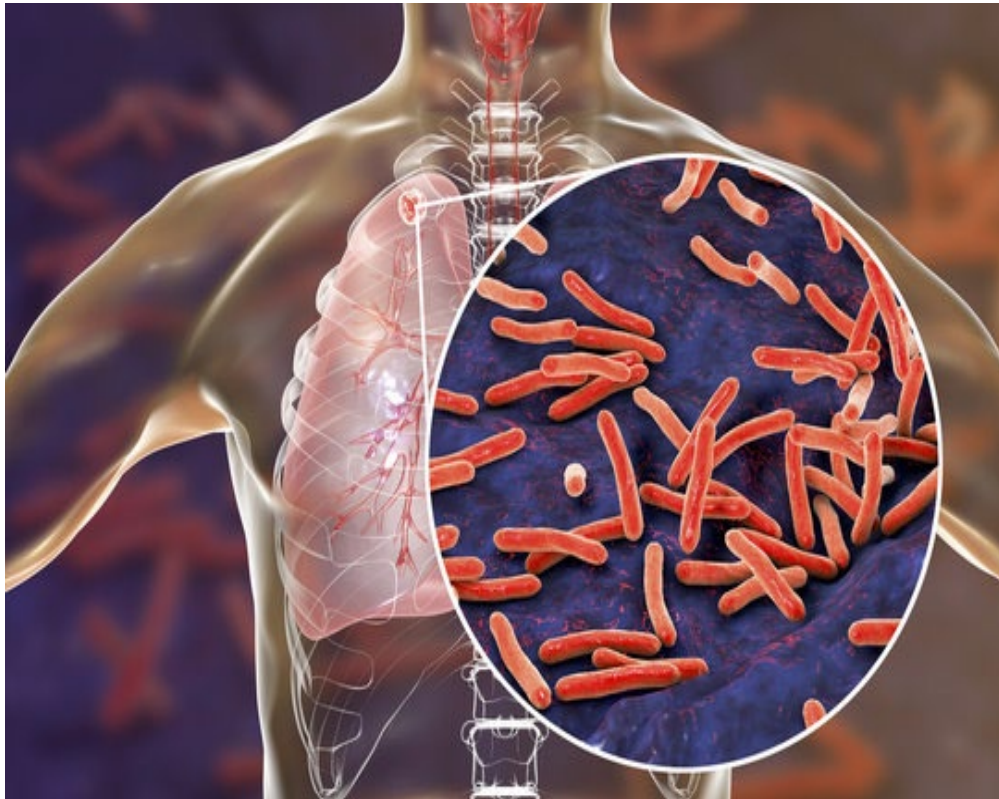


Let's Get Comfortable with BPaLM. Management of DR TB



Eva Muloma, M.D.
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Assistant Professor of Clinical Medicine
Indiana University School of Medicine

25 March 2026, 09:30a-10:15a
2026 World TB Day Celebration

Disclaimer Statement

**I HAVE NO CONFLICTS OF
INTEREST**

**I have no financial interests
or other relationships with
the manufacturers of
commercial products,
suppliers of commercial
services, or commercial
supporters**

Learning Objectives



IDENTIFY WHAT IS BPALM



IDENTIFY INDICATIONS & CONTRAINDICATIONS FOR BPALM



WHAT EVALUATION & MONITORING IS NEEDED



DESCRIBE TWO WAYS IN WHICH CASE MANAGEMENT IS DIFFERENT FROM THAT OF DRUG –SUSC TB



IDENTIFY POSSIBLE ADVERSE EVENTS



NAME AT LEAST 1 PROGRAMMATIC CONSIDERATION



KNOW WHEN TO CONSULT WITH TB EXPERTS

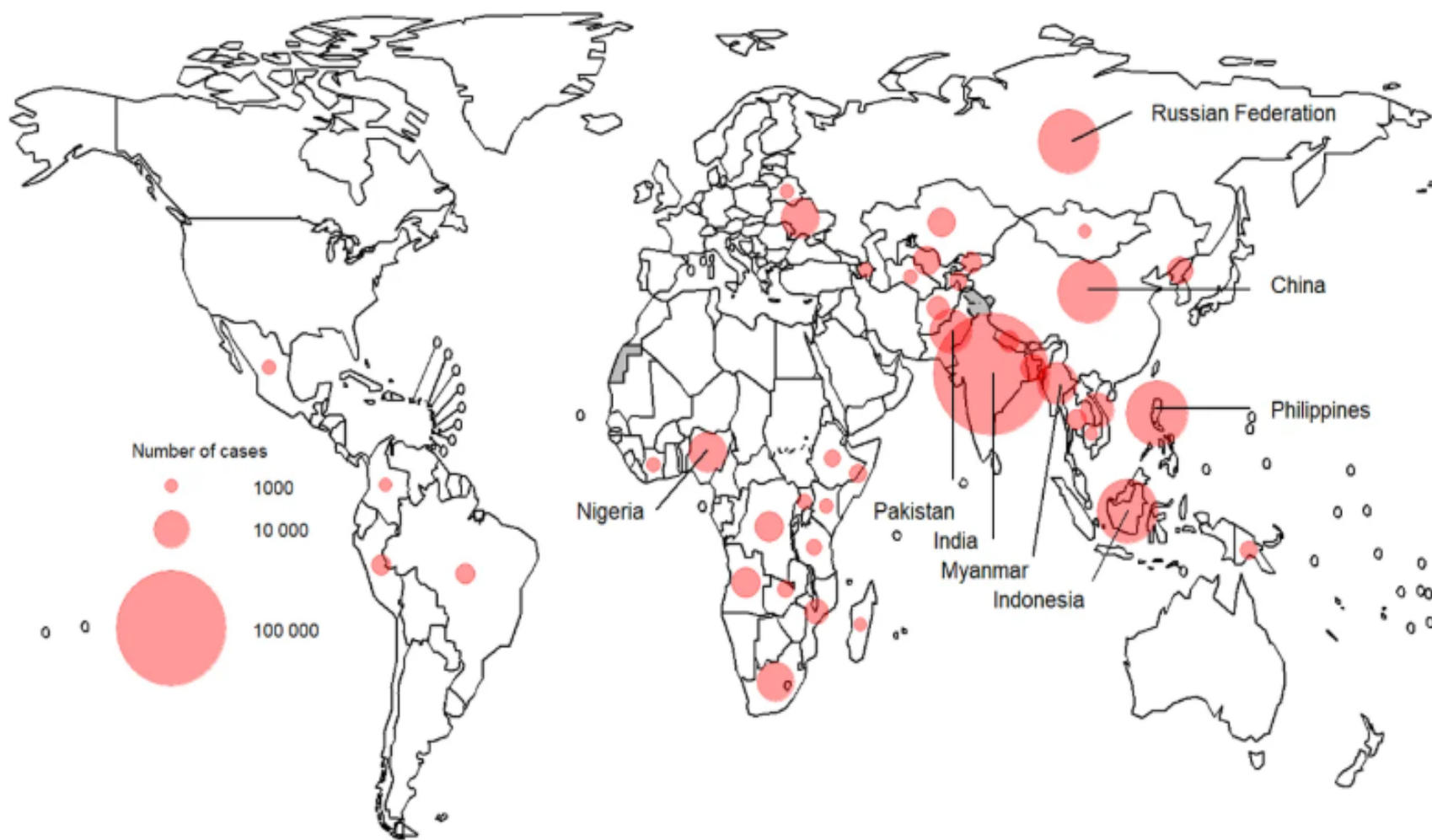
INTRODUCTION & DEFINITIONS

Defining Drug resistant TB

DS-TB	Mono-R-TB	MDR-TB	Pre-XDR-TB	XDR-TB
RIF	RIF	RIF	RIF	RIF
INH	INH	INH	INH	INH
PZA	PZA		Quinolones	Quinolones
EMB	EMB			Group A drugs (Bedaquiline, Linezolid)



Fig. 1.3.5 Estimated number of people who developed MDR/RR-TB (incident cases) in 2022, for countries with at least 1000 incident cases^a



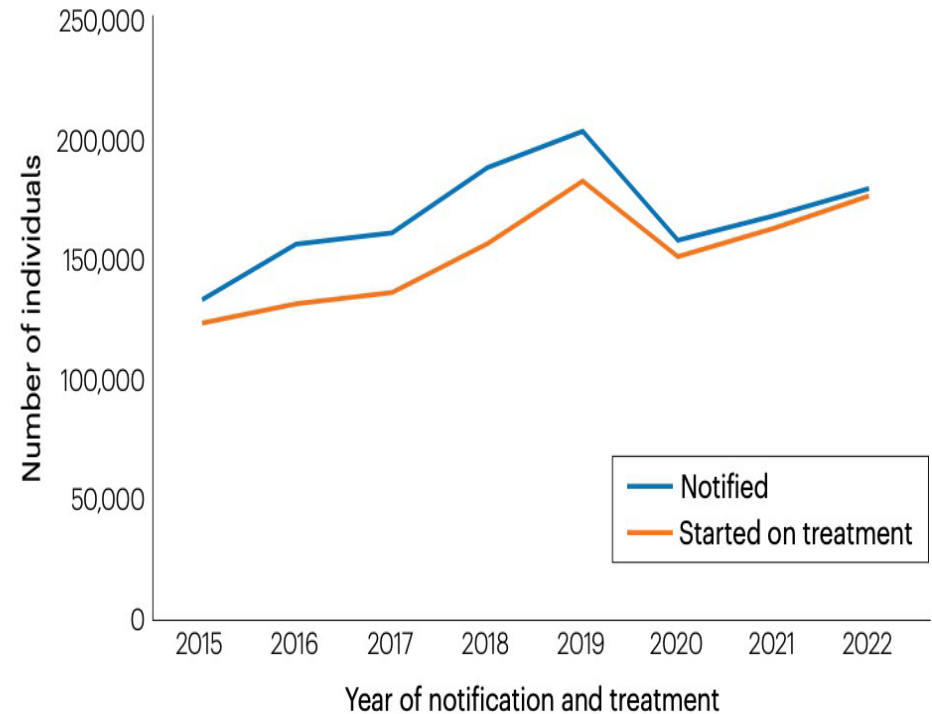
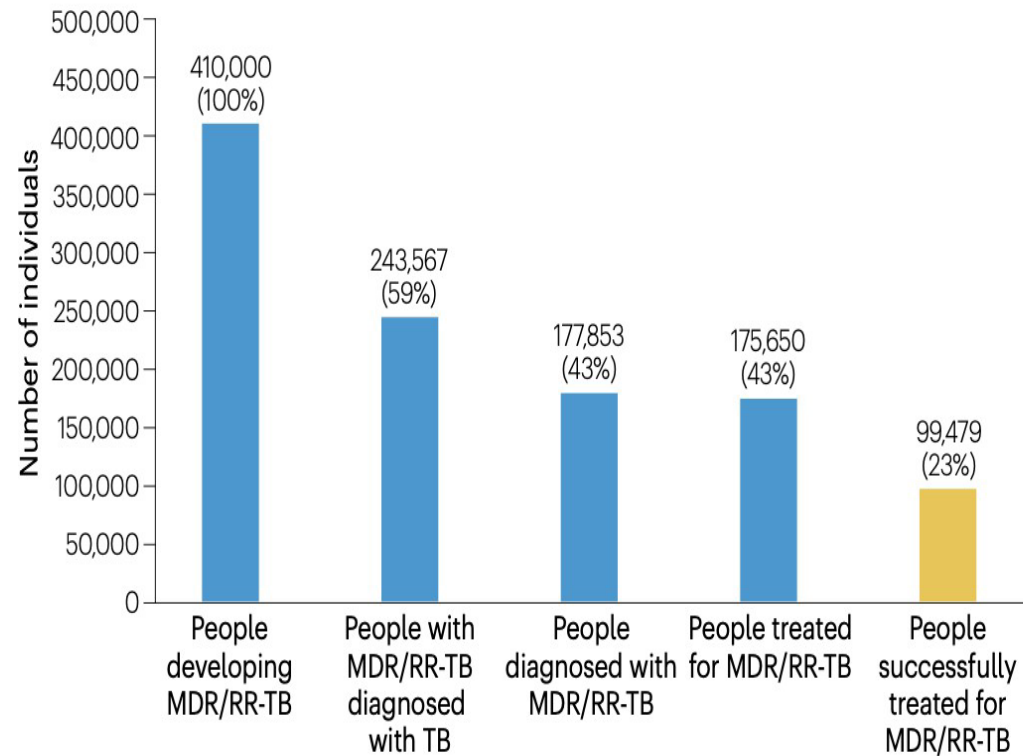
^a The eight countries ranked in descending order of their total number of MDR/RR-TB incident cases in 2022 are India, the Philippines, the Russian Federation, Indonesia, China, Pakistan, Myanmar and Nigeria.

Fig. 1: The three global HBC lists for TB, TB/HIV and MDR-TB used by WHO during the period 2016–2020, and their areas of overlap

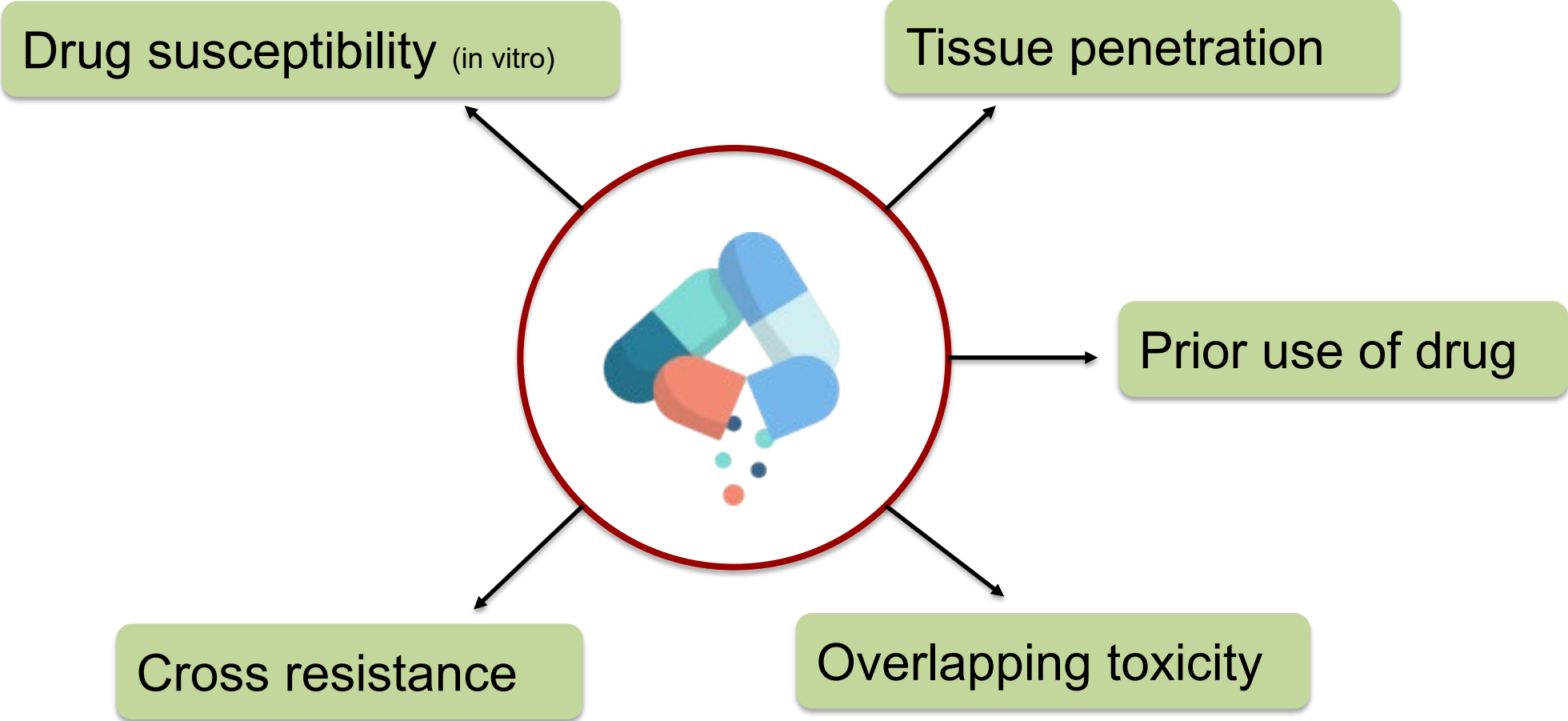


⁴ See the report of the STAG-TB meeting in 2015 (pp8), available at https://www.who.int/tb/advisory_bodies/stag_tb_report_2015.pdf?ua=1

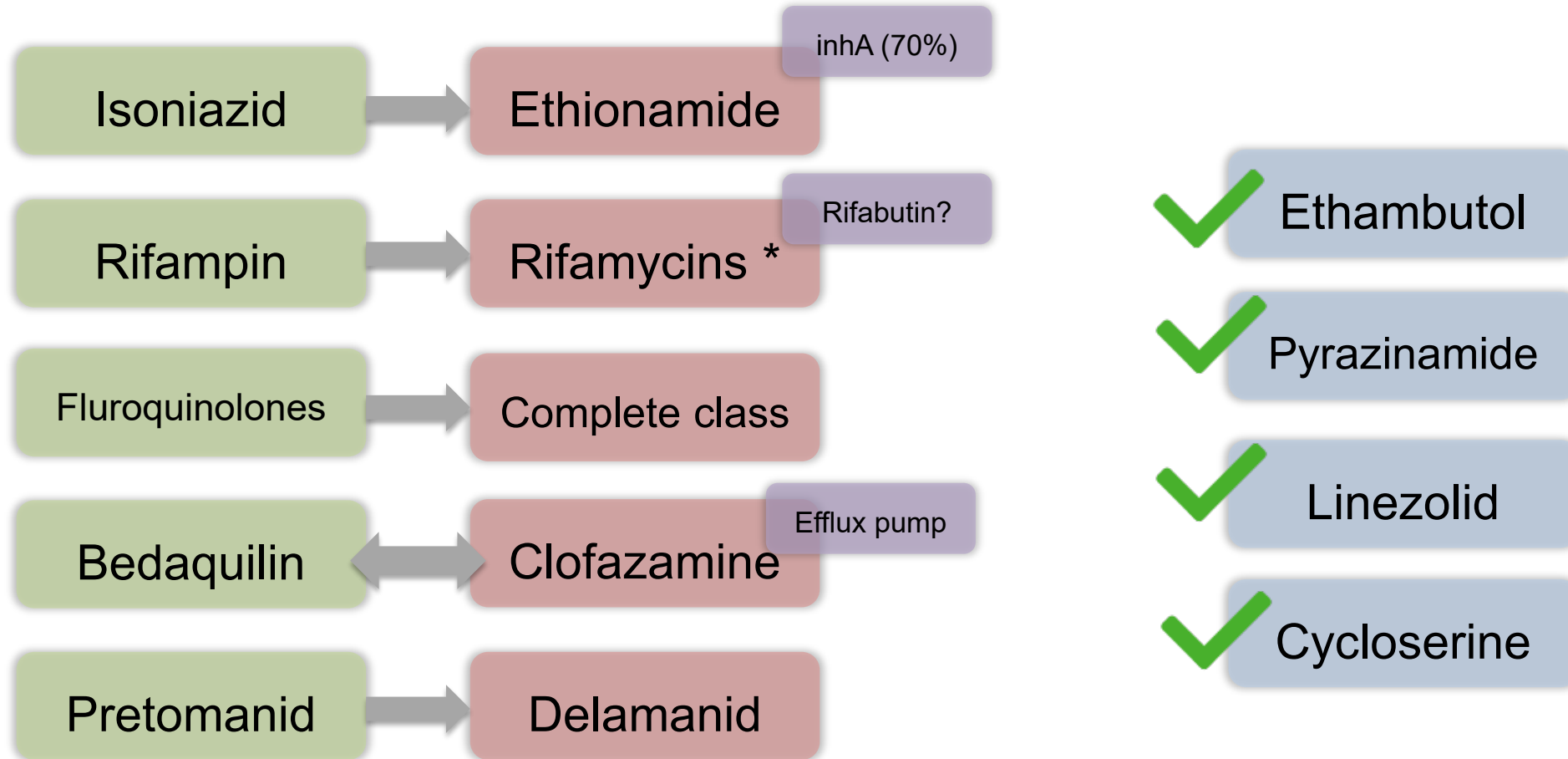
GAPS IN THE CASCADE OF CARE FOR DRUG-RESISTANT TB



Building a regimen for MDR-TB



Cross Resistance



DR-TB Treatment Evolution

- ▶ Long regimens → All-oral → Short regimens → BPaL/BPaLM



**What is BPaLM
& why should I
get comfortable
with it?**

BPALM REGIMEN OVERVIEW

What it is

A 6-month, all-oral DR-TB regimen: bedaquiline + pretomanid + linezolid + moxifloxacin.

Origins and rationale

Built on Nix-TB/ZeNix evidence for BPaL efficacy; adds moxifloxacin to boost bactericidal activity when FQ-susceptible.

Clinical positioning

Targeted option (not universal): requires careful selection, expert oversight, and monitoring for linezolid toxicity and QT prolongation.



BPaL and BPaLM 6-month regimens

Expert consensus dosing recommendations (combining WHO and CDC):

For ages \geq 15 years:

BPaL*

- **Bedaquiline** 400 mg once daily x 2 weeks (load), then 200 mg 3x/week x 24 weeks
- **Pretomanid** 200 mg once daily x 26 weeks
- **Linezolid** 600 mg once daily x 26 weeks

BPaLM* — same as above and add:

- **Moxifloxacin** 400 mg once daily x 26 weeks

Extend either regimen to 9 months (39 weeks) if evidence for delayed response to treatment ($>$ 8 weeks per CDC criteria below).¹⁴



One day of typical BPaL regimen
6 months / <750 pills



One day of typical XDR-TB treatment
18+ months / 14,000+ pills



INDICATIONS FOR BPaLM

BPaLM INDICATIONS

- ▶ Pulmonary TB
- ▶ Age at least 15yrs old
- ▶ MDR TB OR RR-TB
- ▶ ? Severe Rifampin intolerance
(only expert opinion for now)
- ▶ *No data are available in children, pregnant people, or for the use of the 6-month regimens against extra pulmonary TB (like TB meningitis).*

LIFE BEFORE BPALM

**Very long regimens with
toxic medications**

LONG DURATIONS OF TREATMENT




03/25/2026

18

Number of Drugs

2019 IDSA/CDC/ERS/ATS Guidelines

Intensive: At least 5 drugs 

Continuation: At least 4 drugs 



ATS / CDC / ERS / IDSA				WHO
1.	Choose one FQ	Levofloxacin <u>or</u> Moxifloxacin	LFX MFX	WHO Group A: Include all three
2.	Use BDQ and LZD	Bedaquiline	BDQ	
		Linezolid	LZD	
3.	Use CFZ and CS	Clofazimine	CFZ	WHO Group B: Add one or both
		Cycloserine	CS	
4.	Add inj. as needed	Amikacin (<u>or</u> Streptomycin ¹)	AK (SM)	WHO Group C: Add to complete the regimen <u>WHO rank order:</u> EMB DLM PZA IMP/MPM with CLV AK (SM) ETA or prothionamide PAS
5.	Add as needed	Delamanid ²	DLM	
		Ethambutol	EMB	
		Pyrazinamide	PZA	
6.	Add as needed	Ethionamide	ETA	
		Imipenem-cilastatin <u>or</u> Meropenem (<u>plus</u> clavulanate)	IPM MPM (+CLV)	
		<i>p</i> -aminosalicylic acid	PAS	
		High-dose Isoniazid	INH ^{HD}	

Pretomanid not yet included

Capreomycin,
kanamycin,
macrolides
amox/clav



Duration of therapy

2019 IDSA/CDC/ERS/ATS Guidelines

Intensive: **5-7 months** after culture conversion

Continuation: **15-21 months** after culture conversion
15-24 months for pre-XDR and XDR



Summary of Studies that led to BPaLM

Evidence Base

- ▶ **Nix-TB**
- ▶ **ZeNix**
- ▶ **TB PRACTECAL**

A CLOSER LOOK: Nix-TB



109

participants
enrolled



After 6 months of follow-up...

The 6BPaL regimen cured 90% of participants but 57% of participants experienced at least one adverse event.

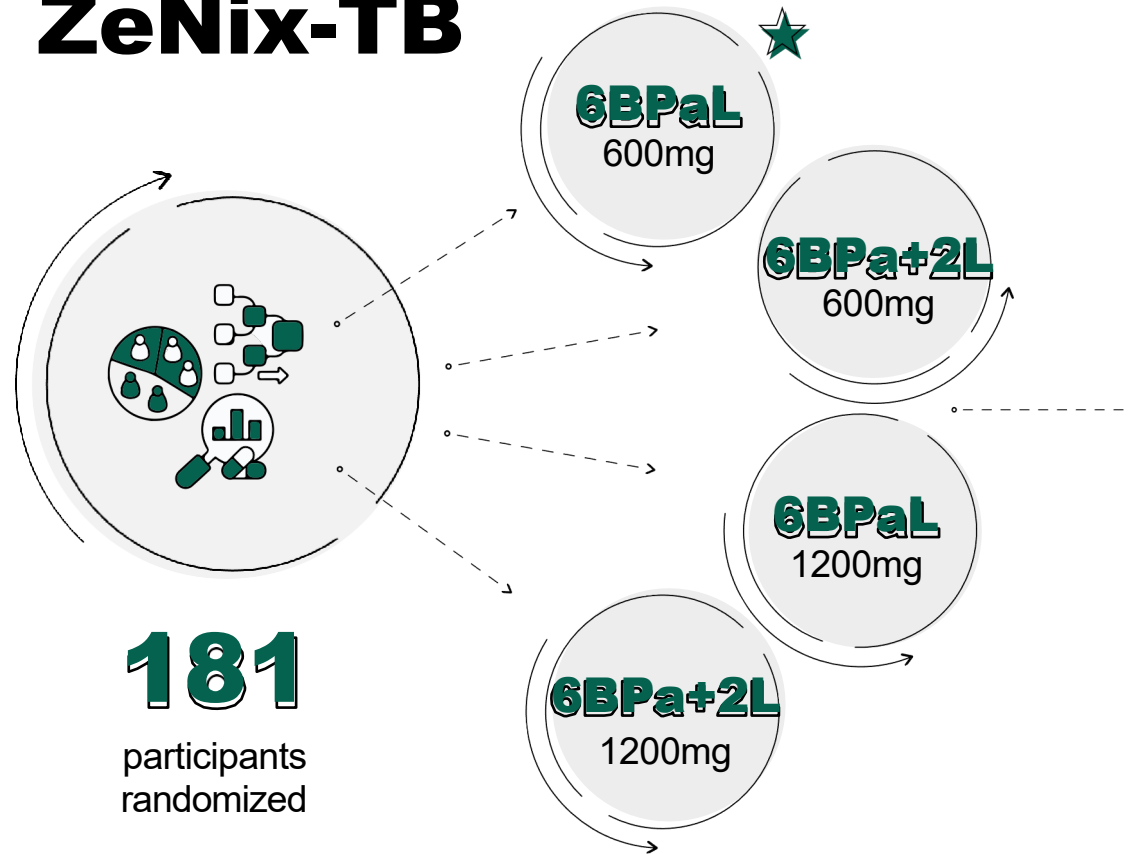
81% of participants reported peripheral neuropathy (nerve pain) and 48% experienced myelosuppression (blood disorders). Because of these adverse effects, only 34% of participants were able to complete six months of linezolid without interruption

- Nix-TB enrolled participants from 3 sites in South Africa
- Mostly adults but also adolescents as young as 14 years old; and
- 56 PLHIV with a CD4 T-cell count of at least 50 cells/mm³

Nix-TB Trial

- ▶ High efficacy with BPaL
- ▶ 6-month regimen
- ▶ High culture conversion
- ▶ Linezolid toxicity noted

A CLOSER LOOK: ZeNix-TB



181
participants
randomized

After 6 months of follow-up...

The 6BPaL(600mg) regimen had the best balance of efficacy and safety – 91% cured and 24% experiencing at least one adverse event.

Dosing linezolid at 600 mg is meant to help to balance the power/potency of linezolid against TB with some of its challenging side effects (e.g., nerve pain and blood disorders).

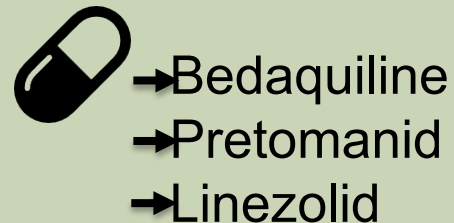
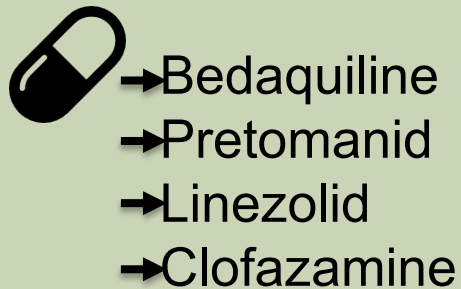
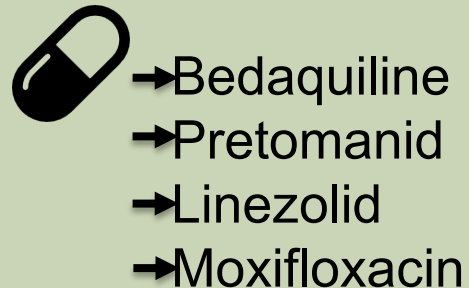
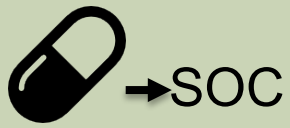
- ZeNix-TB enrolled participants from 4 countries (South Africa Georgia, Moldova, and Russia)
- Mostly adults but also adolescents as young as 14 years old; and
- 36 PLHIV with a CD4 T-cell count of at least 100 cells/mm³

ZeNix Trial

- ▶ **Optimized linezolid dosing**
- ▶ **Lower toxicity**
- ▶ **Maintained efficacy**

6-month regimen RR-TB (TB-PRACTECAL)

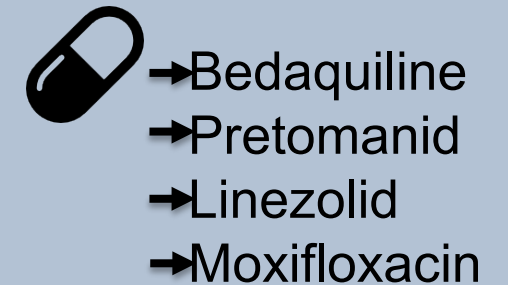
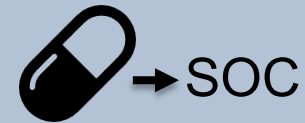
Stage 1



Safety and Efficacy

✓ Culture conversion at 8 weeks 

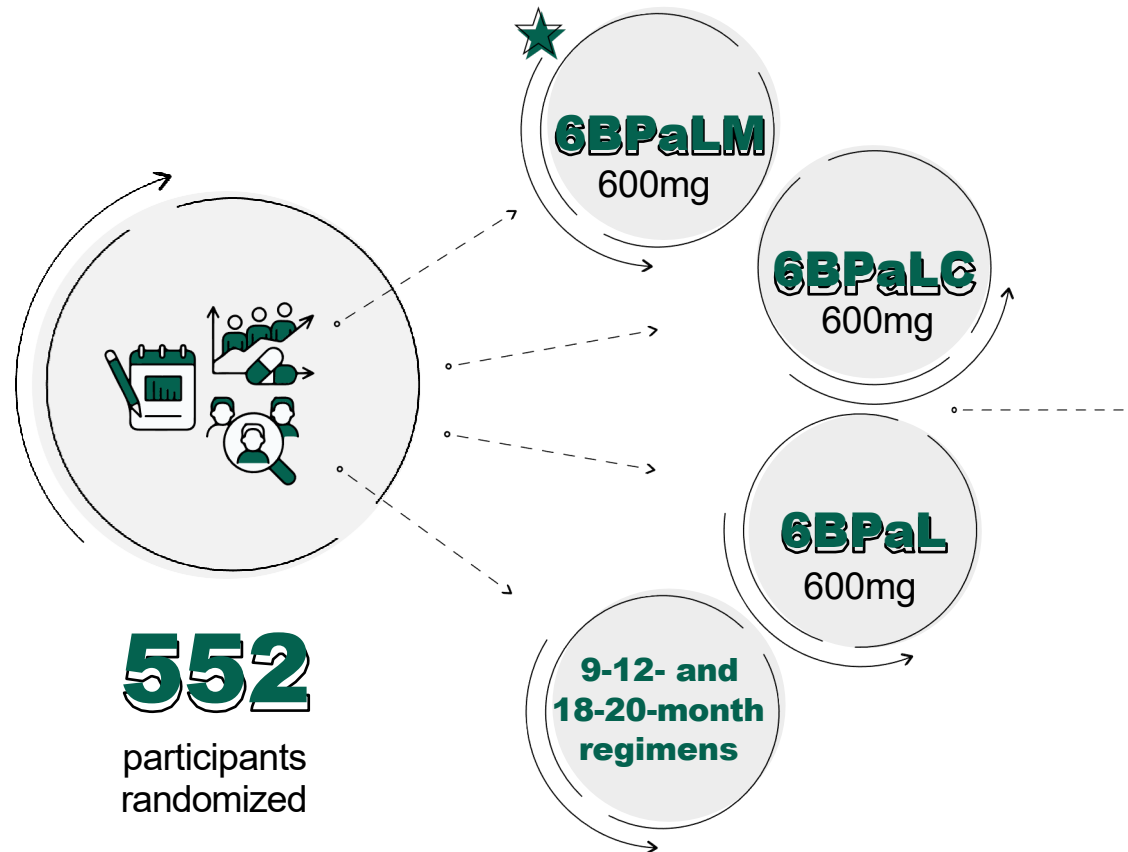
Stage 2



Unfavorable status (Death, tx failure, discontinuation, lost to follow-up, recurrence)



A CLOSER LOOK: TB-PRACTECAL



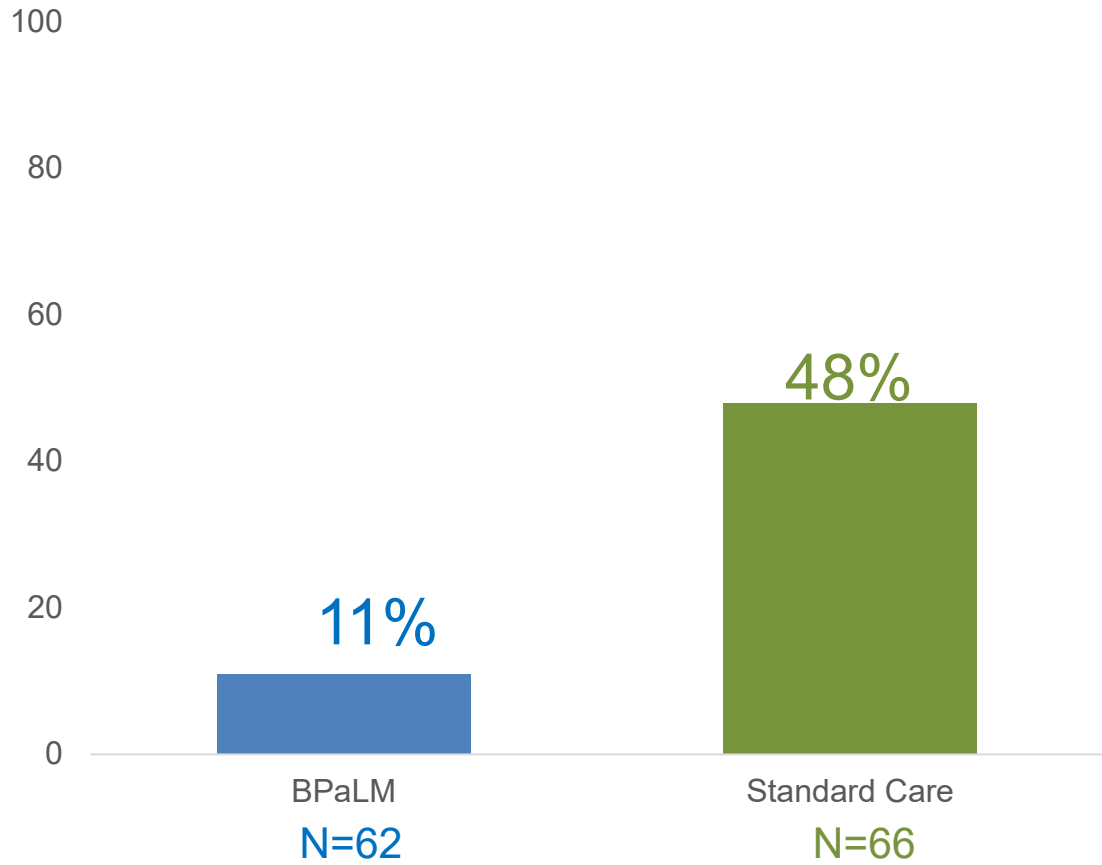
After 1 year of follow-up...

The six-month BPaLM regimen showed favorable efficacy compared to the longer regimens in the control arm – 89% vs. 52% cure rate.

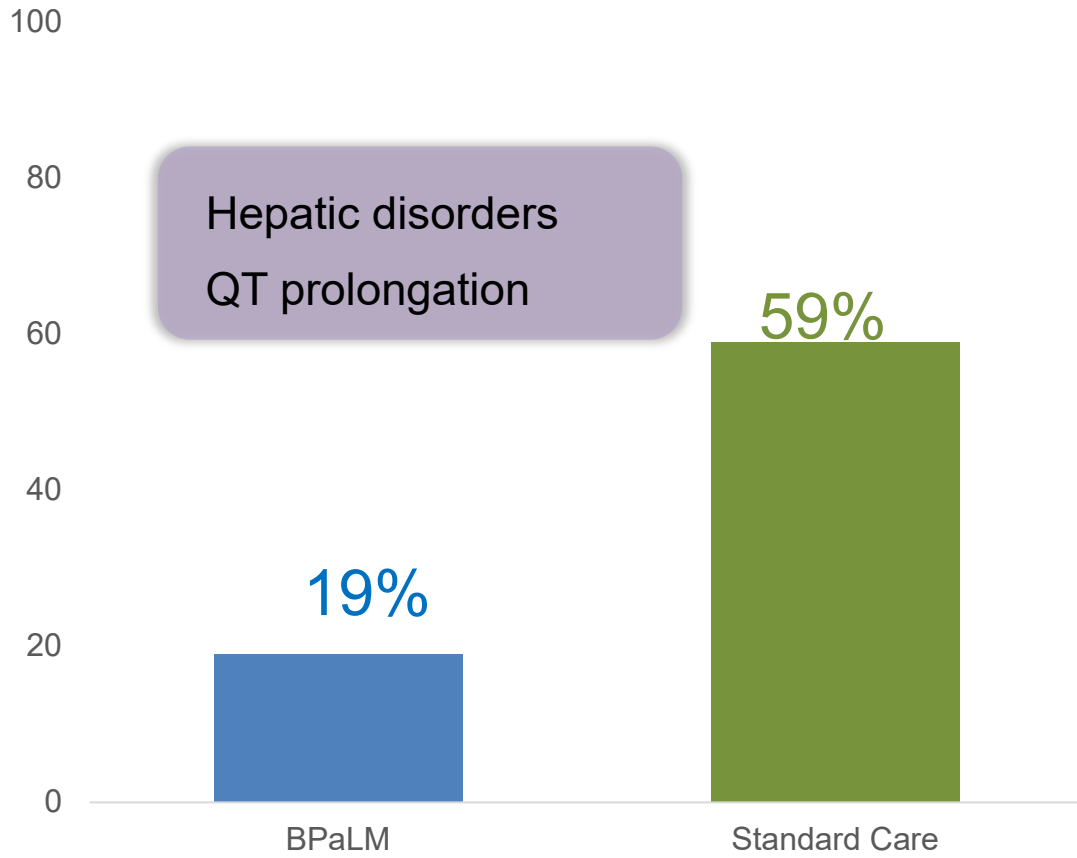
The six-month regimen also showed favorable safety – 80% of participants avoided any major side effects in the BPaLM arm compared to 40% in the control group.

- TB-PRACTECAL enrolled participants from 3 countries (Belarus, South Africa, and Uzbekistan)
- Mostly adults but also adolescents as young as 15 years old; and
- 112 PLHIV irrespective of CD4 T-cell count (median was 250-330 cells/mm³)

Modified ITT analysis
Unfavorable Status



Serious Adverse Events (Grade ≥ 3)



6-month regimen RR-TB (TB-PRACTECAL)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., Timothy D. McHugh, Ph.D., Melvin Spigelman, M.D., David A.J. Moore, M.D., Koert Ritmeijer, Ph.D., Philipp du Cros, M.B., B.S., and Katherine Fielding, Ph.D., for the TB-PRACTECAL Study Collaborators*

ABSTRACT

BACKGROUND

In patients with rifampin-resistant tuberculosis, all-oral treatment regimens that are more effective, shorter, and have a more acceptable side-effect profile than current regimens are needed.

METHODS

We conducted an open-label, phase 2-3, multicenter, randomized, controlled, noninferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant tuberculosis. Patients in Belarus, South Africa, and Uzbekistan who were 15 years of age or older and had rifampin-resistant pulmonary tuberculosis were enrolled. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9-to-20-month standard-care regimen. The primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 77 weeks after ran-



- ✓ Phase 2-3
- ✓ Multinational
- ✓ Randomized
- ✓ Open-label
- ✓ Controlled
- ✓ Non-inferiority



6-month regimen RR-TB (TB-PRACTECAL)

BPaLM was non-inferior and superior to standard of care

GLOBAL TUBERCULOSIS REPORT 2023

Addition and prioritization of a new all-oral 6-month regimen (BPaLM) for RR-TB

*Per protocol analysis showed no statistically significant difference



TB PRACTECAL Trial

- ▶ **Randomized controlled trial**
- ▶ **BPaLM superior to standard care**
- ▶ **Strong safety and efficacy**



**BPaLM:
Review side
effects of
each drug.**

Bedaquiline (BDQ)

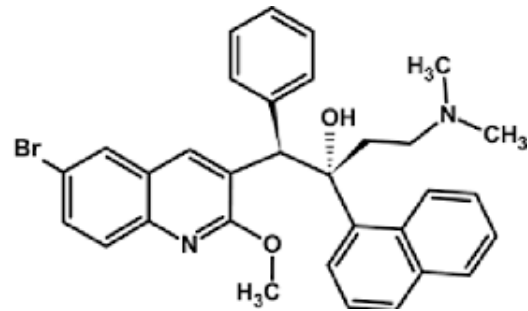
Diarylquinoline

Approved in 2012

MOA

ATP Synthase 

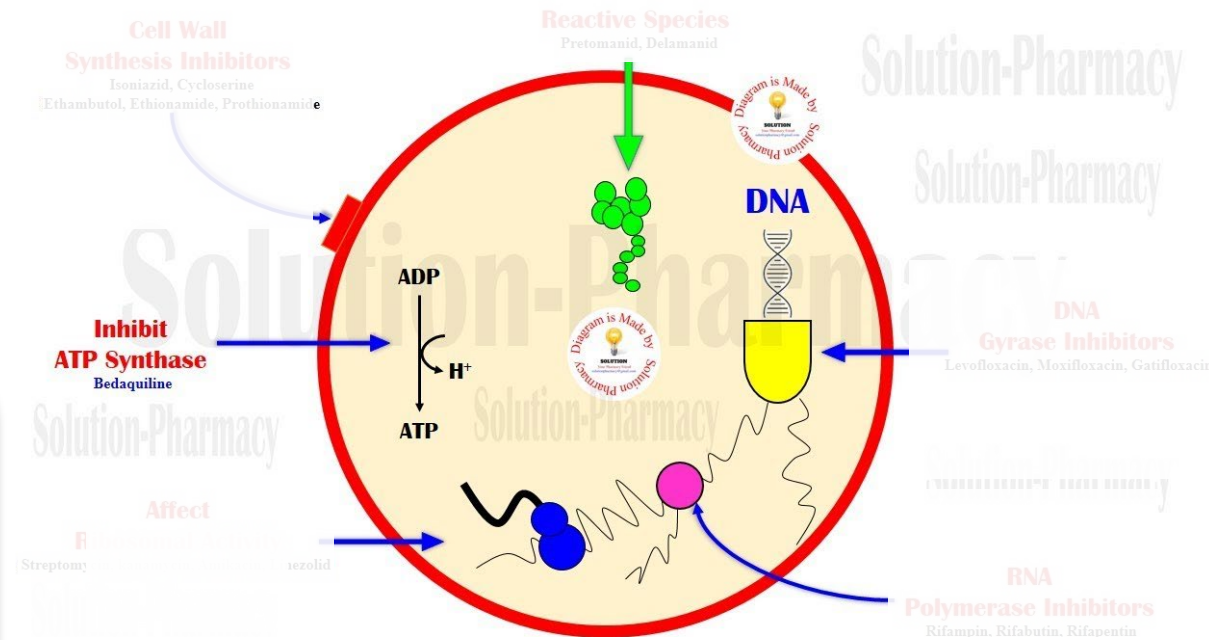
$T_{1/2}$ = 5.5 months



Side effects

QT prolongation

EKG 2-12-24 weeks



Cross reacts: Clofazimine



BEDAQUILINE (SIRTURO)

ADVERSE REACTIONS


- ▶ QTc Prolongation (stop if >500 confirmed 30 mins later)
- ▶ Hepatitis
- ▶ Elevated amylase
- ▶ Hemoptysis
- ▶ Joint pain
- ▶ Headache

Pretomanid (Pa)

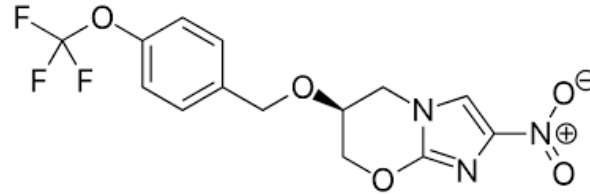
Nitroimidazole

Approved in 2019

MOA

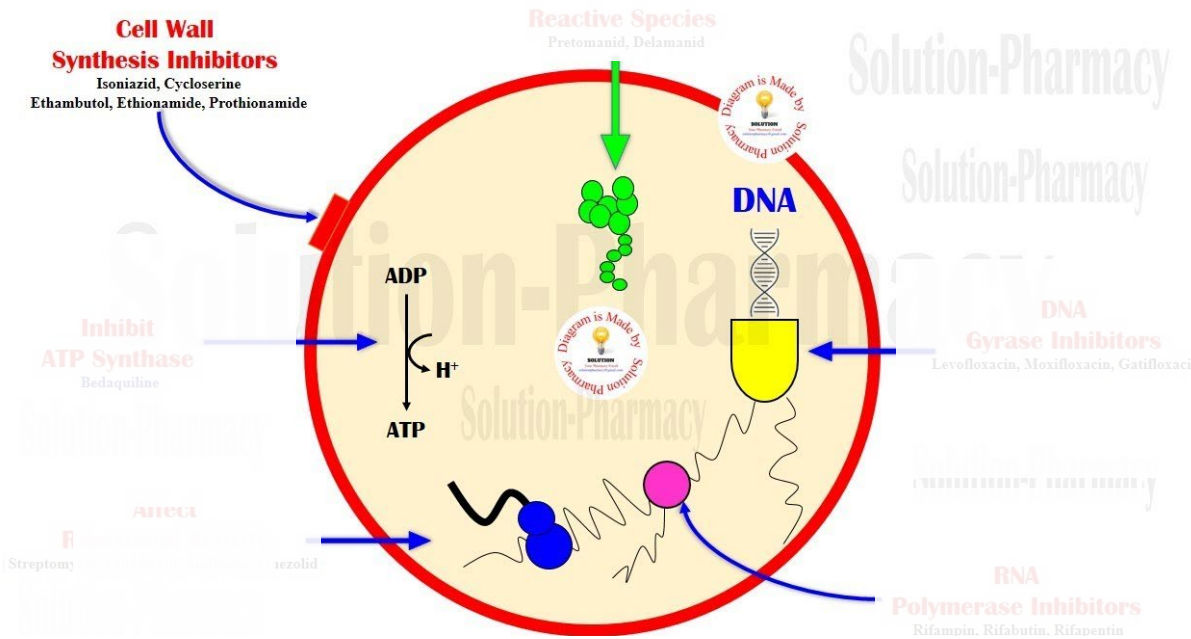
Cell wall synthesis 
Nitric oxide release

Male infertility?



Side effects?

QT prolongation



Cross reacts: Delamanid



PRETOMANID ADVERSE REACTIONS

- ▶ Peripheral neuropathy
- ▶ Anemia
- ▶ GI Upset
- ▶ Elevated liver enzymes
- ▶ Testicular toxicity (in mice but not in non-human primates or humans to date)

LINEZOLID (ZYVOX) ADVERSE REACTIONS

- ▶ **Myelosuppression:** low plt, anemia. leukopenia
- ▶ **Optic and peripheral neuropathy** - most resolve but can be irreversible
- ▶ **Serotonin syndrome**
- ▶ **Diarrhea (including C. diff colitis)**

MOXIFLOXACIN (AVELOX)

ADVERSE REACTIONS

- ▶ Rare tendon rupture, arthralgia
- ▶ QTc prolongation: low plt, anemia. leukopenia
- ▶ Antibiotic-associated diarrhea or C.difficile colitis



BPALM ELIGIBILITY CRITERIA

Indication (Microbiologic)

Adults with RR/MDR-TB and confirmed fluoroquinolone susceptibility; requires timely molecular/phenotypic DST.

Patient Assessment

Baseline ECG/QT risk (bedaquiline + moxifloxacin) and hematologic/neurologic status (linezolid toxicity).

Program Readiness

Use only where labs, ECG monitoring, adverse-event management, and adherence support are reliably available.

BPALM DOSING & DURATION

Duration & delivery

Curry 2022: fixed 6-month BPALM (vs. historical MDR-TB courses up to 2 years). All four drugs are oral, typically daily—no injectables, fewer visit barriers.

Dosing approach

Linezolid often starts at 600 mg daily with planned reductions guided by tolerance and labs. Bedaquiline follows standard loading then maintenance; pretomanid and moxifloxacin are daily fixed doses.

Regimen flexibility

Adjust doses or pause temporarily for adverse events—ideally with TB expert input. Document changes clearly and counsel patients to protect adherence.



LET'S WALK THROUGH A CLINICAL SCENARIO

Drug Resistant TB

- 27yof Burmese Refugee: C/o cough x 3m. CXR: Cavitory ASD. Sputum:4+ AFB. On RIPE, HIV negative. No features of EP TB
- GeneXpert: **Rif resistance: What do you do now?**
 - IDOH (verify + **INH**) was on RIPE
- Pyrosequencing: **rpoB** & **KatG** mutations found
- **What is your diagnosis?**
- **What do you do now?**
 - **Consider holding meds if clinically stable. Why?**
 - **Order pyrosequencing for 2nd line drugs**
- Build a regimen based on pyrosequencing results
 - Pulmonary disease : BPaLM or BPaL
 - EP disease:
 - How many drugs do you need?
 - 5 in intensive phase, 4 in continuation phase

Building A Regimen for EP MDR TB

- Pyrosequencing results: Only INH & Rif resistance: Build your regimen:
 - a) Later generation FQ (levo 750 to 1000mg or Moxi)
 - b) Bedaquiline 400mg po qd x 14d then 200mg po 3x/week. **Adv rxns?**
 - a) (QT prolongation, hepatotoxicity)
 - c) Linezolid . **What's the dose?**
 - a) 600mg po QD (CBC with diff q monthly)
 - d) Clofazimine 100mg po qd. **Adverse reactions.**
 - a) hyperpigmentation, EUA
 - e) Cycloserine: 250-750mg (levels: serum 20-35mg/L in plasma)
 - f) Amikacin (15mg/kg daily) or Streptomycin
 - g) Delamanid (Not FDA approved)
 - h) Pyrazinamide
 - i) Ethambutol
 - j) Ethionamide
 - k) PAS
 - l) High dose Isoniazid



MONITORING, SAFETY, IMPLEMENTATION & NURSE CASE MANAGEMENT



CLINICAL MONITORING

Baseline and ongoing safety checks

Baseline (pre-treatment)

ECG (QT), CBC, liver function tests, and focused neurologic exam as a toxicity reference.

During therapy

Repeat ECG early and after regimen changes; monthly (or more) CBC for linezolid cytopenias.

Clinical follow-up

Routine neuropathy screening, symptom review, adherence checks, and education to enable timely interventions.

Activity	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7-9	
Request and review medical records	Medical/social history, physical exam	Physician assessment every 1-2 weeks	Physician assessment minimum monthly	—————→				→
Drug susceptibility testing (DST)	Review DST results; request 2nd-line DST/MDDR	N/A	N/A	Repeat DST if culture remains (+) after 2M	Repeat as indicated	Repeat as indicated	Repeat as indicated		
Imaging	PA chest [other view(s) if indicated]	N/A	N/A	Consider repeat imaging	N/A	N/A	End of treatment imaging		
Height and weight	Calculate BMI/LBW. Obtain weight monthly	—————→						→
Vision screening	Assess visual acuity and color vision monthly	Monthly while taking Linezolid	—————→					→
Peripheral neuropathy screening	Assess at baseline and monthly	—————→						→
CBC with differential	Obtain at baseline	Obtain every 1-2 weeks	Obtain every 1-2 weeks	Monthly (or more frequently as indicated while on Linezolid)	—————→			→
Metabolic panel (CMP)	CMP to include: K, Ca, Mg, creatinine, bicarbonate, (amylase and lipase)*	Listed components of CMP monthly	—————→					→
Liver function (LFTs)	LFTs to include: ALT, AST, total bilirubin, and alkaline phosphatase	LFTs (at week 2)*, monthly (if symptomatic, consider more frequent monitoring)	—————→					→
Other lab testing	Obtain HIV test; consider hep serology, A1C when risk factor(s) present; TSH* when indicated	Repeat only if indicated→						
Electrocardiogram (ECG)	Obtain baseline ECG (check QTcF)	Week 2 following treatment start (check QTcF)	Repeat as indicated	Week 12 ECG (check QTcF)	Repeat as indicated	Repeat as indicated	Week 24 ECG (check QTcF)		
Sputum monitoring (pulmonary TB)	Sputum x 3 (one early morning) for AFB smear & TB culture	Consider at least 1 sputum 1x/wk until Sm(-) then one every 2 wk until culture conversion	Monthly sputum for TB culture following culture conversion	—————→			Extend 3 months if sputum remains culture (+) after M2→	
Airborne isolation precautions	Continue until deemed non-infectious per local/state guidelines→							
Therapeutic drug monitoring	Not performed at baseline	Obtain Linezolid peak (2hr & 6hr) and trough 1-2wks following treatment start	Repeat peak/trough drug levels if needed until targets achieved→					
Treatment monitoring	Directly observed therapy (DOT)/patient education	—————→						→
Nutritional assessment		—————→						→
Assess overall health, mental, emotional needs		—————→						→

Are there Drug-Drug Interactions?

DRUG RISKS & POPULATIONS

Drug-drug interactions

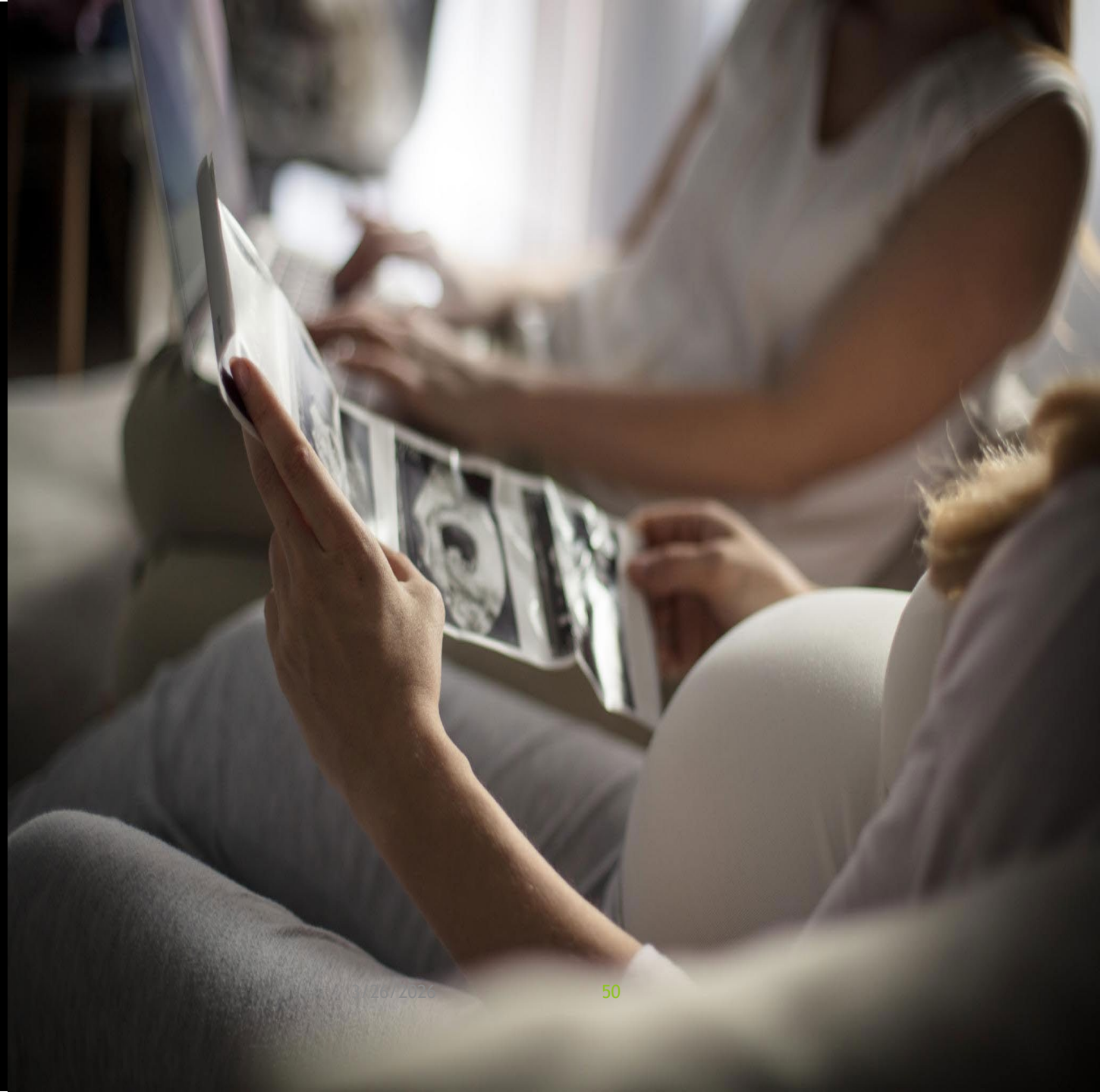
Bedaquiline (CYP450 metabolism) can interact with antiretrovirals, anticonvulsants, and other common meds; reconcile medications at baseline and whenever therapy changes.

Special populations

HIV: select ART to reduce interactions and overlapping toxicities. Pregnancy and pediatrics: limited data—seek expert consultation before use.

Individualized implementation

Pre-existing cardiac disease, anemia, or neuropathy may raise risk; tailor regimen choice to anticipate complications and protect treatment success.





ADVERSE EVENTS

LINEZOLID TOXICITY

Most common clinically significant issue: cytopenias and peripheral/optic neuropathy. Prioritize early recognition and proactive dose adjustment.

QT PROLONGATION

Bedaquiline + moxifloxacin can increase QTc. Use thresholds to guide monitoring frequency, electrolyte correction, and temporary interruption when needed.

KEEP THE REGIMEN

Most toxicities are manageable without stopping BPaLM when response is prompt and systematic. Multidisciplinary care improves safety and outcomes.

SOURCING & EXPERT SUPPORT

Structured sourcing pathways

Coordinate with public health programs, specialty pharmacies, and—when needed—national TB authorities. Bedaquiline and pretomanid may require specific access and regulatory steps.

Engage TB programs early

Early coordination helps prevent treatment delays and supports uninterrupted medication supply across the full regimen course.

Expert consultation is essential

Partner with experienced TB clinicians and consultation services for eligibility, dosing, adverse event management, and sourcing logistics to translate guidance into outcomes.

Sample Footer Text



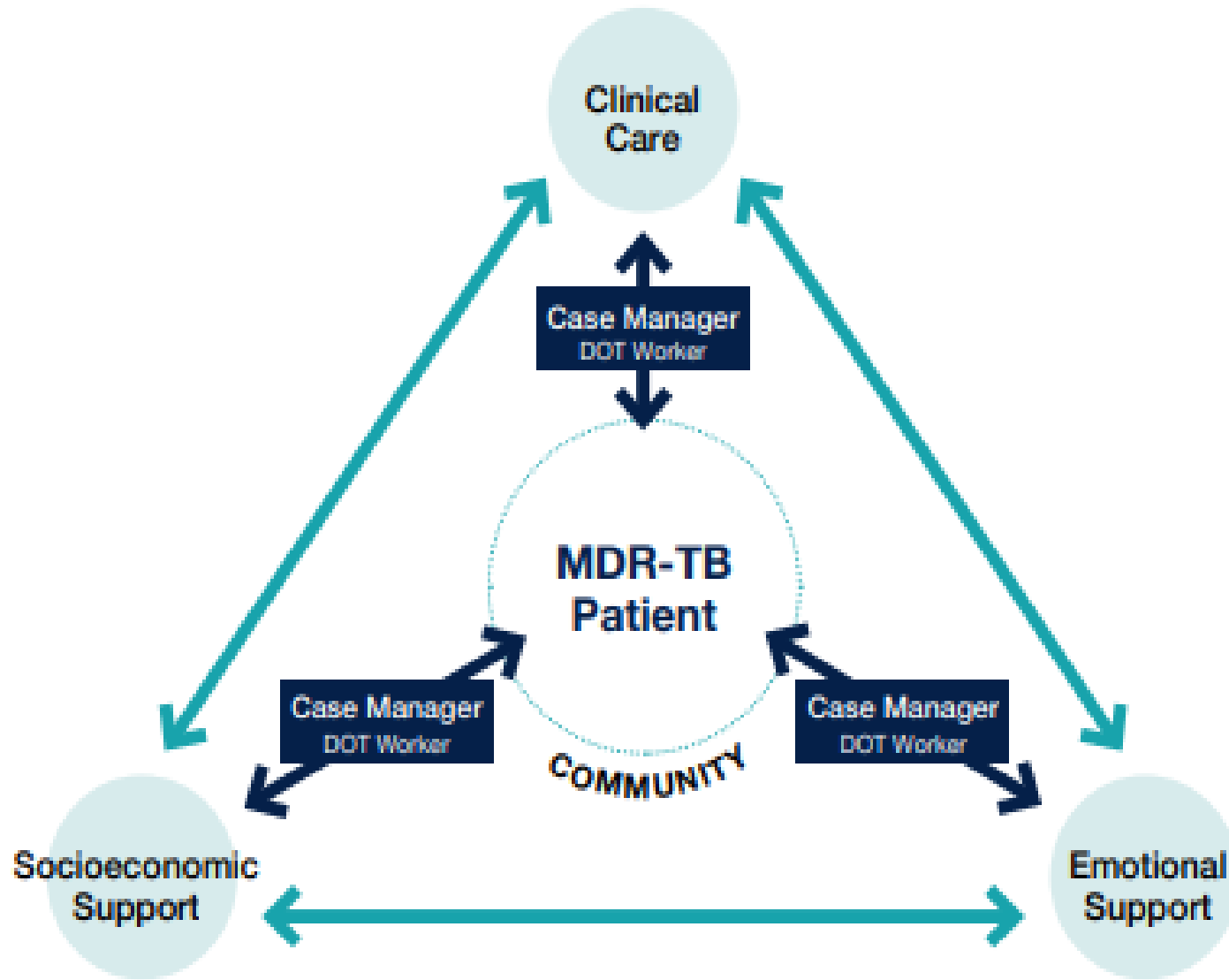
3/27/2019

52

POST-TREATMENT MONITORING

- ▶ End of treatment sputum culture and CXR
- ▶ Post-treatment monitoring for a minimum of 2 years (to monitor for relapse)
- ▶ At 3, 6, 12 and 18 months get:
 - ▶ Symptom review
 - ▶ Medical evaluation
 - ▶ Sputum for AFB and culture
 - ▶ CXR

FIGURE 1. **Community-Based Model of DR-TB Treatment**



Adapted with permission from *The Community Based Model of Multidrug-Resistant Tuberculosis Treatment*, Jaime Bayona, MD, MPH, Socios En Salud Sucursal, Peru

PERSON-CENTERED CARE



STAFF

Healthcare & community workers to conduct clinic and community based active case finding; to conduct TB treatment literacy & to support people requiring treatment.



STUFF

Bedaquiline, pretomanid, linezolid, and moxifloxacin; TB tests to diagnose TB and drug-resistance and to monitor treatment and test for adverse effects of medicines.



SPACE

A place for people undergoing TB testing; to collect treatment regimens; to meet with healthcare providers.



SYSTEMS

Updated national guidelines, medicines lists, and healthcare worker trainings; drug registration or waivers via National Regulatory Authorities; updated tenders to procure “stuff” to support treatment.



SUPPORT

Patient-centered models for administering TB treatment, including nutritional, psychosocial and other packages that ensure a holistic approach to treatment support.

For diagnosis, treatment decisions and response monitoring: rapid molecular and phenotypic diagnostics and DST; smear and culture for monitoring

For safety monitoring: psychosocial assessment, peripheral neuropathy screening, visual acuity and color discrimination screening, chest X-ray, ECG, full blood count, liver function tests

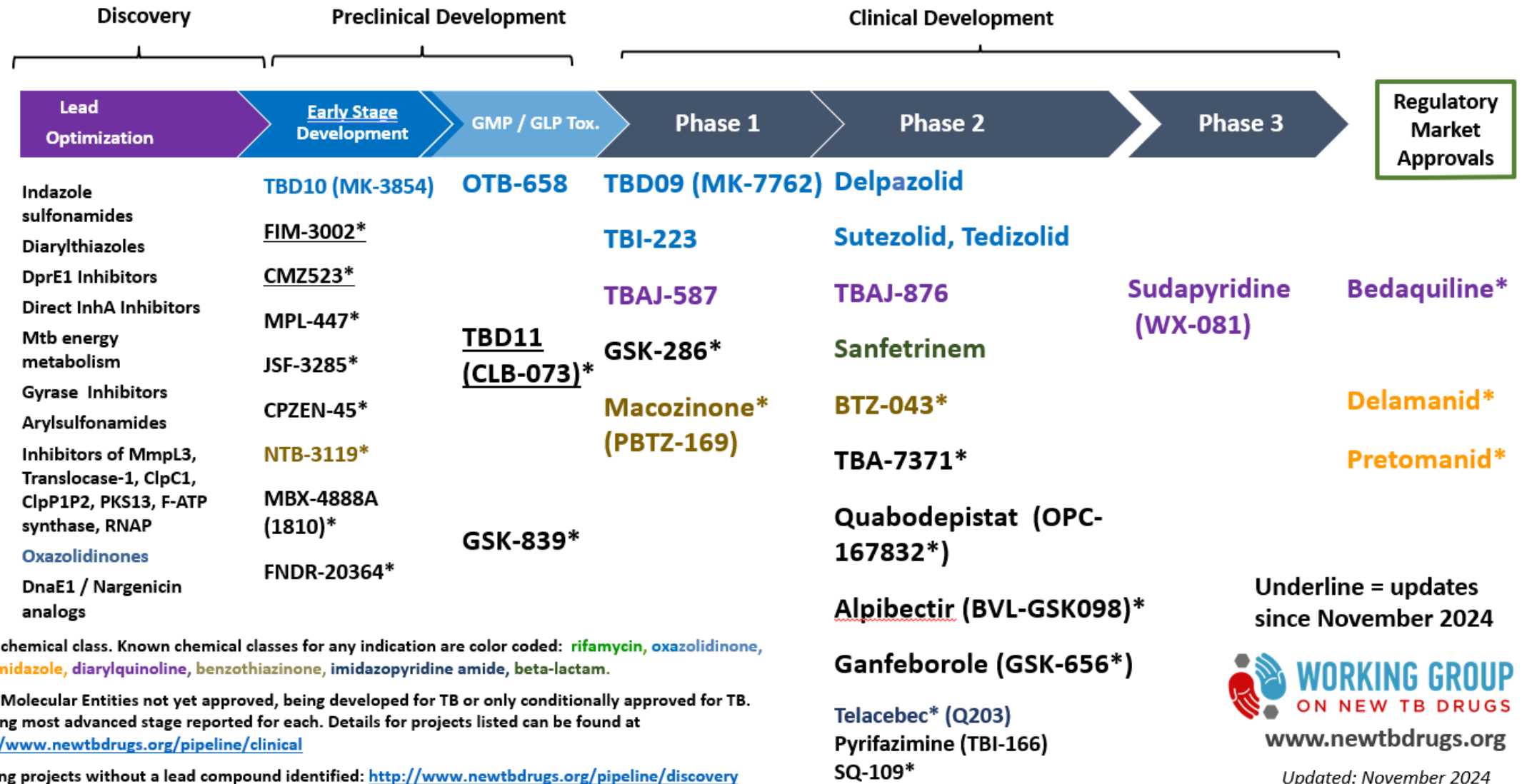
Social protection / material support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowances, housing incentives or financial bonuses

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3RD EDITION / 2022 UPDATES .
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3. Treatment of Drug-Resistant Tuberculosis
[https://www.cdc.gov/tb/publications/guidelines/pdf/Nahid_et_al-2019-
American_Journal_of_Respiratory_and_Critical_Care_Medicine.pdf](https://www.cdc.gov/tb/publications/guidelines/pdf/Nahid_et_al-2019-American_Journal_of_Respiratory_and_Critical_Care_Medicine.pdf)
4. Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. Updated February 2, 2022

□

2024 Global New TB Drug Pipeline¹





ANY
QUESTIONS?