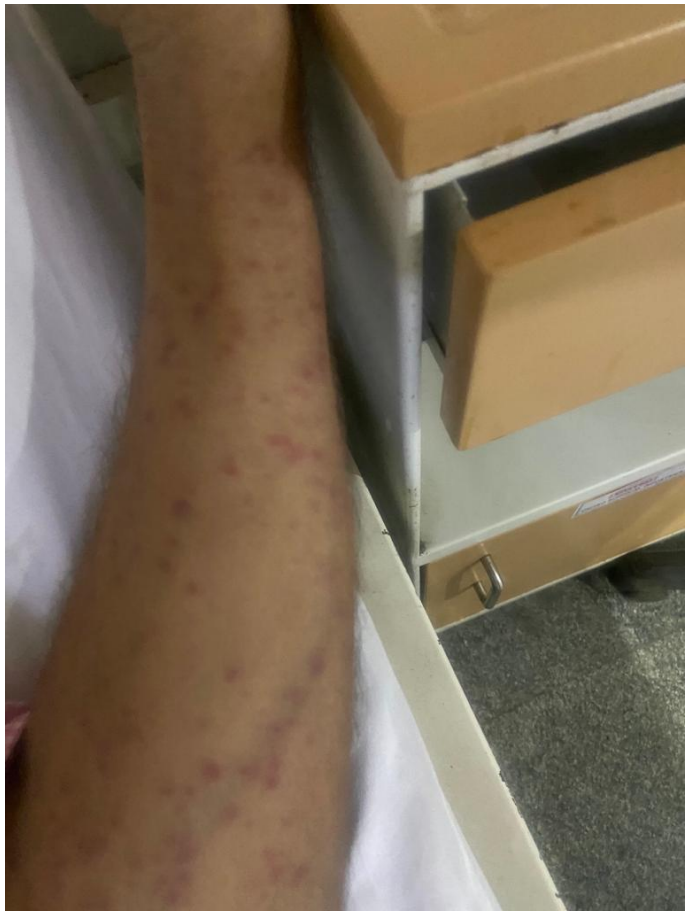
- If **myelosuppression** (suppression of white blood cells, red blood cells or platelets) **occurs:** stop Linezolid. Sometimes it **may be very fast decline of Hb**
- **Consider restarting with a lower dose of Lzd** (300 mg instead of 600 mg) if myelosuppression resolves and if Lzd is considered essential to the regimen
- **Consider non-drug related** causes of hematological abnormality
- Some patients respond well to an initial blood transfusion that raises HB above 8gm/dl

### Point to note –

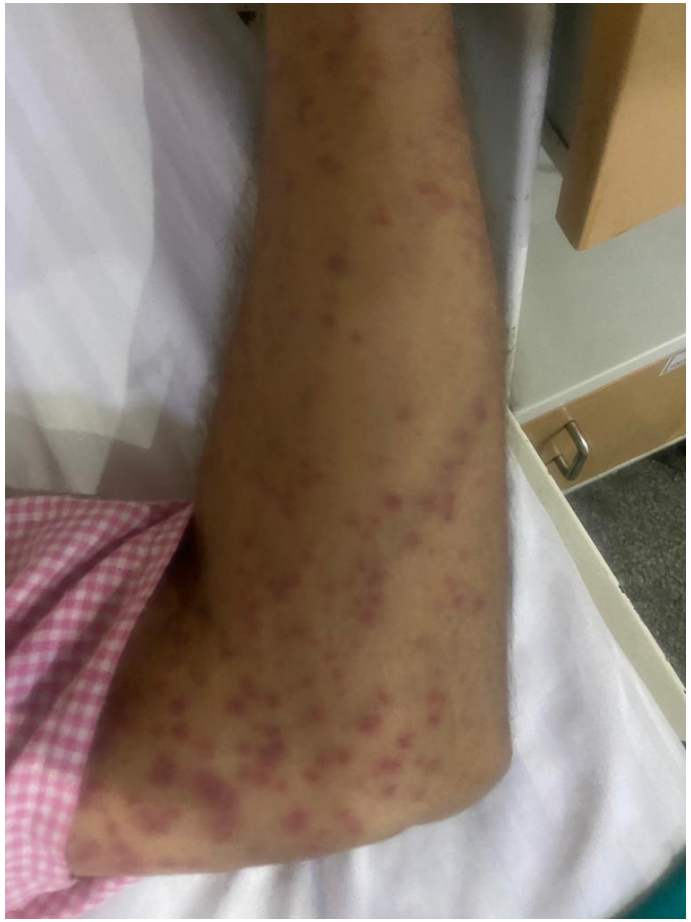
- ✓ Lzd containing regimen must not be offered to patients with pre- treatment serum Hb below 8gm/dl, that cannot be rapidly corrected
- ✓ Hematological abnormalities (leukopenia, thrombocytopenia, anemia, red cell aplasia, coagulation abnormalities and eosinophilia) can rarely occur with several other anti-TB drugs, e.g. **rifampicin induced thrombocytopenia**

# *Rifampicin induced Thrombocytopenic purpura…1*

**Other than Lzd, Rifampicin is another drug causing hematological abnormalities**



Day 5



Day 7

# *Peripheral neuropathy*

# *Peripheral neuropathy*

## Suspect agent(s): ***Lzd, Cs, H***, Am, FQ, rarely Eto and E

- **Risk factors for peripheral neuropathy** include diabetes, Low BMI, nutritional deficiency, HIV, alcoholism etc.
- **Look for (and train all peripheral workers) simple symptoms:**
  - **Numbness , Burning, prickly ( pins and needles)  feelings in the feet**
  - **Feel hurt when bed covers touch the skin.**
  - **Inability to distinguish hot or cold water while bathing**
  - **Slipping off of footwear without knowledge**
  - **Inability to place his soles on the ground.**
  - **Frequent sores or ulcers on the feet.**
  - **Worsening of symptoms at night or increase in leg pain while walking**

# *Peripheral neuropathy*

Suspect agent(s): ***Lzd, Cs, H***, Am, FQ, rarely Eto and E

- To prevent peripheral neuropathy all patients on NTEP regimen for MDR-TB should receive daily **pyridoxine**
- Commonest offending agent is Lzd, almost 60–70% of the patients on Lzd 600 mg/day may develop neuropathy.
- Early recognition of neuropathy symptoms and early dose reduction of Lzd helps to prevent the progression. I**f there is still no improvement, hold Lzd (don't delay)** and patient should be referred to Nodal DR-TB center & consult neurologist
- Correct any vitamin or nutritional deficiencies

# *Medical treatment of Peripheral neuropathy*

- Usually occurs later in treatment, while hematological abnormalities occur earlier in treatment
- Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms
- Pregabalin (75 mg) + methylcobalamine (750 mg) twice a day also used (take care of giddiness/sleepiness). Pregabalin dose upto 150-300 mg twice daily
- Gabapentin has been helpful for many individuals. Adults should be treated initially with a single dose of 300 mg on Day 1, increased to 300 mg twice a day on Day 2, and 300 mg 3 times a day on Day 3.
- Tab Gabapentin NT (a combination of Gabapentin 100 mg and Nortriptyline 10 mg) once daily, to be taken in the evening. May be increased upto Gabapentin/Nortriptyline (Tab Gabapentin NT 300 mg/10 mg)

# *Medical treatment of Peripheral neuropathy*

- **Treatment with tricyclic antidepressants** such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried (to be avoided with Bdq as mild MAO inhibitor: may cause Serotonin syndrome).
- **Duloxetine**:

  - Initiate **Cap Duloxetine 20 mg twice daily (BD) for 30 days, followed by once daily (OD) for the next 30 days.**

  - If no relief is seen with the BD dose within the first **15 days**, increase the dose to **20 mg three times daily (TDS)**.
- **Avoid Duloxetine with Linezolid as it** may cause Serotonin syndrome

- Refer to Nodal DR-TB center and to specialist for further management (may delay the treatment)

# Peripheral neuropathy screening tool

Annexure 2. Brief peripheral neuropathy screening tool (17)

| Patient Initials: | | | | | | | | Patient ID: |
|---|---|---|---|---|---|---|---|---|
| 1. Visit (Circle One) | All Subjects | Baseline | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 26 |
| | | 3 Month | | 6 Month | | 12 Month | | 24 Month |
| | 9 Month Treatment Only | Week 30 | | | Week 34 | Week 39 | | |
| | Other | Early Withdrawal | | | Unscheduled (For New or worsening peripheral neuropathy during treatment) | | | |
| 2. Date of assessment | | | | | | | | |

| Interference with Walking or Sleeping | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3. In the last 2 weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one) | | | | | | | | | | Yes | No |
| 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 | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 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.<br>• Enter a score for each symptom<br>• If a symptom has been present fin the past, but not since the last visit, enter '00 – currently absent'<br>• If a symptom has never been present, enter '11 – Always been Normal' | | | | | |
|  |  |  |  |  |  |
| 00<br>Very Happy,<br>No Symptoms | 02<br>Just a little bit | 04<br>A little more | 06<br>Even More | 08<br>A whole lot | 10<br>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? | | |

| Perception of Vibration | | |
|---|---|---|
| • Press the ends of a 128 Hz tuning fork together so the sides touch and let go. Place the vibrating tuning fork on the bony prominence on the patient's wrist to be sure that they can recognize the vibration or "buzzing" quality of the tuning fork.<br>• Again, press the ends of the tuning fork hard enough so that the sides touch and let go. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of the great toe and begin counting the seconds. Instruct the Subject to tell you when they stop feeling the vibration or "buzzing". Repeat for the great toe on the other foot.<br>Vibration Perception Grade Scale:<br>0 – Vibration felt for > 10 seconds (normal)<br>1 – Vibration felt for 6-10 seconds (mild loss)<br>2 – Vibration felt for 5 seconds or less (moderate loss)<br>3 – No feeling of vibration (severe loss)<br>9 – Unable to evaluate or did not assess | | |
| 7. Measured vibration grade of great toe DIP joint | Right | Left |
| | | |

| Deep Tendon Reflexes |
|---|

- The Annexure 2 – **Peripheral neuropathy screening tool.**
- ***Frequency*** – baseline, week 4, 8,12,16,20,26, 3month, 6-month, 12-month, 24 month, (if on treatment ) 9- month, week 30, week 34, week 39, or unscheduled (for new or worsening peripheral neuropathy during treatment )
- ***Categorisation*** – minimal ; modest and severe. (based on the interference to *walking / sleeping caused by this pain/ache or burning* )

- **Perception of vibration** – using 128 hz tuning fork.
- Grading of vibration perception
- Deep tendon reflex

# *Optic Neuritis*

# *Optic neuritis*

Suspected agent(s): **E, Lzd**, Eto, Cfz, H

- Symptoms: Blurred vision, loss of colour vision, visual field defects, decreased visual acuity

- Stop E and Lzd. Do not restart
- Refer patient to an ophthalmologist
- Condition usually reverses with cessation of the drug
- Improve diabetes control in diabetic patients

# *Lactic acidosis*

## Suspected agent(s): Lzd

- Normal levels: 0.5 to 2.2 millimoles per litre (mmol/L)

- Stop Lzd if lactic acidosis occurs.

**Point to note -** Lactic acidosis can be managed at the Nodal DR-TB center as per standard protocol and monitored with a blood test that measures lactic acid

- **General Symptoms**:
  - Nausea and vomiting
  - Abdominal discomfort or pain
  - Fatigue and weakness
  - Muscle pain or tenderness
  - Difficulty breathing or rapid, deep breathing (Kussmaul breathing)
- **Neurological Symptoms**:
  - Confusion or mental sluggishness
  - Dizziness or lightheadedness
  - Reduced alertness or even unconsciousness in severe cases
- **Cardiovascular Symptoms**:
  - Low blood pressure (hypotension)
  - Rapid heart rate (tachycardia)
- **Other Symptoms**:
  - Cold or clammy skin
  - Symptoms of shock in severe cases

# *Information to peripheral field workers*

| Drugs | Side effects |
|---|---|
| Bdq, Cfz, Mfx, Pa and DLM | Cardiac side effects: |
| Linezolid | anaemia, thrombocytopenia, peripheral neuritis and optic neuritis |
| Cycloserine: | Seizures, depression and suicidal tendency |
| Clofazimine | dark brown discoloration of the skin |
| Ethionamide, PAS | Hypothyroidism |
| Second line Injectables | hearing loss, giddiness, kidney damage |
| Z,H,R, Eto, BDQ, Pa: | Jaundice, nausea |

# Active drug safety monitoring (aDSM)

- Timely and intensive monitoring for identifying and managing adverse events are essential components of the PMDT services; this will help improve the patient's adherence to treatment, better treatment outcomes and reduce mortality
- Management of AE may require withholding or discontinuing the offending drug
- Proper training of staff and support to the patient are very important.
- Ancillary drugs should be made available to the patient free of cost.
- Timely, accurate and complete reporting and analysis of adverse events are required.
- Any SAE should be managed at the appropriate health facility level and reported in Ni-kshay within 24 hours by the health facility managing the SAE

# Reporting of AE & SAE…1

- All SAEs and AE's (non-serious adverse events) which are possibly, probably or very likely related to any anti-TB drug must be reported
- If pregnancy occurs during MDR-TB treatment, the regimen should be modified as per PMDT guidelines
- Any death of a patient occurring during treatment, regardless of causality, must be reported as SAE and a verbal autopsy *(Annexure 30)* should be undertaken. HF doctor should carry out verbal autopsy for all DR-TB patient died during treatment.
- Patient should be questioned before starting treatment and at each subsequent consultation in order to obtain a detailed description of any sign of toxicity or ADR, which they might have experienced.

# Reporting of AE & SAE…2

- ***The standard prescribed formats for*** **–**
  - aDSM – treatment initiation form to be filled up for every patient for every DR-TB episode
  - aDSM – treatment review form need to be maintained for all patients with SAE.
  - NTEP will ensure that strict aDSM is implemented by all NDR-TBC and district physicians for ambulatory patients.
  - The primary responsibility of filling up the forms will be with nodal officer; SMO or MO should help
  - Ensure the data entry in Nikshay by SA at NDR-TBC and senior DR-TB TB-HIV supervisor at DDR-TBC centre; maintained in hard copies until ADR module active in Nikshay.
- Concerned DTO should make necessary arrangements if above staff posts are vacant

# Death audits

- Death audits using verbal autopsy as well as review of clinical records can be a valuable tool for understanding commonest causes of mortality and guide the program to optimize its service delivery mechanisms to address these identified causes.
- The doctor – HF in coordination with nodal/ district DR-TB sites should mandatorily review every patient of death of diagnosed DR-TB patients irrespective of treatment and record them. A template of 'NTEP verbal autopsy form' is placed as ***Annexure 30 (PMDT guidelines 2021)***.

# *Take Home Messages*

- ADRs are **common** with **drugs for DR-TB** management
- ADRs may be common cause of **premature termination of treatment** / **LTFU**
- All levels of HCW need **proper training** for **early identification, early treatment/referral** for appropriate management
- Ensure **local availability** or **linkages** with specialists
- Ensure availability of common ancillary drugs for managing ADRs
- Proper management of ADRs can **improve successful treatment outcome**

# THANK YOU