Ministry of Health and Family Welfare
Government of India

MDR TB Management

NTEP

Date:

Causes of DR-TB

Genetic mutation	Drugs (Inadequate supply or poor quality)	Providers/Programmes (Inadequate regimen)	Inadequate drug intake
Caused by random chromosomal mutations at predictable frequencies • **H** resistant bacilli 1 in 10^6, • **R** resistant bacilli 1 in 10^8, • **HR** resistant bacilli 1 in 10^{14}	• Non-availability of certain drugs (stock-outs or delivery disruptions) • Poor quality • Poor storage conditions • Wrong dosages or combination	• Unsupervised treatment • Absence of guidelines or inappropriate guidelines • Non-compliance with guidelines • Inadequate training of health staff • No monitoring of treatment • Poorly organized or funded TB control programmes	• Poor adherence • Lack of information • Non-availability of free drugs • Adverse drug reactions • Social & economic barriers • Malabsorption • Substance abuse disorders

Type of TB

- Drug susceptible TB (93%) – sensitive to first-line drugs
- Drug-resistant TB (7%)- it. includes
  - H mono/poly DR-TB – Isoniazid resistant / resistant to INH & first-line drugs other than Rifampicin
  - Multidrug resistant TB (MDR-TB) – Rifampicin resistance with or without Isoniazid resistance
  - Pre-extensively drug-resistant TB (Pre-XDR-TB) – MDR-TB with additional Fluoroquinolone resistance detected
  - Extensively drug-resistant TB (XDR-TB) – Pre-XDR-TB with resistance to Linezolid or Bedaquiline or both detected.

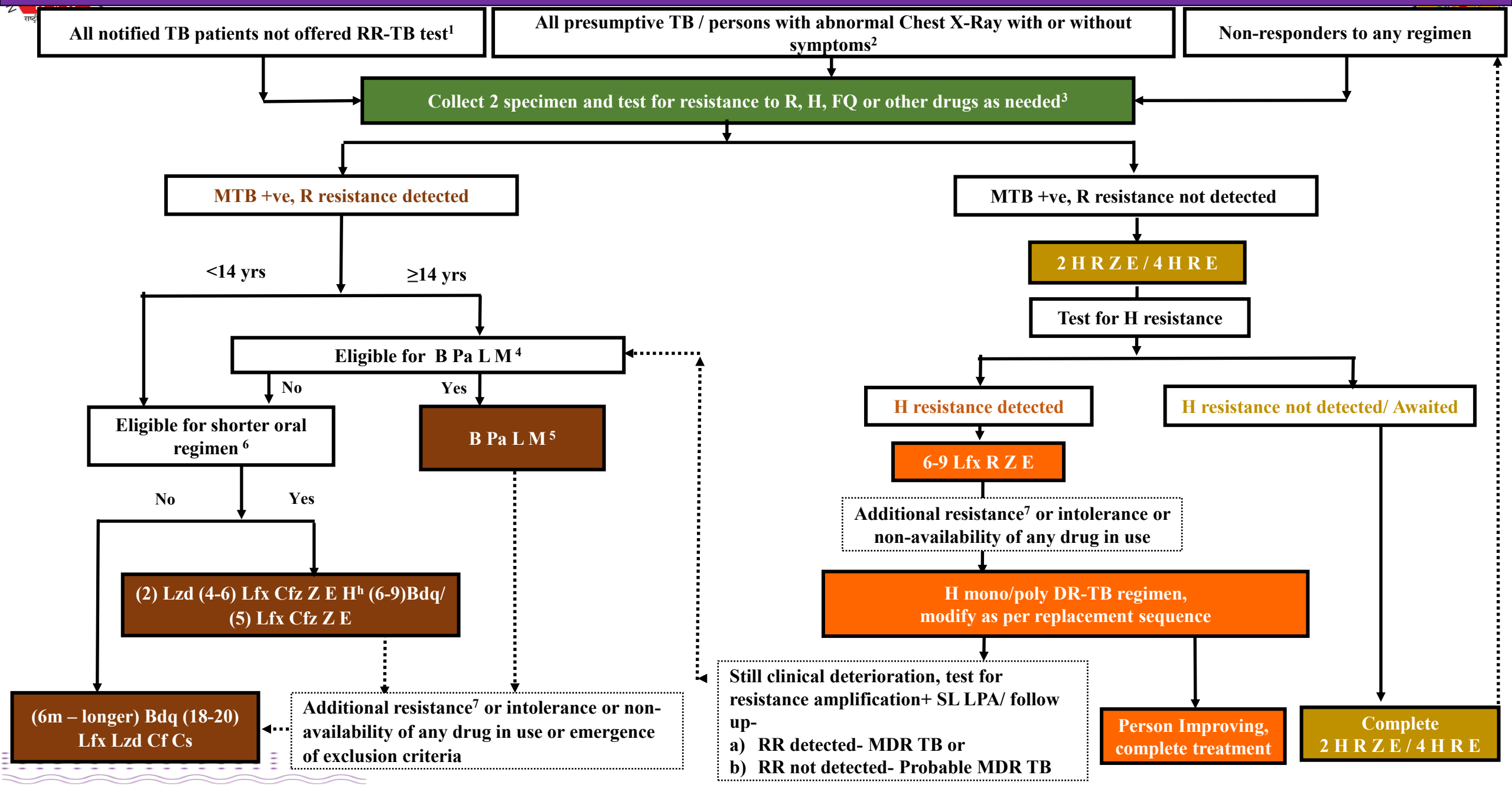
National Drug Resistance Survey - DST summary 2014-16

DST pattern	New cases	Previously treated (PT) cases	All TB cases
Total DST results available	3065	1893	4958
Susceptible to all drugs	2374 (77.46%)	1196 (63.18%)	3570 (72.01%)
Any drug resistance	691 (22.54%)	697 (36.82%)	1388 **(28.00%)**
MDR	87 (**2.84%**)	220 (11.62%)	307 **(6.19%)**
MDR + any FQ (Pre-XDR)	21 (24.14%)	46 (20.91%)	67 **(21.82%)**
Any Isoniazid resistance	**11.06%**	**25.09%**	

BPaLM/BPaL regimen introduction

Global Trials	• March 2020: Nix-TB trial results ($BPaL_{1200\ mg}$) • Jul 2021: ZeNix-TB trial results ($BPaL_{600\ mg}$) • May 2022: TB PRACTECAL trial results ($BPaL_{600\ mg}M$)
WHO recommendation	• Jun 2020: WHO guidelines on DRTB treatment update: Recommended BPaL regimen in OR • May 2022: WHO released rapid communication of key changes in treatment of DR-TB
ICMR study	• ICMR (NIRT) in collaboration with CTD and WHO India started a study on BPaL regimen in Nov 2020.
NTEG recommendation	• May 2022: NTEG recommended phase wise introduction of BPaLM/BPaL regimen in India • Dec 2022: Indian Guidelines developed in line with the WHO guidelines update
Approval process	• Dec 2022: File was moved for BPaLM/BPaL regimen for treatment of MDR/RR-TB. Hon'ble HFM desired Health Technology Assessment (HTA) • Aug 2023: Office Memorandum and policy brief received from ICMR

Integrated Diagnostic and Treatment Algorithm for Drug Susceptible and Resistant Tuberculosis



Integrated Diagnostic and Treatment Algorithm for Drug Susceptible and Resistant Tuberculosis

All notified TB patients not offered RR-TB test[1]

All presumptive TB / persons with abnormal Chest X-Ray with or without symptoms[2]

Non-responders to any regimen

Collect 2 specimen and test for resistance to R, H, FQ or other drugs as needed[3]

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Non-responders to any regimen

Collect 2 specimen and test for resistance to R, H, FQ or other drugs as needed[3]

MTB +ve, R resistance not detected

2 H R Z E / 4 H R E

Test for H resistance

H resistance detected

H resistance not detected/ Awaited

6-9 Lfx R Z E

Additional resistance[7] or intolerance or non-availability of any drug in use

H mono/poly DR-TB regimen, modify as per replacement sequence

Still clinical deterioration, test for resistance amplification+ SL LPA/ follow up-

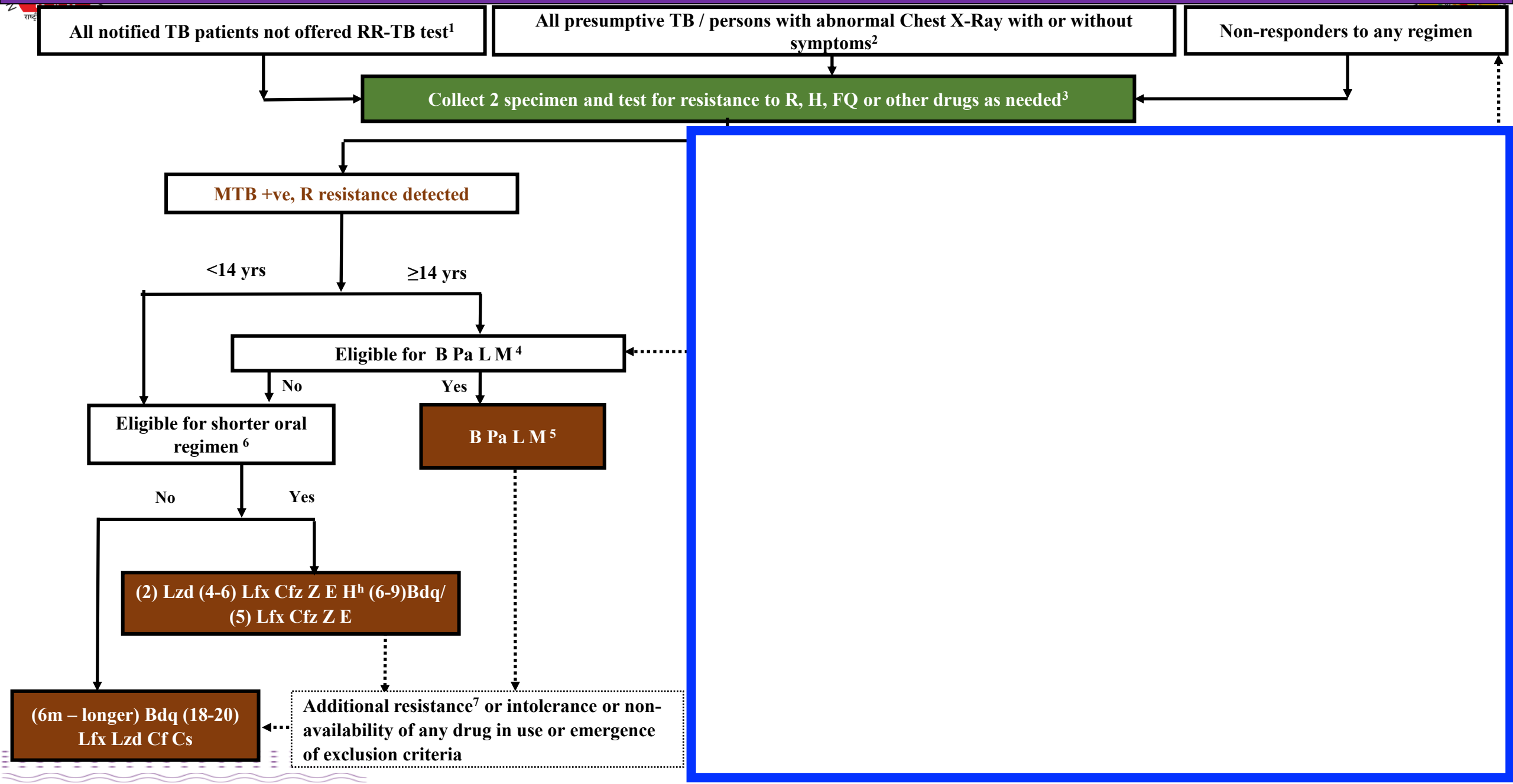
a) RR detected- MDR TB or

b) RR not detected- Probable MDR TB

Person Improving, complete treatment

Complete 2 H R Z E / 4 H R E

Integrated Diagnostic and Treatment Algorithm for Drug Susceptible and Resistant Tuberculosis



Pre-Treatment Evaluation (PTE) for MDR/ RR-TB

Clinical evaluation	Laboratory-based evaluation
• History and physical examination (including previous drug use, alcohol/substance abuse, family planning methods etc.) • Previous history of ATT taken, especially Bdq, Pa, Dlm and Lzd (defined as more than one month exposure). • A thorough clinical examination • Assess nutritional status [Height (m), Weight (kg), BMI] • Neurological evaluation, if required • Ophthalmic evaluation, visual acuity, and color vision test	• Random blood sugar (RBS) • HIV testing following counselling • Complete blood count (Hb, TLC, DLC, platelet count) • Liver function tests# • Serum electrolytes (Na, K, Mg, Ca) • Urine pregnancy test (in women of reproductive age group) • Chest X-ray • ECG • *# HBsAG and other viral markers (Hepatitis A, C and E) to be done in case of jaundice*

6-9m BPaLM-Inclusion & Exclusion Criteria for Eligibility

Inclusion Criteria

i. Persons with age **14** years and above, **New** microbiologically confirmed **MDR/RR-TB.**

ii. H/o exposure

   a. **less than one month** intake of Bdq, Lzd and/ or Pa in the past

   b. **more than one month** intake of Bdq, Lzd and/ or Pa and documented **sensitivity** to the drugs.

   c. Persons who had not failed treatment with Bdq or Lzd containing shorter or longer regimen, and sensitivity to the drugs are documented

iii. QTcF in ECG is ≤ 450 ms in males or ≤ 470 ms in females, OR

   In case abnormal serum electrolytes & QTcF > 450 in male or >470 in female, after correction of electrolytes, QTcF comes < 450 in male & <470 in female

iv. Women: -

   a. Non-lactating women, Lactating and not breast-feeding

   b. Non-pregnant, or pregnant women with <20 / <24 weeks gestation and willing for medical termination of pregnancy (as per MTP gazette notification)

Exclusion Criteria

i. Persons with age below **14 years**

ii. Person with documented resistance to Bdq, Lzd and/ or Pa.

iii. Persons with significant liver dysfunction [LFT (Liver enzymes and/ or total bilirubin) >**3xUpper Limit of Normal (ULN)]**

iv. People with **severe forms of extrapulmonary-MDR-TB** like CNS TB, spinal/ skeletal TB or disseminated TB

v. Persons with **significant Cardiac conduction abnormalities** in the heart- including structural heart disease, syncope, long QT syndrome, AV blocks, Reentry arrhythmias etc.

   i. Persons currently having uncontrolled cardiac arrhythmia that requires medication

   ii. Persons with history of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalemia, family history of long QT syndrome.

   iii. Persons with **normal serum electrolytes** and **QTcF > 450 ms** in males & **QTcF > 470 ms in** females in ECG, both at baseline

Or In case abnormal serum electrolytes, after correction of electrolytes, still QTcF > 450 in male & >470 in female

Hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to a patient receiving any QTc prolonging drugs.

Relative Contra-indications

Relative Contraindications	Notes
Concurrent use of medications that have known interactions or overlapping toxicities with BPaLM	• Use of strong inhibitors or inducers of cytochrome P450 enzyme* • Drugs that prolong the QT interval **(anti-fungals, antiarrhythmics, antipsychotics etc.)** • Currently on, or prior use within three days of treatment Drugs that increase serotonin levels and other serotoninergic-antidepressants/ tricyclic antidepressants • Monoamine Oxidase Inhibitors (MAOIs) or prior use within two weeks of treatment • Concomitant use of any drug known to induce myelosuppression • If a patient requires an oral magnesium-containing substance e.g. *magnesium trisilicate, magnesium sulphate* this must be dosed two hours separate from the fluoroquinolone.
Severe anaemia, thrombocytopenia or leukopenia	• Haemoglobin (Hb) level < 8.0 g/dL • Platelet count < 100 000/mm3 • Absolute neutrophil count < 750/mm3
Severe renal failure	• Serum creatinine > 3.0 × ULN • Owing to limited experience with the use of this regimen, caution should be exercised in patients with severe renal failure
Severe neuropathy	• Peripheral neuropathy of grade 3 or grade 4

6-9m BPaLM regimen: Baseline DST

- Since Bdq and Lzd resistance levels in India are low, the BPaLM regimen can be initiated in all the eligible MDR-TB patients irrespective of availability of baseline DST to these drugs. Modification of the regimen may be considered whenever the DST results are available.

6-9m BPaLM regimen: Drugs Doses

- Administered orally. All patients above 14 years of age receive these doses.
- There are no weight bands.
- Dosage are given below in table-

Bedaquiline	First Two Weeks	400 mg once daily	(4 × Bdq 100 mg tablets)
	Weeks 3rd-26/39*	200 mg three times a week	(2 × Bdq 100 mg tablets)
Pretomanid	Weeks one to 26-39*	200 mg daily	(1 × Pa 200 mg tablet)
Linezolid	Weeks one to 26-39*	600 mg once daily	(1 x 600 mg tablet)
Moxifloxacin	Weeks one to 26-39*	400 mg once daily	(1 x 400 mg tablet)

*Extension criteria will detailed in implementation considretation and treatment session

- Dose modification, treatment extension, follow up monitoring etc will be discussed in subsequent sessions.

Pyridoxine - Regimen, dosage and administration

- Pyridoxine (Pdx) will be administered as per weight band given below: (Reference: for the entire duration of treatment as per weight band in line with the Guidelines for PMDT in India -– 2021).

Drugs	**16-29 kg**	**>30 kg**
Pyridoxine (Pdx)	50 mg	100 mg

- Pyridoxine supplementation has been shown to reduce the incidence of neuropathy in patients, supporting its inclusion in treatment protocols to mitigate drug-induced neuropathy.
- Pyridoxine to be used in the BPaLM regimen to provide added protection against neuropathy.

BPaLM: Follow-up

Follow-up assessments	Timeline
Duration	26 weeks (extended up to 39 weeks)
Clinical review, including weight and BMI, concomitant medication, adherence, signs/symptoms suggesting adverse events	Monthly
CBC (with Hb, platelets) and ECG	Day 15, 30, then monthly till month six, and more frequently if clinically indicated
Visual acuity, and color vision test	Week 09, 13, 26 and more frequently if clinically indicated
Smear microscopy	With culture at the C&DST lab
Culture	**Monthly from month two onwards (i.e., at month 2, 3,4,5,6).** If the culture results of month 4 or later are positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion or reversion and if the repeat specimen is culture negative, then collect and send the subsequent monthly or end-of- treatment specimen.
DST	NAAT MTB/XDR or FL and SL LPA (Lfx, Mfx, Am, Eto) and LC DST (Mfx 1.0, Lzd, Z, Bdq, Pa*, Dlm*) if culture +ve at the end of month 4, end of Rx and as and when clinically indicated during treatment
Urine pregnancy test	As and when clinically indicated
Chest X-Ray and LFT#	At the end of month three, the end of treatment, as and when clinically indicated
S. Electrolytes (Na, K, Mg, Ca)	As and when clinically indicated in case of any QTcF prolongation
Specialist (Ophthalmic, Neurological) consultation	As and when clinically indicated
Surgical evaluation	After culture conversion
Long term follow-up	At 06, 12, 18, and 24 months after completion of treatment (Clinical, CXR, Smear and C&DST, if symptomatic) and whenever the patient returns to the health system

9-11Month Shorter Oral MDR/RR-TB Regimen

A	(2) Lzd (4-6) Lfx Cfz Z E H^h (6-9) Bdq	(5) Lfx Cfz Z E
B*	(4-6) Lfx Cfz Eto Z E H^h (6-9) Bdq	(5) Lfx Cfz Z E

B in case of Lzd intolerance/ resistance

- Eligibility Criteria –
  - i. RR detected/inferred
  - ii. MDR/RR-TB with **FQ resistance not** detected.
  - iii. No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Cfz or Lzd as applicable) for more than one month (unless susceptibility to these medicines is confirmed)
  - iv. Non extensive Pulmonary TB
  - v. No severe forms of extra-pulmonary MDR TB like CNS TB , spinal/ skeletal TB (Miliary TB or TB with multiorgan involvement or disseminated TB).
  - vi. Lzd containing shorter oral MDR/RR-TB regimen can be given even in case of **both KatG & InhA** mutations are present. INHA-lower-level INH resistance that is linked to ETH cross-resistance, CATG- higher-level INH resistance
  - vii. Eto is contraindicated during the first 32 weeks of pregnancy due to teratogenic effects. Non-pregnant or pregnant women with < 24 weeks gestation and is willing for MTP, if Eto is considered in the regimen –LZD containing shorter oral MDR/RR-TB regimen can be given in pregnancy.

9-11Month Shorter Oral MDR/RR-TB Regimen

- IP can be extended to month 05 or 06 based on smear results at the end of month **04 or 05** of treatment. This will be done for a maximum of 2 months (i.e., total duration of IP is not more than 6 months). If the IP is extended up to 6 months then all 3 drugs **Bdq, Hh and Eto** are stopped together
- The **dosage of Lzd** is 600 mg for 14 years & above.
- For children <14 years is as per weight band as given below:

Medicine	Weight- based Daily dose	Formulation	Weight bands among patients under 15 years old							Usual upper Daily dose
			5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg	
Linezolid	15 mg/kg od in 1–15 kg	20 mg /mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	600 mg
	10–12 mg/kg od in >15 kg	600 mg tab	0.25	0.25	0.25	0.5	0.5	0.5	0.75	

Additional resistant to Z is detected in the baseline sample on C&DST or Res to FQ/InhA & KatG mutation is detected in month 04 sample, reassessed at N/DDR-TBC initiation of longer oral M/XDR-TB regimen

Dosage of 9-11 months shorter MDR/RR-TB regimen drugs for adults

Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
High dose H (Hh)	300 mg	600 mg	900 mg	900 mg
Ethambutol(E)	400 mg	800 mg	1200 mg	1600 mg
Pyrazinamide(Z)	750 mg	1250 mg	1750 mg	2000 mg
Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily ; Week 3–24: Bdq 200 mg 3 times per week			
Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
Ethionamide (Eto)*	375 mg	500 mg	750 mg	1000 mg
Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

18-20 months Longer oral M/XDR-TB regimen

- **(6 or longer) Bdq + (18-20) Lfx Lzd Cfz Cs**

- As per integrated algorithm, patients who cannot be initiated on BPaLM or 9-11 month shorter oral MDR/RR-TB regimen due to reasons of ineligibility, additional resistance, intolerance, non-availability of any drug or emergence of exclusion criteria will be managed with an longer oral M/XDR-TB regimen modified in accordance with the replacement sequence.

- For XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months.

18-20 months Longer oral M/XDR-TB regimen

GROUPS & STEPS	MEDICINE	ABBREVIATION
Group A **Include all three medicines**	Levofloxacin or Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs Trd
Group C **Add to complete the regimen and when medicines from Group A and B cannot be used**	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or Meropenem	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide or Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Replacement sequence of Group C drugs for longer oral M/XDR-TB regimen was recommended in the order of - **delamanid, amikacin, pyrazinamide, ethionamide, PAS, ethambutol, penems.**

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
2	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
3	High dose Mfx (Mfxh)	400mg	600mg	800mg	800mg
4	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
5	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
6	Cycloserine (Cs)[3]	250 mg	500 mg	750 mg	1000 mg
7	Linezolid (Lzd)	300 mg	600 mg	600 mg	600 mg
8	Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6-11 years of age 100 mg twice daily (200 mg) for 24 weeks for ≥12 years of age			
9	Amikacin (Am)[1]	500 mg	750 mg	750 mg	1000 mg
10	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
11	Ethionamide (Eto)[3]	375 mg	500 mg	750 mg	1000 mg
12	Na - PAS (60% weight/vol)[2,3]	10 gm	14 gm	16 gm	22 gm
13	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
14	Imipenem-Cilastatin (Imp-Cln)[3]	2 vials (1g + 1g) bd (to be used with Clavulanic acid)			
15	Meropenems (Mpm)[3]	1000 mg three times daily (alternative dosing is 2000 mg twice daily) (to be used with Clavulanic acid)			
16	Amoxicillin-Clavulanate (Amx-Clv) (to be given with carbapenems only)	875/125 mg bd	875/125 mg bd	875/125 mg bd	875/125 mg bd
17	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

[1] *For adults more than 60 yrs of age, dose of SLI should be reduced to 10mg/kg (max up to 750 mg)*

[2] *Patients receiving PAS with 80% weight/volume the dose will be changed to 7.5gm (16-29 kg); 10 gm (30- 45 Kg); 12 gm (46-70 Kg) and 16 gm (>70 kg)*

[3] *Drugs can be given in divided doses in a day in the event of intolerance*

18-20 months Longer oral M/XDR-TB regimen..1

Treatment extension

- Total duration of longer oral M/XDR-TB regimen is 18–20 months.

- If month 5 culture result is not available at the end of month 6, decision to taper the dose of Lzd to 300 mg will be based on month 4 culture result.

- If the month 5 or 4 culture result (whichever applicable) remains positive, the dose of Lzd (600 mg) and the regimen is extended by 1 month to month 7 and for a maximum till month 8 based on monthly culture results of month 6 and 7 respectively and clinical/radiographic response.

18-20 months Longer oral M/XDR-TB regimen..2

- If the month 8 culture is also positive, subject the culture isolate to FL-LPA, SL-LPA and C&DST. If any additional resistant to Group A, B or C drugs in use is detected, the patient needs to be reassessed at N/DDR-TBC for modification of longer oral M/XDR-TB regimen immediately on receiving the report.

- The duration of Bedaquiline is limited to 6 months. Extension beyond 6 months is to be considered in patients in whom an effective regimen cannot otherwise be designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.

- Maximum duration of treatment is not more than 20 months. A treatment duration of 15– 17 months after culture conversion is suggested for most patients. The duration may be modified according to the patient's response to treatment.

6-9 months H mono/poly drug-resistant TB regimen (1)

- 6-9 months H mono/poly DRTB regimen- Lfx R Z E, no separate IP and CP.
- It can be extended directly to 9 months in certain conditions.
  - In patients with extensive disease;
  - uncontrolled comorbidity;
  - extra- pulmonary TB;
  - if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly extended to 9 months. There would be no monthly extensions in this regimen..

6-9 months H mono/poly drug-resistant TB regimen (2)

Situation	Sequence of using replacement drugs
1. If Lfx or Z can't be used	Replace with Lzd. If Lzd also cannot be given, replace with Cfz* + Cs.
2. If both Lfx and Z can't be used	Add 2 drugs of the 3 – Lzd, Cfz*, Cs in order of preference based on resistance, tolerability & availability.
3. If R resistance	Switch to appropriate BPaLM, shorter or longer oral regimen.

*whenever DST is available

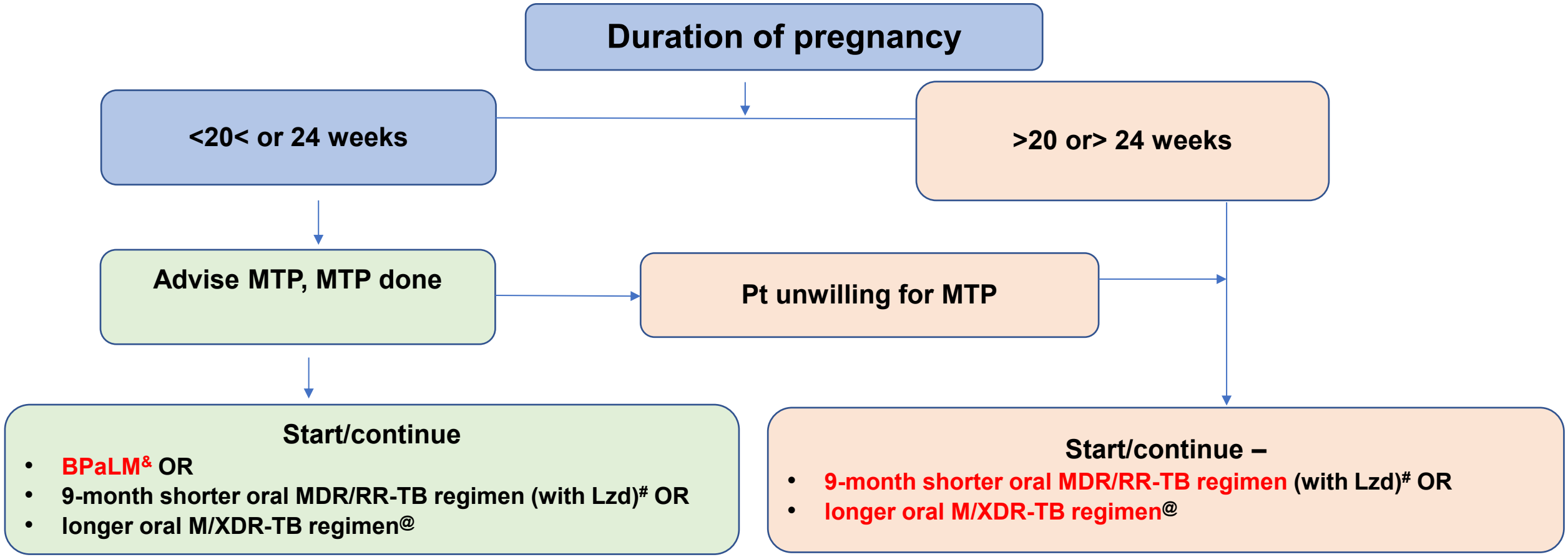
c) The patients not responding or failing in the H mono/poly DR-TB regimen, demonstrating resistance to R will be considered as '*probable MDR TB case*' and further evaluated for treatment with the MDR-TB regimen in the **preferred order** of

- ❖ BPaLM if eligible,
- ❖ 9-month shorter oral MDR/RR-TB regimen if eligible or
- ❖ longer oral M/ XDR-TB regimen.

Pregnancy and lactation

- **Pa is not recommended during the lactating period** unless the mother is willing to *replace breastfeeding with formula feed*. Thus, the recommendation of the BPaLM regimen doesn't apply to pregnant and breastfeeding women.
- Use of **Bdq in pregnancy, lower mean birth weight,** infants were followed up over time, ***no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in infants*** until one year of age were observed .
- All **women of childbearing age** who are awaiting results of C&DST as well as those receiving DR-TB treatment, should be **should be *tested for pregnancy* as part of the PTE, advised, and counselled** intensively **to *use birth control measures*** because of the ***potential risk to both mother and foetus***. It should be remembered ***that oral contraceptives might have decreased efficacy*** due to vomiting and drug interactions with DR-TB drugs.
- **Pregnant women with MDR/RR-TB, strictly, needs counselling for MTP,**

Pregnancy and Lactation.



& Regimen: 6/9 Bdq, Pa, Lzd, Mfx

 # Regimen: 4-6 Bdq (6m or longer) Lfx/Mfx, Cfz, Lzd (2m), Hh, Z, E / 5 Lfx/Mfx, Cfz, Z, E. Lzd can be replaced with Eto if required post MTP or only after 32 weeks' gestation

@ Regimen:18-20 Lfx, Bdq (6m or longer) Lzd, Cfz, Cs. Modify regimen if one or more drug cannot be used due to reasons of resistance, tolerability, contraindication, availability etc

- *in the order of Z E PAS*
- *Eto may be considered after 32 weeks' gestation, if required*
- *Am may be considered in post-partum period only. Am will not be started in the final 12 months of treatment*

Children

- Safety and effectiveness of BPaLM regimen with Pa in children < 14 years have not been established.
- Children below 14 years can be treated with 9-11 month shorter or 18-20 month longer oral regimens as per eligibility in consultation with the pediatrician available or linked to the N/DDR-TBC.
- In **05-14 Yr**-Shorter Oral 09 mth or Longer Oral regimen
- **<5yr: Bdq is not available for this grp.**
  - In Shorter Oral 09-11 mth regimen -Bdq is replaced by Am/Km;
  - in Longer oral regimen -Bdq is replaced by Dlm

Pregnancy and lactation

The following additional monitoring is recommended for pregnant women managed with any MDR/RR-TB regimens:

i. These mothers should **deliver in a tertiary care institute or at least at a place where a pediatrician is available.**

ii. CBC, including Hb, need to be monitored monthly and more frequently if clinically indicated.

iii. USG foetal anomalies scan at 18 weeks and **USG growth scan at 32 weeks**. A fetal echo is to be done only if there is an abnormality on the scan.

iv. More frequent **ECG and serum electrolytes** may be considered as clinically indicated.

v. The **option of 2nd trimester MTP** can be considered if the mother is fit for it, based on a fetal scan of 2nd trimester.

Pregnancy and lactation

vi. Strict **aDSM** is to be done.

vii. ANC registration and **obstetrician follow-up** are to be done regularly.

viii. If **Eto is considered** in the regimen, and if the **basal TSH in PTE is deranged, then TSH must be done monthly** and once it is normal (less than 2.5), then quarterly during treatment. **Check the infant** for early evidence of **hypothyroidism**.

ix. In **case para-aminosalicylic acid (PAS) and Eto are given (which cause hypothyroidism) and Lzd (which causes myelosuppression) to a newborn who has been exposed to a cocktail of drugs, certain baseline investigations at birth like CBC and TSH** should be done.

Older age

- Clinical studies of the combination regimen of Pa, Bdq, and Lzd did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

- Hence, health status and **underlying co-morbidities** must be assessed carefully before considering patients aged 65 years and over for BPaLM regimen, and if included, they would need much **closer monitoring.**

BPaLM-PLHIV

- BPaLM regimen can be given to eligible MDR/RR-TB and Pre-XDR-TB regardless of their HIV status and CD4 count provided they fulfil all other eligibility criteria. However, care should be taken when CD4 counts are below 100 cells/mm3. It is important to consider drug–drug interactions when administering TB and HIV medications in combination with respect to the following points:
    - Efavirenz induces metabolism of Bdq, so its co-administration with Bdq may result in reduced Bdq exposure and loss of activity; Efavirenz also reduces Pa exposures significantly ; therefore, co-administration is to be avoided.; therefore, an alternative antiretroviral agent (potentially dolutegravir (DTG), although there is currently insufficient evidence for this) should be used if the BPaLM regimen is considered.
    - Ritonavir may increase Bdq exposure, which could potentially increase the risk of Bdq-related adverse reactions; however, increased risk has not been noted in studies administering both drugs concurrently. Individuals who are prescribed both Bdq and ritonavir should be monitored closely for adverse events, including QTc prolongation.
    - Zidovudine should be avoided, if possible, because both zidovudine and Lzd may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.
    - These cases should be managed through consultation between the ART centre and DR-TB centre.

People with renal insufficiency

- Generally, Bdq, Lzd and Mfx are **considered safe in renal insufficiency**
- Renal insufficiency may be caused by TB infection itself or by previous use of aminoglycosides. Patients with renal insufficiency and initiated on **BPaLM or 9-month shorter oral MDR/RR-TB regimen or longer oral M/XDR-TB regimen** may develop **severe anaemia and electrolyte imbalance.**
- Patients with renal insufficiency should be **carefully evaluated before** the start of any MDR/RR-TB regimen if the PTE rules out the exclusion criteria. Owing to limited experience with the use of this regimen, caution should be exercised in patients with severe renal failure.

People with liver disorder

- In various DR-TB regimens under NTEP, **R, H, Z, PAS, Eto, Bdq and Pa are potentially hepatotoxic** drugs. Hepatitis rarely occurs with the FQs.
- The potential for **hepatotoxicity is increased in the elderly, alcoholics, malnourished and in patients with pre-existing liver disease.** In general, most **SLDs can be safely used** in the presence of mild hepatic impairment, as they are relatively less hepatotoxic than FLDs.
- For patients on **BPaLM regimen**, routine liver function test (LFT) is recommended at month three in all patients and then as and when clinically indicated. DR-TB patients having **deranged LFT** during PTE should be strictly **monitored** and more frequently as clinically indicated while on treatment. Once a patient on SLDs develops hepatitis, other etiologies should be excluded, such as viral hepatitis, alcoholic hepatitis, drug- induced hepatitis by non-TB drugs etc.

People with liver disorder

- Close **monitoring of liver enzymes** is recommended, and the drugs may need to be stopped if significant liver inflammation is apparent.

- For the management of hepatotoxicity, please refer to the algorithm for management of hepatotoxicity as mentioned in **annexure-3** (details are mentioned in aDSM presentation).

People with diabetes mellitus

- Blood sugar levels may be **difficult to control** in patients with MDR/RR-TB and diabetes, and **insulin may be required** to gain adequate blood sugar control during treatment.
- Patients with diabetes are also at increased risk of **peripheral neuropathies**, which may be further exacerbated following exposure to **Lzd and H^h**. These patients must be **counselled** to report **symptoms of peripheral neuropathies early** because such symptoms may necessitate a change in regimen – either to the **Eto-containing 9-month shorter oral MDR/RR-TB regimen** (bearing in mind this will still include H^h in the IP), or an **individualized longer oral M/XDR-TB regimen without Lzd.**

People with diabetes mellitus

- The concomitant use of **metformin at high doses** and **Lzd** may increase the risk of **lactic acidosis.**
- Also, the long-term use of **Lzd, H^h and cycloserine** (Cs) in patients with diabetes can lead to an increased risk of **peripheral neuritis.**
- Baseline **optic neuropathy or retinopathy or maculopathy** **may worsen** after **Lzd** use; hence, eye evaluation is recommended before and during treatment.
- **Regarding potential baseline renal damage in diabetics, Am or Sm should be used with caution.** Patients with DR-TB and diabetes may need close follow-up and support, with quick identification of drug–drug interactions and adverse events.

People with Anemia

- Patients with TB commonly have anaemia of chronic disease. Many patients with TB also suffer with nutritional deficiencies, and low Hb may also be a result of iron deficiency and low iron stores.
- Iron deficiency may resolve naturally once effective TB treatment (even including Lzd) leads to resolution of TB symptoms and improvement in the patient's anaemia, diet and appetite.
- Extended use (≥ 2 weeks) of Lzd has been associated with reversible myelosuppression. and requires intensive monitoring.
    - Therefore, the Lzd-containing regimen must not be offered to patients with a pretreatment serum Hemoglobin below 8 g/dL that cannot be rapidly corrected (i.e. with blood transfusions) before starting MDR/RR- TB treatment.
    - Some patients **respond well to an initial blood transfusion that raises their Hb above 8 g/ dL** and allows them to at least **start a Lzd-containing regimen**. Lzd will not necessarily cause myelosuppression in patients with baseline anaemia.

People with Anemia

- Some patients respond well to an initial blood transfusion that raises their Hb above 8 g/dL and allows them to at least start a Lzd-containing regimen. Lzd will not necessarily cause myelosuppression in patients with baseline anaemia.
- Although blood transfusions may help to reverse anaemia following withdrawal of Lzd, they may not resolve Lzd-induced myelosuppression with ongoing exposure to the drug.
- Oral supplementation of iron is often not well tolerated and is not immediately effective at the start of treatment, at a time when the pill burden can be overwhelming and the risk of multiple drug side effects is high.

BPaLM Implementation Considerations

BPaLM: Follow-up

❖Follow up culture are to done at week 9, 13, 18, 22, 26 and 39(in case of extension), if patients on BPaLM show **clinical deterioration** or no improvement by 9 weeks

- An **additional smear, rapid molecular test and C&DST to all drugs.**

❖ After 9 weeks, if the patient is not improving clinically or radiologically, send sputum/ EPTB specimen for C&DST and refer the pt to D/NDRTBC.

Interruptions (1)

1. All possible efforts should be made to support the patient and manage the adverse events to ensure uninterrupted treatment and intake of all medicines in the regimen.

2. However, when severe toxicity occurs, the medicine should be stopped.

   - In case of **treatment interruptions and extended treatment duration** for missed doses. Patient must complete 26 weeks of prescribed doses within 30 week and for 39 weeks of prescribed doses within 43 weeks.

   - If above conditions are not fulfilled, the patient may be declared as treatment failed and considered for an appropriate treatment regimen change at the N/DDR-TBC

Missed doses

5. Patient must complete 26 weeks (182 days) / 39 weeks (273 days) of treatment period with all core medicines i.e., B, Pa, L.

6. In case of ***missed doses of any of core medicine(B, Pa, L) in BPaLM regimen***, in following conditions the patient must be resumed and complete the BPaLM course by prolonging the treatment duration for number of missed doses:

   - Consecutive treatment interruption up to 2-weeks; or
   - Non-consecutive treatment interruption up to 4-weeks .

Interruptions (4)

1. In the event of treatment interruption, **re-introduction** of the regimen could be considered **within 4 weeks of interruptions, ONLY after re-assessment of the patient by the N/DDR TBC.**

2. In case of treatment interruptions and extended treatment duration to make up for missed doses, it is necessary for patients to complete **6 months** of the regimen (i.e. **26 weeks of prescribed doses**) **within 7 months** (**30 weeks**) and for patients in whom treatment is extended, it is necessary to complete **9 months of treatment** (i.e. **39 weeks of prescribed doses**) **within 10 months (43 weeks).**

- In case above not complied, further, the treatment outcome to be declared as 'treatment regimen change'.
- **The patient to be sent for clinical review and assessment at NDR TBC to consider for 18-20 longer oral M/XDR-TB regimen**

Regimen and Dose Modification (1)

❖**Dose modification of Bdq, Pa, and Mfx** is **not** recommended during treatment.

❖**For intolerance (grade 3-4) to FQ:** Drop Mfx, complete the rest of the regimen as **BPaL** and extend the treatment up to 39 weeks.

❖**Mfx not to be dropped because of resistance to Mfx**

❖**Permanent discontinuation of Bdq, Pa or Lzd** because of intolerance, toxicity, grade 03/ grade 04 ADR, drug resistance at any point of time, the patient must be declared as '**treatment failure**' and referred to NDR-TBC for evaluation.

Dose Modification (2)

- All efforts must be made to ensure that the dosage of Lzd 600 mg daily to be continued for the entire duration of treatment.

- **For intolerance (grade 3-4) to LZD Dose**

a. ***Within the first 9 weeks of treatment initiation***, **if Lzd (600 mg daily) need to be discontinued,** due to severe/ grade 03 toxicity (myelosuppression and/or peripheral neuropathy or optic neuritis), despite efforts to restart Lzd at 600mg, then discontinue the BPaLM regimen and declare the outcome as **'treatment failed'.** The patient must be sent to the Nodal DR TB center for further evaluation and management.

Dose Modification (3)

❖**For intolerance / grade 3-4) to Lzd 600mg** in patients ***after 9 weeks of treatment initiation***: -

i. All efforts must be made to ensure that the patient consumes Lzd at full or lower dose upto 26-39 weeks.

ii. The patient must be sent to N/DDRTBC, for detailed assessment regarding the temporary interruptions, reintroduction of Lzd at full dose. If **reintroduction is not possible, lower the dose to 300mg.**

iii. In case of reduction in the dose of Linezolid, the treatment **must be extended upto 39 weeks** and the patient must be followed up, more frequently by the physician clinically, radiologically and microbiologically.

Rationale for Mfx continuation in the regimen (1)

With BPaLM, number of drugs and duration of the treatment has been decreased as compared to the current regimen for MDR/RR-TB. Further reducing the number of drugs may increase the risk of relapses in long term follow up.

(A) TB PRACTECAL study:

- https://doi.org/10.1016/S2213-2600(23)00389-2 (TB PRACTECAL, Lancet Respiratory Medicine, Feb 2024)
- https://www.nejm.org/doi/full/10.1056/NEJMoa2117166 (TB PRACTECAL, New England Journal of Medicine, 2022)

1. **TB PRACTECAL** trial had 3 arms including BPaLM, BPaLC, BPaL compared with the WHO standard of care. In the BPaLM arm 32/138 participants (23%) were FQ resistant and Mfx continued throughout the treatment duration in all 138 patients irrespective of FQ resistance status.

2. **Culture conversion:** Culture conversion at 12 weeks was observed for 99/121 (82%) patients for whom conversion could be defined in the standard care group and 107/120 (89%) patients in the BPaLM group (risk difference 7.3 percentage points [95% CI −1.5 to 16.2][1]. In stage 1 of the trial, the percentages of patients with culture conversion in liquid medium at 8 weeks after randomization were 77%, 67%, and 46% in the BPaLM, BPaLC, and BPaL groups, respectively. 78 of 99 patients in the standard-care group (79%) and 85 of 96 patients in the BPaLM group (88%) had culture conversion at 12 weeks.[2]

Rationale for Mfx continuation in the regimen (2)

3. **Low recurrence and probable protection against amplification of bedaquiline resistance**: disease recurrence was observed in 5/115 (4%) participants in the BPaLC group, 4/111 (4%) participants in the BPaL group and 1/138 (1%) participants in BPaLM group. New resistance to bedaquiline was observed in three of four isolates from the participants with disease recurrence in the BPaL group; of these, an isolate from one participant also showed resistance to clofazimine.[1] At week 48, there were no recurrences of tuberculosis in the BPaLM group. [2]

4. **Better treatment outcome**: The network meta-analysis found successful outcomes in 55/62 (89%) patients treated with BPaLM compared with 46/60 (77%) patients of those treated with BPaL (absolute risk reduction 1.15 [95% CI 0.95–1.38]). BPaLM regimen also demonstrated **a sustained treatment success after 108 weeks** in 94% of patients as compared to 82% in BPaLC and 83% in BPaL arms.

Rationale for Mfx continuation in the regimen (3)

5. Comparable time to culture conversion: Median time to culture conversion was 56 days (IQR 28 to 83 days) in the standard care group and 55 days (IQR 28 to 57 days) in the BPaLM group (unadjusted hazard ratio 1.38 [95% CI 1.05 to 1.81]. [1]

6 The **safety outcomes also favored BPaLM**, with lower percentages of patients with adverse events of grade 3 or higher or serious adverse events for all outcomes (at week 72, at week 108, and during treatment). [2]

7. The **QTcF interval at week 24 was lower in the BPaLM group** than in the standard-care group and more closely resembled the QTcF in the BPaL group. The QTcF in the BPaLC group was similar to that in the standard-care group. This finding corroborates evidence suggesting that clofazimine is a primary driver of QTcF prolongation in bedaquiline-containing regimens. [2]

Rationale for Mfx continuation in the regimen (4)

(B) US programmatic data (3)

https://doi.org/10.1016/S2213-2600(23)00426-5 (US programmatic data)

- CDC report compares patients who were initiated on the BPaLM regimen in the USA between 2019 and 2022, with patients receiving BPaL, a regimen previously documented to have uptake in US tuberculosis programmes, as a complement to the randomised TB-PRACTECAL study.
- 84/116 (72%) patients with BPaL regimen and 29/36 (81%) patients with BPaLM regimen completed treatment.
- TB relapse reported was 3% in BPaL regimen and 0% in BPaLM regimen in the above cohort.
- TB death reported was 1% in BPaL regimen and 3% in BPaLM regimen in the above cohort.

BPaLM : Extension

Regimen Extension

a. The dose reduction of the Lzd to 300, because of Lzd grade 3-4 intolerance, can be considered after 09 weeks. If dose of Lzd is reduced to 300 mg the period of the BPaLM regimen will be extended upto 39 weeks

b. In case of grade 3-4 intolerance to FQ, drop Mfx, complete the rest of the regimen as **BPaL** and extend the treatment up to 39 weeks.

❖ Extension of treatment upto 39 weeks should be done with strict clinical evaluation and smear and culture microbiological follow-up at monthly interval.

BPaLM Dose Modification: Regimen change

Regimen Change as per baseline DST:

Those patients who has been initiated with BPaLM regimen, in case of baseline resistance to Bdq, Lzd or Pa (whenever available)

The treatment need to be changed to (18-20) longer oral regimen as applicable and the outcome to be given as **“treatment regimen changed ”.**

ADR Screening

❖**Patients Screening for Lzd ADR**: Patients must be actively screened for any early development of Linezolid induced adverse events especially myelosuppression, neuropathy and optic neuritis.

❖This is done more frequently in patients of following higher risk groups

i. Patients with co-morbidities like diabetes mellitus, PLHIV, history of substance abuse, hypothyroidism, and abnormal baseline electrolytes.
ii. Low BMI-< 18.5 kg/m^2
iii. Pre-existing anemia Hb <8.00 (gm/dl)
iv. Nutritional deficiencies
v. Lack of gain in appetite/ weight or weight loss.

Detailed ADRs topic is discussed in the respective session.

Peripheral Neuropathy

The following table has been suggested by the national experts for screening of peripheral neuropathy which can be used at the peripheral health institution/ community level.

	Symptoms	Grade 1 / Mild	Grade 2 / Moderate	Grade 3 / Severe	Grade 4 / Potentially life-threatening
1.	Numbness, burning, prickly (pins and needles) feelings in the feet				
2.	Feel hurt when bed covers touch the skin				
3.	Cramps in the muscles of the leg or muscle weakness.				
4.	Inability to distinguish hot or cold water.				
5.	Worsening of symptoms at night or increase in leg pain while walking.				
6.	Slipping off of footwear without knowledge				
7.	Inability to place his soles on the ground.				
8.	Frequent sores or ulcers on the feet				
9.	Diminution in the vision				

Long term follow-up

- Patients who completed TB treatment remain at risk of TB recurrence (re-infection or relapse).
- TB patients require regular follow-up until 2 years after successful treatment completion to achieve the desired outcome of recurrence-free survival.
- Hence, the patient must be assessed at **6, 12, 18 and 24 months after completion of treatment.**

Switching Between The Regimen

- Patients who are required to be shifted from **BPaLM or 9-month shorter oral MDR/RR-TB regimen to an individualized longer oral M/XDR-TB regimen due to reasons** of **resistance, tolerability, availability, Interruptions and the emergence of exclusion criteria,** need to be re-evaluated for necessary modification of longer oral M/XDR-TB regimen and initiated on a full course of an individualized longer oral M/XDR- TB regimen after discussion with state difficult-to-treat TB clinic.
- Similarly, patients who are placed on a **longer oral M/XDR-TB regimen** based on the **history** of exposure to SLDs for more than one month awaiting **DST** results and later found to be eligible for the **BPaLM or 9-month shorter oral MDR/RR-TB regimen** (and in whom resistance is not detected on baseline specimen to H, i.e. both InhA and KatG or to FQ or Z, Bdq, Pa*, Dlm*) can be switched to any of these shorter regimens, provided that treatment has not lasted for more than one month. If patients are switched in this way, the BPaLM or 9-month shorter oral MDR/RR-TB regimen is given for the full duration without any changes to its composition or duration.

BDQ Dosing while switching the regimen

- At the time of switching between regimens, if the loading dose of Bdq (first 14 days):

  i. Is still ongoing with no dose interruption, then complete the loading dose and shift to the thrice weekly doses after 14 days to complete the treatment duration.

  ii. is over, there is no need to repeat the loading dose. Start Bdq with a fresh bottle/strip with the thrice weekly doses along with the first dose of other medicines in the new regimen and continue the thrice weekly doses to complete the treatment duration.

Final Outcomes.1

Treatment failed:

A patient whose treatment regimen needs to be terminated or changed permanently to a new regimen option or treatment strategy. The reason for the changing the regimen permanently include:

a) No clinical response and/ or no radiological response

b) No bacteriological response (no bacteriological conversion achieved or bacteriological reversion after initial conversion; bacteriological reversion is considered only when it occurs in the continuation phase)

- For BPaLM regimen: “bacteriological reversion” would be considered only during the period between 26-39 weeks in cases where treatment duration has been extended to 39 weeks. It will not be considered in BPaLM regimen of treatment duration of 26 weeks). 50 National Guidelines for Management of Drug-Resistant TB

c) ADRs,

d)Evidence of additional drug resistance to medicines in the regimen.

Failure outcome definitions for BPaLM: Failure will include

- The culture of sample collected at month 04 or later is positive for M.TB.
- Amplification of resistance to B, Pa and or L
- No clinical response

Final Outcomes.2

Cured

- A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed
- treatment as recommended by the national policy with evidence of bacteriological response1 and no evidence
- of treatment failed.

Treatment completed

- A patient who completed treatment as recommended by the national policy whose outcome does not meet
- the definition of cure or treatment failed.

Died

- A patient who died2 before starting or during the course of treatment.

Lost to follow-up

- A patient who did not start treatment or whose treatment was consecutively interrupted for one month or
- more. (not applicable to BPaLM)

Not evaluated

- A patient for whom no treatment outcome was assigned

Final Outcomes.3

Treatment regimen changed:

- The patients who has been initiated on treatment, in case of baseline resistance to the drugs in the regimen (when available) is found, the treatment need to be changed to an appropriate regimen and the outcome to be given as “treatment regimen changed”.
- The patient needs to be moved out of the denominator of the previous regimen. The outcome of only the changed regimen needs to be reported. The same would be applicable for patients who switched between the DS-TB and the DR-TB regimens.

Treatment regimen changed outcome definitions for BPaLM: Treatment regimen changed will include:

i. Discontinuation of B, Pa or Lzd because of intolerance, toxicity at any point of time

ii. Baseline DST resistance to B/Pa/L when available

The treatment regimen changed because of intolerance and baseline DST resistance are to be recorded in Ni-kshay and analyzed separately.

Final Outcomes.4

❖Sustained treatment success

An individual assessed at every six months (for DR-TB and DS-TB) and at 12 months, 18 months and 24 months (for DR-TB only) after successful TB treatment who is alive and free of TB.

Treatment management

- In **BPaLM =/> 85%** **supervised dose** **is of critical importance.**

- By Program staff, or at least by Treatment supporter

Ministry of Health and Family Welfare
Government of India

Thank You

Date: