Drug Resistant Tuberculosis

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

Drug Resistant Tuberculosis

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When Does Lab Report Resistance?

- When molecular testing shows mutation c/w drug resistance
- When 1% or more of the mycobacterial population grows on a culture which contains a drug at a certain specified concentration - In comparison to amount which grows on a plate without the drug
  - If treatment is given with the drug, eventually all the mycobacteria in that population will become resistant

XDR-TB

Extensively Drug Resistant Tuberculosis

Isoniazid

Ethambutol

Rifampin

Streptomycin

Ethionamide

Ofloxacin

Rifabutin

Kanamycin

Capreomycin

CDC Classification: Drug Resistant Tuberculosis

$MDR_{H\&R}$

Resistant to…

Rifampin ✚ Isoniazid

Pre-XDR

Resistant to…

Rifampin ✚ Isoniazid ✚ Fluoroquinolone OR Amikacin ***OR*** Kanamycin ***OR*** Capreomycin

XDR

Resistant to…

Rifampin ✚ Isoniazid ✚ Fluoroquinolone ✚ Bedaquiline ***OR*** Linezolid ***OR*** Amikacin Kanamycin Capreomycin

No Mention of Rifampin Mono-Resistant TB

WHO Overarching Principals for New Definition of XDR TB January 2021

- **Simple:**
- **Measurable:**
- **Relevant to programs:**
  - Should signal a very serious form of TB and the need for such patients to have a regimen that is different to the regimen for patients with MDR-TB, or other less serious forms of DR-TB.
- **Future-proof:**
  - Accomplished by use of “Group A” drugs instead of specific drugs; allows new Group A drugs in the future.
    - CDC definition includes linezolid and bedaquiline in place of Group A designation; ignores delamanid and pretomanid and all future drugs

WHO Classification: Drug Resistant TB

January 2021

Group A Drugs
Levofloxacin/Moxifloxacin
Bedaquiline
Linezolid

Note: No mention of the injectable agents by WHO

- **Rifampin Resistant (RR)/MDR** (INH and rifampin resistant)
  - Grouped together
- **Pre-XDR-TB:** TB caused by M. tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to **any fluoroquinolone**
- **XDR-TB: TB** caused by M. tuberculosis strains that fulfill the definition of MDR/RR-TB and that are also resistant to any **fluoroquinolone and at least one additional Group A drug.**

INH Resistant TB

- MTB resistant to either low or high level INH
- May be mono-resistant or associated with resistance to other drugs (except rifampin as it then is MDR TB)

Diagnosis of Drug Resistant TB:

First step - consider the possibility -------

WHEN Patient Notes:

- Prior TB treatment
- Inadequate prior treatment
  - Inadequate regimen
  - Drug shortage
  - Drug toxicity
  - DST not done to guide RX
- Poor response to treatment
- Poor adherence to past treatment

WHEN Patient

- Is from areas where DR TB is common
- Has recurrent/relapsed TB
  - with history of poor adherence
- Has history of exposure to a person with DR TB

Management of Patient MDR/RR TB is Suspected/Identified

- Stop RIPE treatment
  - If patient seriously ill contact a consultant to help with an empiric regimen pending more information
- Request Xpert testing if not yet done (remember can be done on smear or culture.
- Submit specimen to CDC for Molecular Detection of Drug Resistance (MDDR – sequencing) to confirm rifampin resistance testing if Xpert identifies rifampin resistance
  - Even if DST results are complete – we cannot test for linezolid, BDQ, clofazimine,
- Obtain initial assessments needed to decide on the initial regimen
  - LAB: CBC, CMP, calcium, magnesium, potassium, TSH
  - Assess for visual acuity, Ishihara, peripheral neuropathy
  - EKG
  - Identify other medical comorbidities/medications

Diagnosis of Drug Resistant TB

Initial specimen

- **Xpert (NAAT)**
  - Sputum specimen or culture
  - Gives same day information as to possible rifampin resistance
  - If positive for rifampin resistance further testing needed to confirm or identify false negative
- **Whole genome sequencing**
  - Initial culture
  - Many states preform on all isolates
    - In Texas not a diagnostic tool rather an epidemiological tool
    - In Texas the isolates are batched
  - Florida, New York
    - A diagnostic tool; results in one week

If Xpert is positive for MTB and rifampin resistance

- Additional testing (CDC/other reference lab)
  - Confirm rifampin resistance with pyrosequencing or Sanger sequencing or targeted Next Genome Sequencing
- If rifampin resistance confirmed, molecular testing:
  - All first line drugs and fluoroquinolones
  - bedaquiline, linezolid, clofazimine
  - Not yet available for pretomanid
- Culture based drug susceptibility studies for all first- and second-line drugs
  - Not yet available for bedaquiline, clofazimine or linezolid or pretomanid at CDC lab
  - Refer to other labs if mutations noted on molecular testing

Also Consider asking for Molecular Testing when:

- There is clinical or epidemiological evidence of INH mono-resistant TB
  - Treatment is different
  - If ethambutol is stopped prior to diagnosis of INH resistance that leaves rifampin “unprotected” and at risk of development of rifampin resistance.
- To document FQN susceptibility ideally before it is added to a treatment regimen
- To identify drug resistance in Group A drugs not part of DST testing
  - Bedaquiline, linezolid, clofazimine, pretomanid

What about Discrepancies in Rifampin Susceptibility?

Molecular tests and Culture Based DST

- **Rifampin?**
  - **Molecular testing** done by whole genome sequencing pyrosequencing, Sanger or next genome sequencing (not Expert) is:

"Gold Standard"

- Culture may miss rifampin resistance
  - MGIT (liquid media) misses more than solid media testing
- Often may be due to lower level of rifampin resistance
  - But these are clinically significant – cannot be treated with standard regimen

Treatment of Drug Resistant TB

INH Resistant Tuberculosis

Treatment of Drug-Resistant TB

An Official Clinical Practice Guideline

ATS, CDC, ERS, IDSA Drug Resistant TB Guideline CID Dec 2019

- We *suggest adding a later generation FQN* to a 6 month regimen of daily rifampin, ethambutol and PZA for patients with INH resistant TB

- In patients with INH resistant TB treated with a daily regimen of later-generation FQN, rifampin, ethambutol and PZA, we *suggest that the duration of PZA can be shortened to 2 months* in selected situations (non-cavitary and lower-burden disease or toxicity)

INH Resistant TB

WHO Consolidated Guidelines Module 4

Guidelines Development Committee (GDC) recommended

2025

- In patients with confirmed ***rifampicin susceptible*** INH resistant TB, treatment with rifampin, EMB, PZA and ***levofloxacin is recommended*** for duration of 6 months.
  - PZA given for at least 3-4 months associated with better outcomes

- In patients with confirmed rifampin susceptible, INH resistant TB, it is *not recommended* to add streptomycin or other injectable agents to the treatment regimen.

Clinical Scenarios: Implementation

- When INH resistance and **rifampin susceptibility known and before treatment start**:
  - Treat with Rifampin/EMB/PZA/FQN
  - Confirm FQN susceptibility
  - Start timing of modified regimen with start of FQN

- INH resistance noted **after start of RIPE while still on RIPE**
  - **Confirm rifampin susceptibility before adding FQN**
  - **Confirm FQN susceptibility**

- INH resistance noted **after start of RIPE but patient switched to RI** only before confirming DST results:
  - **Confirm rifampin susceptibility on a new specimen before starting acquired rifampin resistance possible!**
  - **Confirm FQN susceptibility**

Treatment of MDR TB pre-2019

- 20-24 months of treatment
- 6-8 months of an injectable
- 4-6 less effective second line drugs
- 50% cure, 10% mortality

When Bedaquiline resistance we are right back here

From this to ----

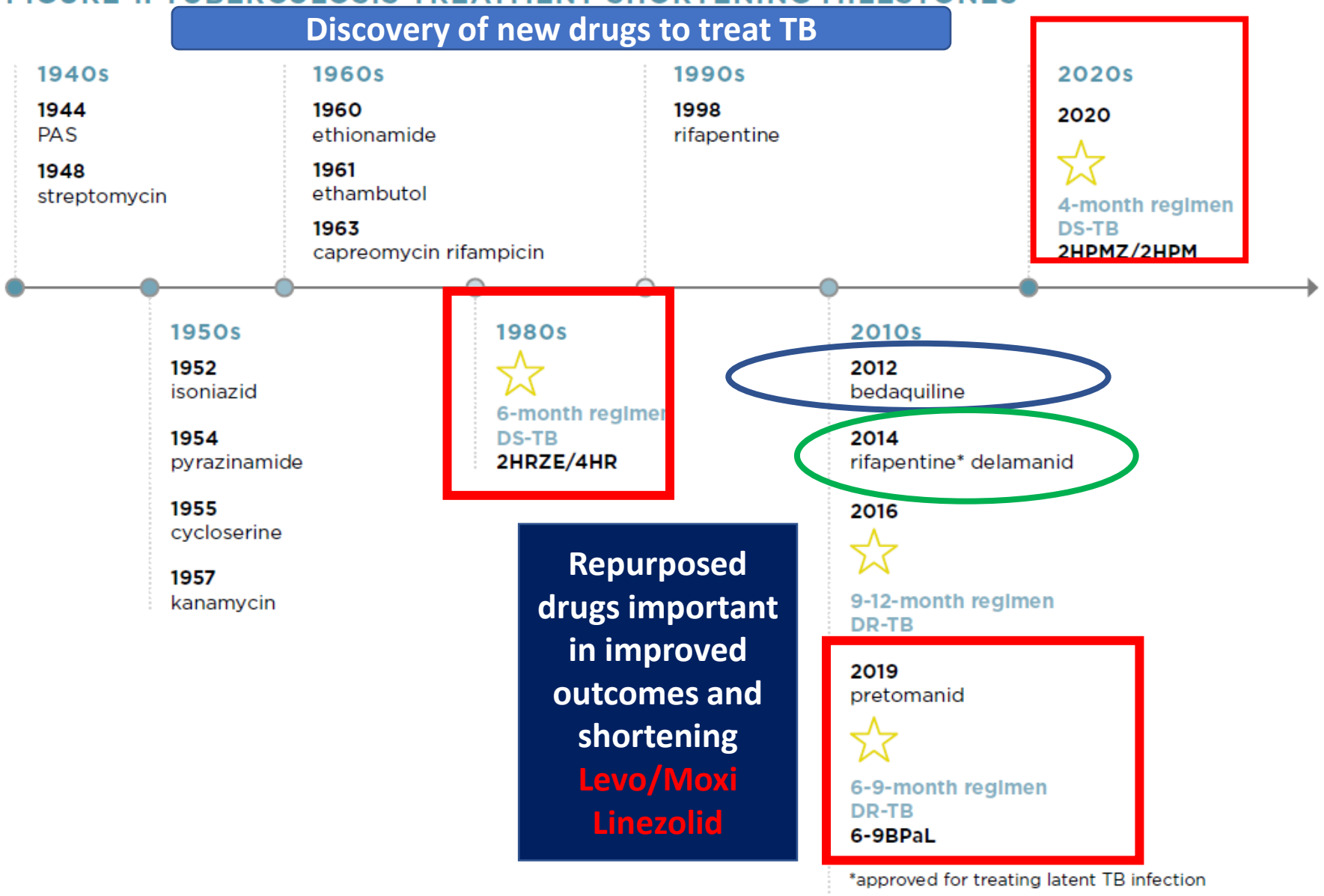
The medicine and syringes to treat one MDR-TB patient for one year.

Patients need treatment for 18–24 months

IDSA fact sheet 2013

- **Staggering Medication Burden**

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

TAG PIPELINE REPORT 2012

Novel Compounds to Treat Active TB Disease

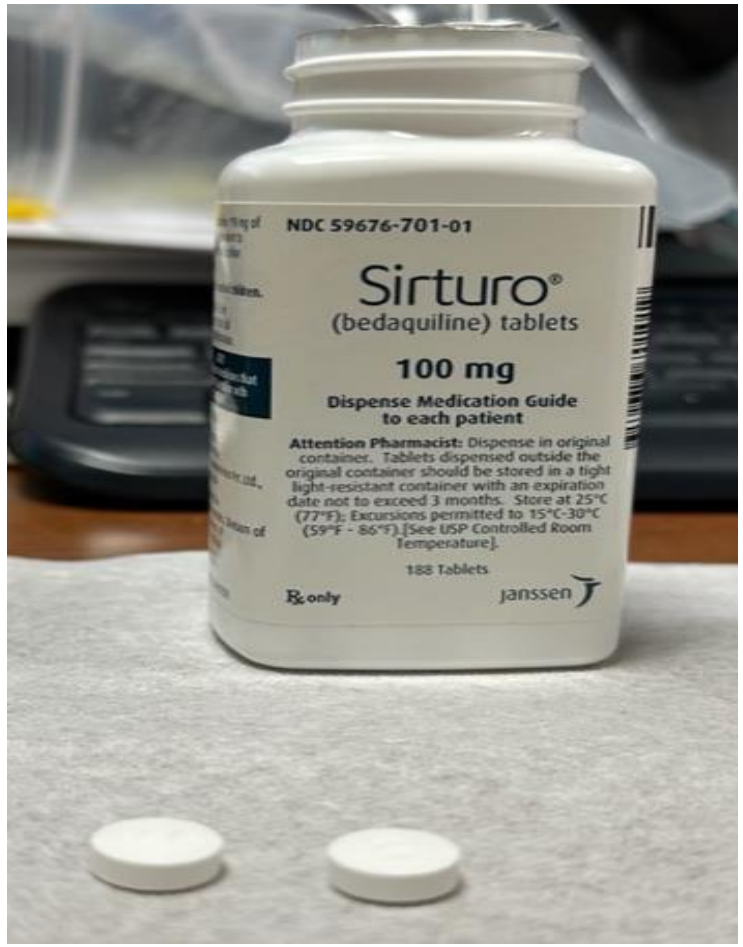
TABLE 3. Novel and Second-Generation Compounds in Late-Stage Clinical Studies for Active TB as of June 2012

Agent	Class	Sponsor	Status	Indication	New Combination Study
delamanid (OPC-67683)	nitroimidazole*	Otsuka	Phase III	DR-TB	—
AZD5847	oxazolidinone	AstraZeneca	Phase IIa	TBA	—
sutezolid (PNU-100480)	oxazolidinone	Pfizer	Phase IIa	DR-TB	—
bedaquiline (TMC207)	diarylquinoline*	TB Alliance/ Janssen	Phase II	DS-TB	NC001, NC003
		Janssen	Phase II	DR-TB	
PA-824	nitroimidazole*	TB Alliance	Phase II	DS-TB/ DR-TB	NC001, NC002, NC003
SQ109	diamine	Sequella/ PanACEA‡	Phase II	DS-TB/ DR-TB	—

*indicates new drug class
†DS-TB indicates drug-sensitive TB; DR-TB indicates drug-resistant TB; TBA indicates to be announced
‡The Pan-African Consortium for Evaluating Anti-tuberculosis agents

2012:Bedaquiline available for compassionate use
Pa-824 - Pretomanid

2022: Bedaquiline - Core Drug for MDR/XDR TB



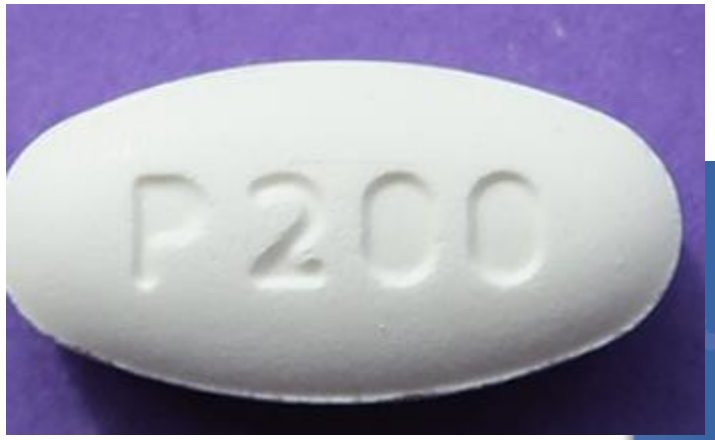
TB Alliance

ABOUT WHY NEW TB DRUGS? R&D ACCESS NEWS DONATE

FDA Approves New Treatment for Highly Drug-Resistant Forms of Tuberculosis

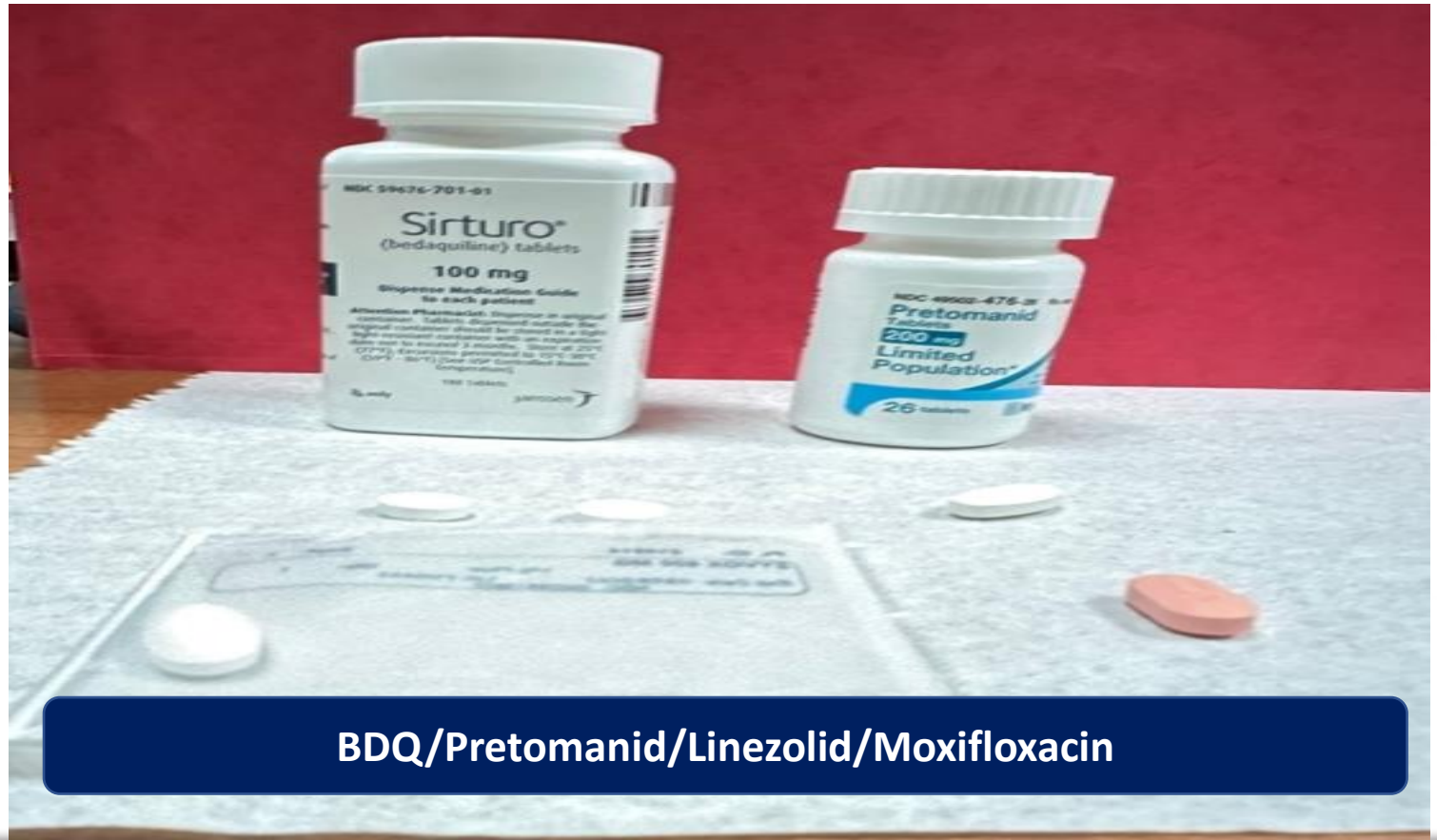
Pretomanid, developed by the non-profit TB Alliance, has received U.S. approval in combination regimen with bedaquiline and linezolid for people with XDR-TB or treatment-intolerant/non-responsive MDR-TB

August 14, 2019 Approved As
“THE” Regimen
BPaL
later - BPaLM

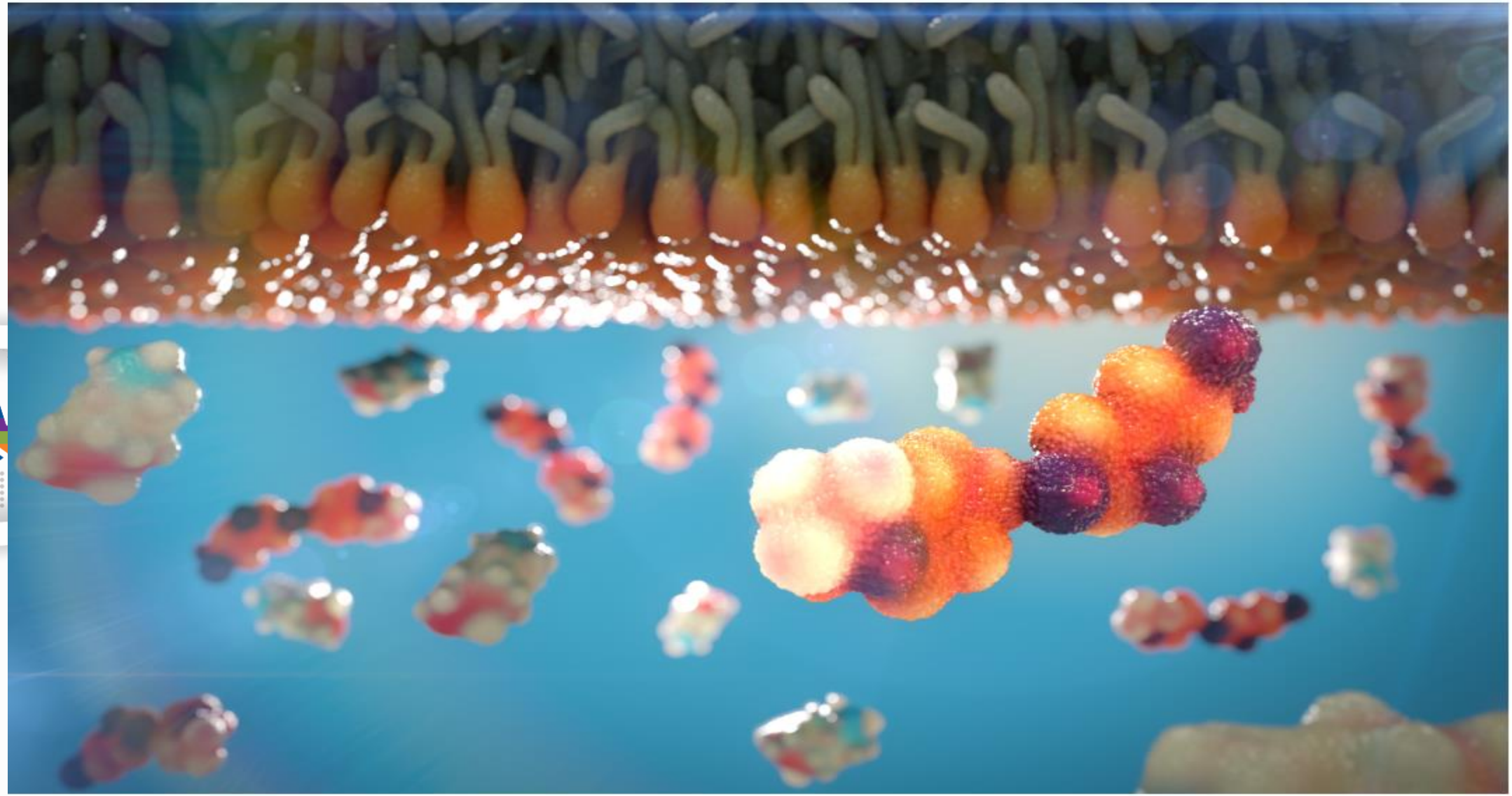


BPaLM (BPaL plus Moxifloxacin)

- 7 tablets x 2 weeks, then 5 tablets



BDQ/Pretomanid/Linezolid/Moxifloxacin



Artist's rendering of the pretomanid compound.

ATS, CDC, ERS, IDSA Updates on the Treatment of Drug Susceptible and Drug-Resistant TB

Am J Respir Crit Care Med Jan 2025

Q3: Treatment of Rifampin-Resistant, Fluoroquinolone Resistant TB	
Recommended BPaL Regimen‖	
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk
Q4: Treatment of Rifampin-Resistant, Fluoroquinolone-Susceptible TB	
Recommended BPaLM Regimen¶	
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk
Moxifloxacin	400 mg daily for 26 wk

Treatment Options for RR/MDR TB
Six-month (26 weeks) regimens

WHO Consolidated TB Guidelines 2025

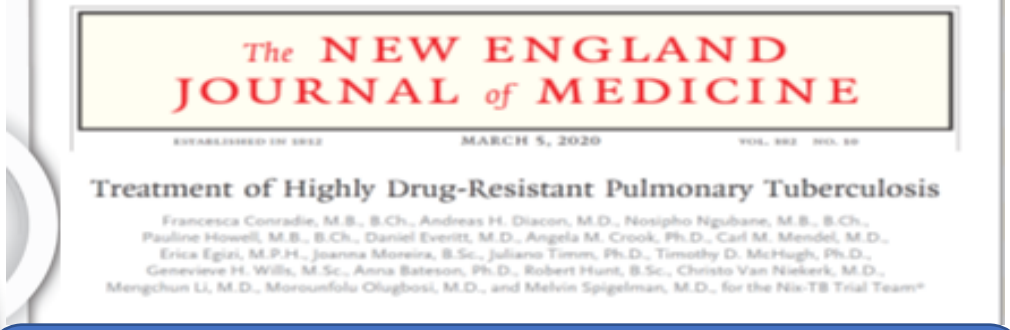
- **BPaLM:** BDQ/Pretomanid/Linezolid/Moxifloxacin 26 weeks
  - Recommended for all unless FQN resistant or intolerant
    - Linezolid dose 600 mg once daily

- **BPaL:** BDQ/Pretomanid/Linezolid 26 weeks x 6 months
  - Recommended if FQN resistant MTB
    - Linezolid dose 600 mg once daily as identified by ZeNix study

- **BDLLfxC (BEAT TB):**
  BDQ/Delamanid/Levofloxacin/Linezolid/Clofazimine Stop clofazimine if FQN susceptible or stop Moxifloxacin is FQN resistant
  - Recommended when pretomanid cannot be used (children, pregnancy)
  - In U.S. Delamanid is compassionate use drug

BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid


The NEW ENGLAND JOURNAL of MEDICINE

MARCH 5, 2020

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Bedaquiline 400 mg (14 days); 200 mg M/W/F
Pretomanid 200 mg daily
Linezolid 1200 mg daily

All Oral
Open Label – Observational
*109 patients
65% XDR
51% HIV +
84% cavitary on CXR
Unresponsive to treatment or intolerant

Favorable Treatment Outcomes
XDR TB 89%
MDR TB 92%
Relapse
XDR TB: 1/MDR TB: 1

Time to Culture Negative: MDR vs XDR TB

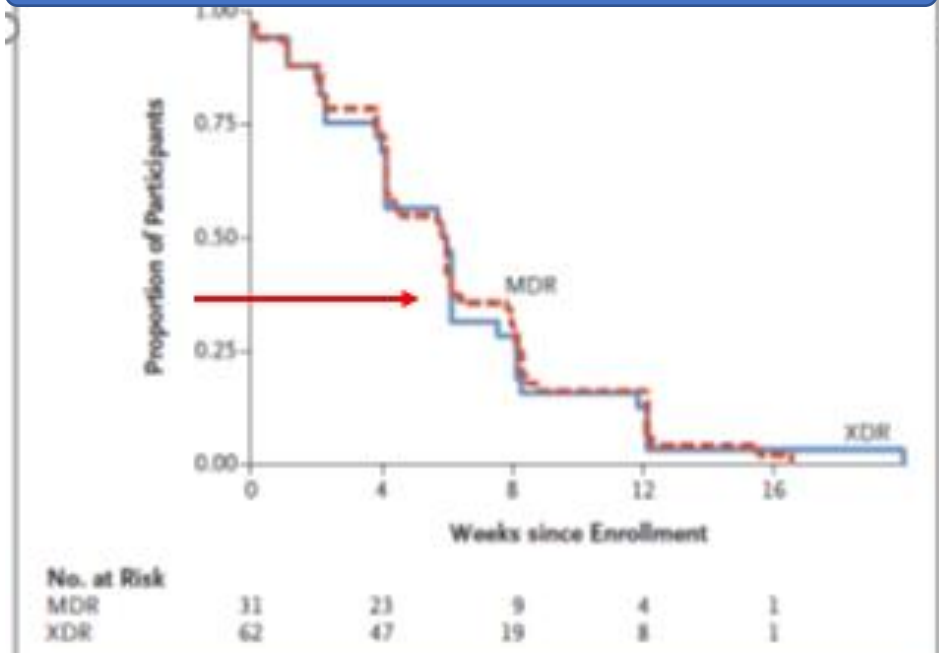


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

BUT …… BPaL Adverse Events

- Adverse Effects:
  - HIV negative: 100%
  - HIV positive: 100%

- Adverse Effects by Linezolid dose
- 1200 mg once daily: 100%
- 600 mg twice daily: 100%

Myelosuppression 48%
Peripheral neuropathy 81%

ZeNix: Linezolid Optimization Trial

ZeNix

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment

NEJM September 2022

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

Randomize

- B-Pa-L L=1200 mg/d x 6 mos
- B-Pa-L L=1200 mg/d x 2 mos
- B-Pa-L L=600 mg/d x 6 mos
- B-Pa-L L=600 mg/d x 2 mos

6 months of treatment

Additional 3 months if sputum culture positive at 4 months

1° follow up for relapse-free cure 6 months after end of treatment; Full f/u 24 mos after end of treatment

N=30 XDR-TB per group AND
up to 15 pre-XDR or intolerant/non-responsive MDR-TB per group

Pa dose = 200 mg daily; B Dose = 200 mg daily x 8 weeks, 100 mg x 18 weeks

ZeNIX: Linezolid Optimization Trial

MDR or XDR TB Treatment Failure or Intolerant

Safety 600 mg x 26 wk.

24% Peripheral neuropathy

2% Myelosuppression

- Only 13% required Linezolid dose modification at 600 mg/day dose

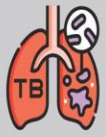
Efficacy

- LZD - 1200mg x 6 mo. - 93%
- LZD - 1200 mg x 9 wks. - 89%
- **LZD - 600 mg x 6 mo. - 91%**
- LZD - 600 mg x 9 wks. – 84%

Implementation of BPaL in the United States: Experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant TB disease

Haley et al., 2023 | *Clinical Infectious Diseases*

IDSA
Infectious Diseases Society of America



Several trials demonstrate an all-oral, six-month regimen of bedaquiline, pretomanid, and linezolid (BPaL) has 90% efficacy for treatment of highly drug-resistant tuberculosis (TB). However, significant toxicity results from linezolid 1200 mg. After U.S. FDA approval in 2019, the BPaL Implementation Group (BIG) rapidly implemented this regimen for rifampin-resistant (RR) and rifampin-intolerant (RI) TB using an initial linezolid 600mg dose adjusted by serum drug concentrations and clinical monitoring.

BIG COHORT (N=70)

Characteristics

- Ages 14-83 y, 90% non-U.S.-born
- 6% HIV, 13% liver ds, 16% peripheral neuropathy, 20% diabetes, 26% anemia

TB Disease

- 87% had RR-TB, 13% had RI-TB
- 24% had extrapulmonary disease

BPaL Treatment

- 94% initiated linezolid 600 mg
- 2 excluded (changed to rifampin-based therapy)

Outcomes reported for 68 persons

100% COMPLETED BPAL

Median duration 189 days

0 failed treatment

3% relapsed after completion

3% died after completion

TOXICITY WAS LOW

9% hematologic abnormalities

12% neurologic abnormalities

0 prolonged QT interval

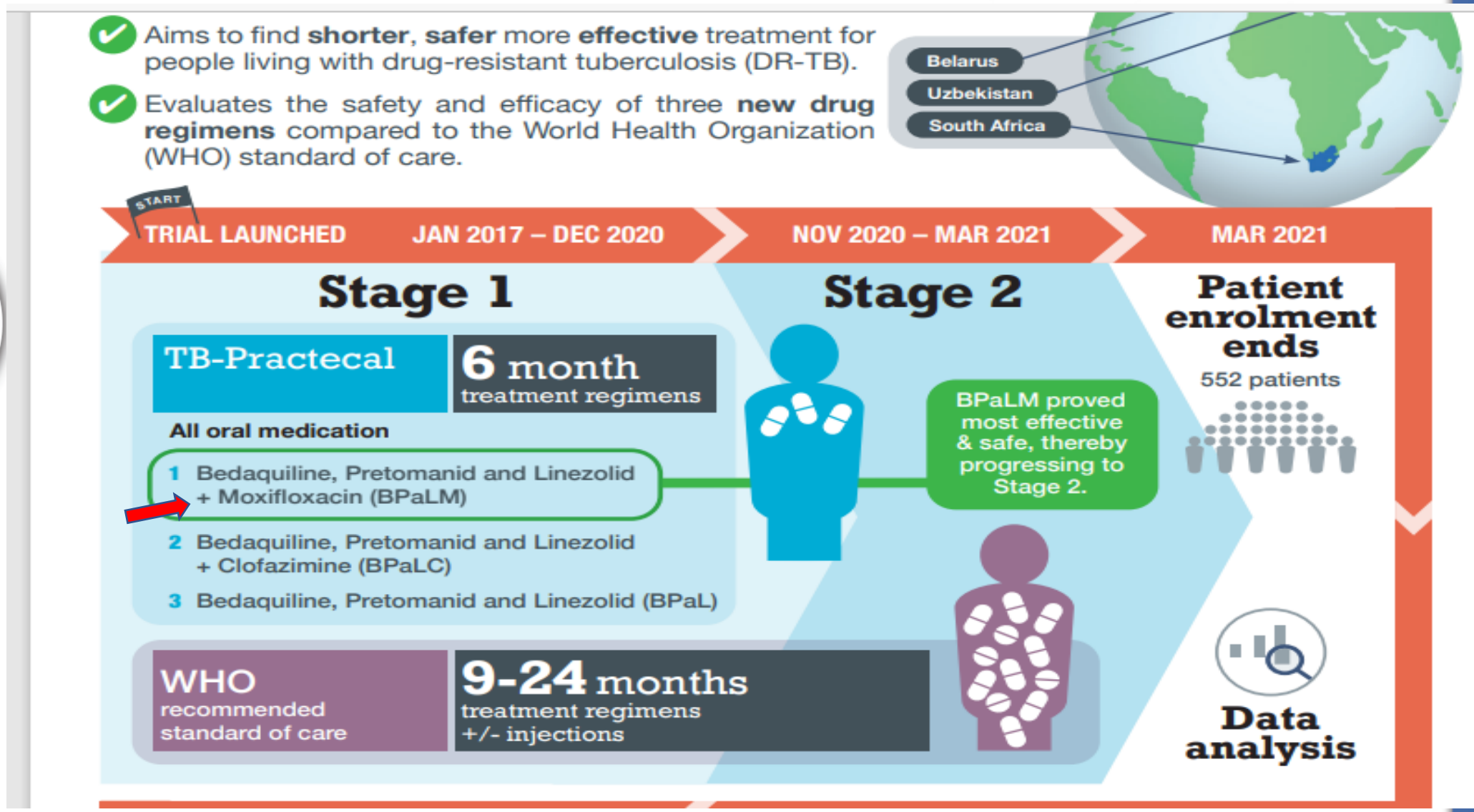
Only 4% stopped linezolid prematurely
62% had linezolid dose/interval adjusted
49% required linezolid only 3 time/week

This U.S. BIG cohort demonstrates that early implementation of an all oral, shorter and effective regimen for RR-TB and RI-TB is feasible. Lower initial linezolid dosing that is individualized lthrough TDM, close monitoring, and early management of adverse events likely enhanced BPaL safety and treatment completion.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad312

TB-Practecal Clinical Trial

randomized, controlled



TB PRACTECAL –

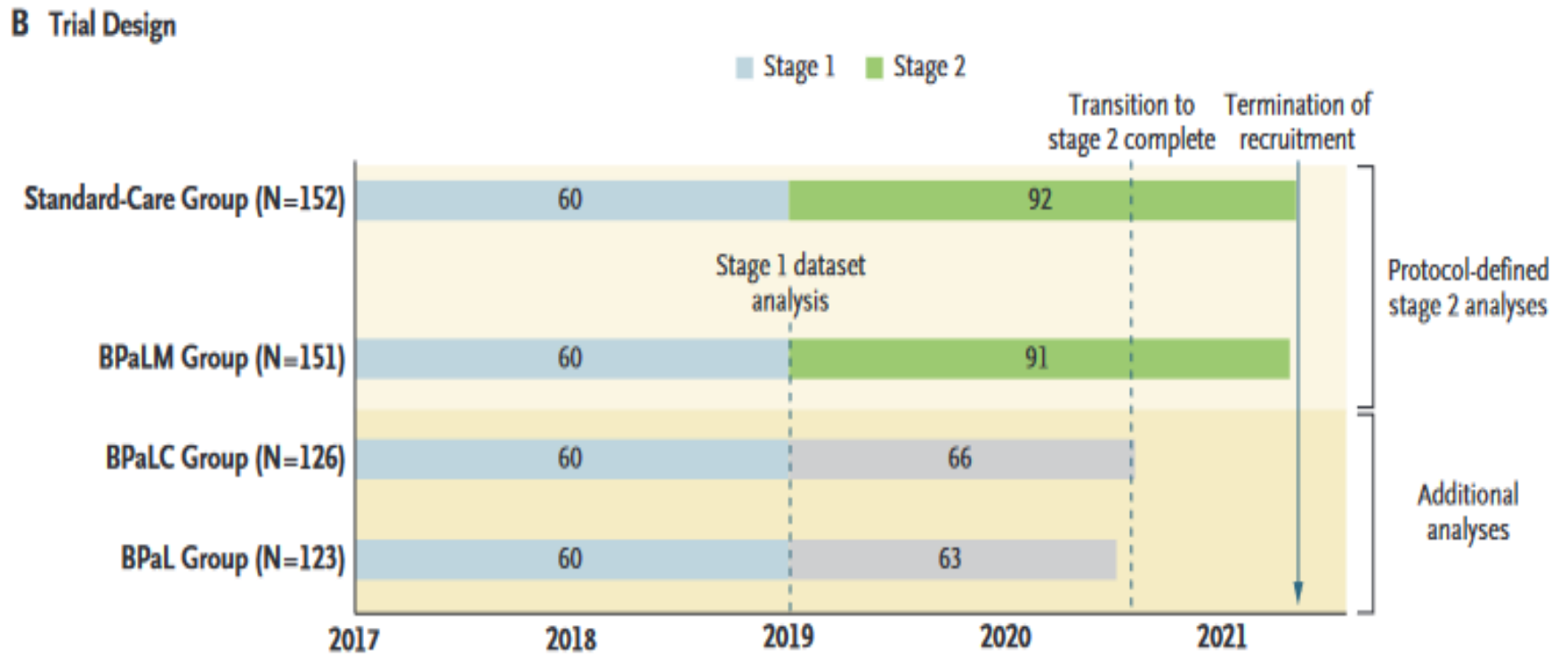
- Regimen 1:
- bedaquiline + pretomanid + linezolid + **moxifloxacin** for 26 weeks (**BPaLM or BPaL plus Moxi)**

- Regimen 2:
- bedaquiline + pretomanid + linezolid + **clofazimine** for 26 weeks

- Regimen 3:
- bedaquiline + pretomanid + linezolid for 24 weeks

- Standard of Care in Country at the time

TB-PRACTECAL
Belarus, South Africa and Uzbekistan

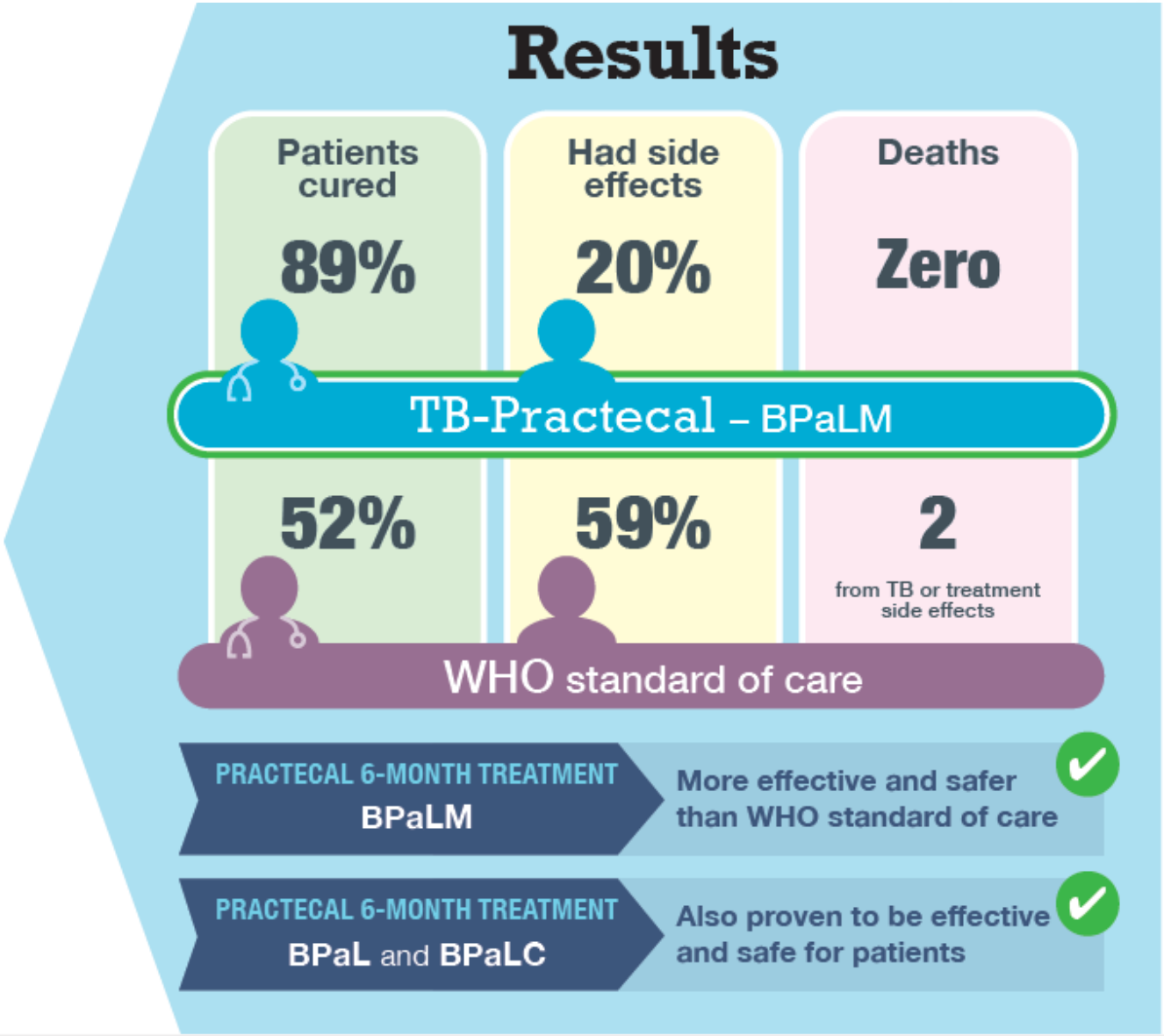


26 % FQN resistant in BPaLM group

Patient Population per protocol analysis SOC 33, BPaLM 57, BPaLC 58, BPaL 52

NEJM December 22, 2022

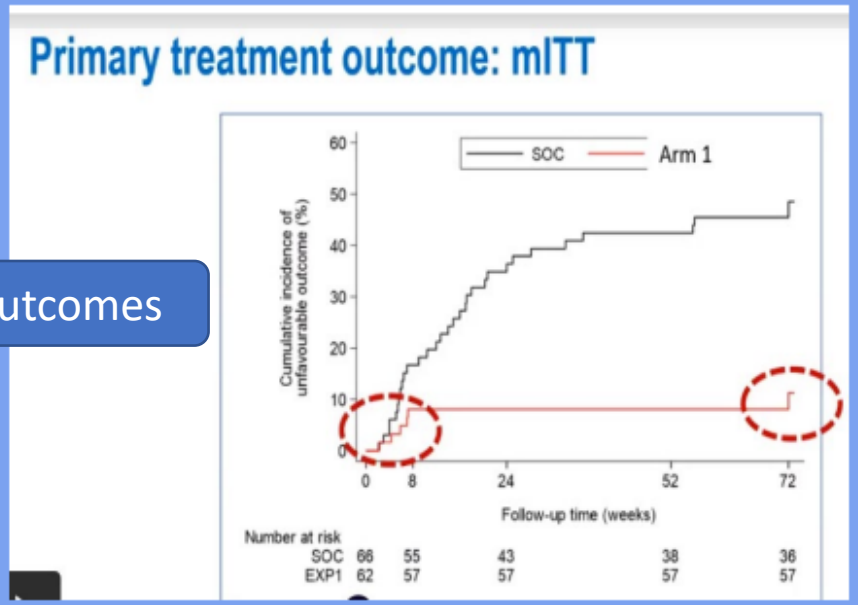
TB PRACTECAL



TB-PRACTECAL - Efficacy

- Arm 1: BPaLM: 89% favorable
- Arm 2: BPaLC: 81% favorable
- Arm 3: BPaL(modified): 77% favorable
- Arm 4: SOC: 52% favorable

Cumulative incidence of unfavorable outcomes



Short course treatment options for drug resistant TB when BPaLM or BPaL is not an option

6 – 9 months

All oral

Core drugs:

Bedaquiline

Pretomanid

Linezolid

Moxifloxacin

- **BDQ, LZD (2), Moxi core** 9 months
  - WHO includes in regimen:
    - BDQ, LZD (2), Moxi, high dose INH, EMB, PZA, Clofazimine x 4-6 months
    - moxifloxacin, clofazimine, EMB, PZA x 4 months
  - U.S. would likely include in regimen:
    - BDQ, LZD, Moxi throughout 9 – 12 months plus
    - Clofazimine or PZA
    - Cycloserine

(B)BDQ = bedaquiline, Pa = pretomanid, (L) LZD = linezolid, (M) Moxi = moxifloxacin

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Payam Nahid, Sundari R. Mase, Giovanni Battista Migliori, Giovanni Sotgiu, Graham H. Bothamley, Jan L. Brozek, Adithya Cattamanchi, J. Peter Cegielski, Lisa Chen, Charles L. Daley, Tracy L. Dalton, Raquel Duarte, Federica Fregonese, C. Robert Horsburgh, Jr., Faiz Ahmad Khan, Fayez Kheir, Zhiyi Lan, Alfred Lardizabal, Michael Lauzardo, Joan M. Mangan, Suzanne M. Marks, Lindsay McKenna, Dick Menzies, Carole D. Mitnick, Diana M. Nilsen, Farah Parvez, Charles A. Peloquin, Ann Raftery, H. Simon Schaaf, Neha S. Shah, Jeffrey R. Starke, John W. Wilson, Jonathan M. Wortham, Terence Chorba, and Barbara Seaworth; on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

This official clinical practice guideline was approved by the American Thoracic Society, the European Respiratory Society, and the Infectious Diseases Society of America September 2019, and was cleared by the U.S. Centers for Disease Control and Prevention September 2019

Am J Respir Crit Care Med Vol 200, Iss 10, pp e93–e142, Nov 15, 2019

All Oral Regimen!

	Drugs	Comments
Group A	Levofloxacin or moxifloxacin; bedaquiline; linezolid	Include all three medicines (unless they cannot be used)
Group B	Clofazimine; cycloserine or terizidone	Add both medicines (unless they cannot be used)
Group C	Ethambutol; delamanid; pyrazinamde; imipenem-cilastatin or meropenem (both must be given with clavulanic acid); amikacin or streptomycin; ethionamide or prothionamide; para-aminosalicylic acid	Add to complete a four-drug to five-drug regimen and when medicines from groups A and B cannot be used

Table 2: 2018 WHO grouping of medications for second-line drug-resistant tuberculosis[130]

Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	aOR 0.4 (0.3 to 0.5)	aOR 2.0 (1.4 to 2.9)
Fluoroquinolone: Moxifloxacin	Strong		Very Low	aOR 0.5 (0.4 to 0.6)	aOR 3.8 (2.8 to 5.2)
Fluoroquinolone: Levofloxacin	Strong		Very Low	aOR 0.6 (0.5 to 0.7)	aOR 4.2 (3.3 to 5.4)
Linezolid	Conditional		Very Low	aOR 0.3 (0.2 to 0.3)	aOR 3.4 (2.6 to 4.5)
Clofazimine	Conditional		Very Low	aOR 0.8 (0.6 to 1.0)	aOR 1.5 (1.1 to 2.1)
Cycloserine	Conditional		Very Low	aOR 0.6 (0.5 to 0.6)	aOR 1.5 (1.4 to 1.7)
Injectables: Amikacin	Conditional		Very Low	aOR 1.0 (0.8 to 1.2)	aOR 2.0 (1.5 to 2.6)
Injectables: Streptomycin	Conditional		Very Low	aOR 0.8 (0.6 to 1.1)	aOR 1.5 (1.1 to 2.1)
Ethambutol	Conditional		Very Low	aOR 1.0 (0.9 to 1.2)	aOR 0.9 (0.7 to 1.1)
Pyrazinamide	Conditional		Very Low	aOR 0.7 (0.6 to 0.8)	aOR 0.7 (0.5 to 0.9)
Injectables: Carbapenems w/ clavulanic acid	Conditional		Very Low	aOR 1.0 (0.5 to 1.7)	aOR 4.0 (1.7 to 9.1)
Delamanid	Concur with WHO conditional recommendation				
Ethionamide Prothionamide		Conditional	Very Low	aOR 0.9 (0.8 to 1.0)	aOR 0.8 (0.7 to 0.9)
Injectables: Kanamycin		Conditional	Very Low	aOR 1.1 (0.9 to 1.2)	aOR 0.5 (0.4 to 0.6)
P-Aminosalicylic Acid		Conditional	Very Low	aOR 1.2 (1.1 to 1.4)	aOR 0.8 (0.7 to 1.0)
Injectables: Capreomycin		Conditional	Very Low	aOR 1.4 (1.1 to 1.7)	aOR 0.8 (0.6 to 1.1)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	aOR 1.6 (1.2 to 2.0)	aOR 0.6 (0.5 to 0.8)
Amoxicillin-clavulanate		Strong	Very Low	aOR 1.7 (1.3 to 2.1)	aOR 0.6 (0.5 to 0.8)

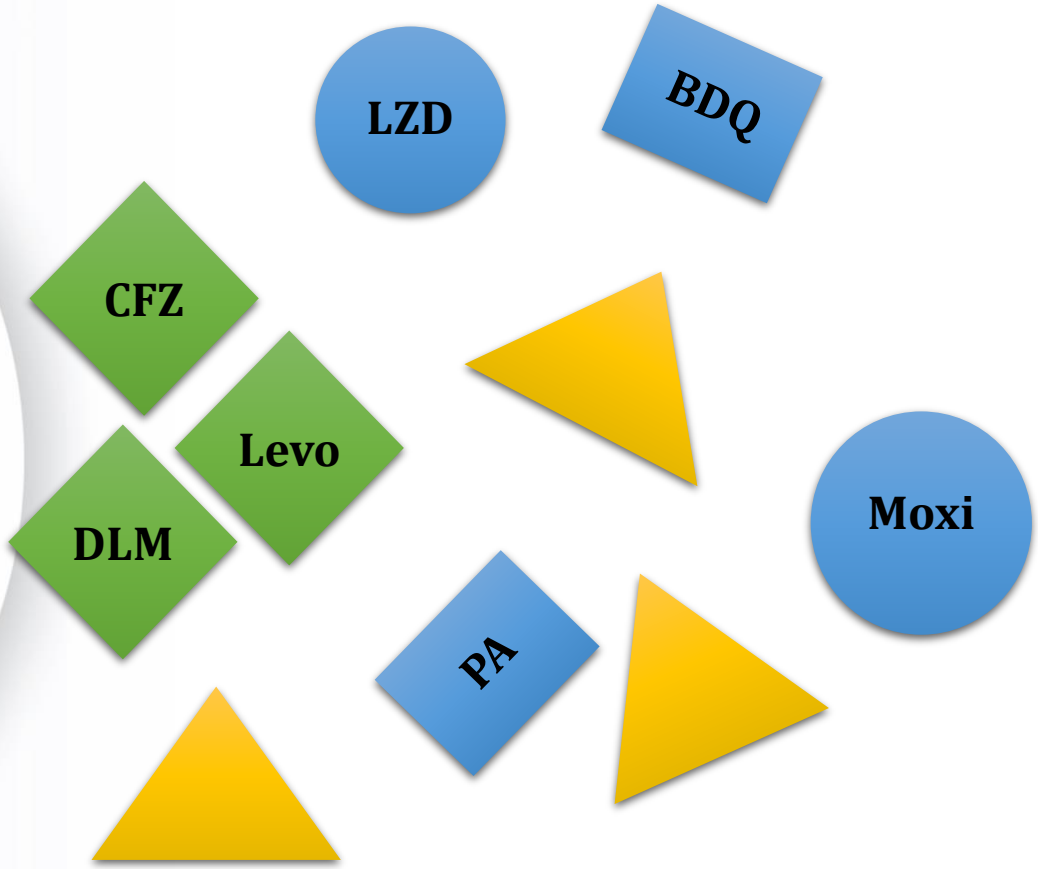
Figure 1. Summary of recommendations on drugs for use in a treatment regimen for patients with multidrug-resistant tuberculosis, including strength of recommendation, certainty in the evidence, and relative effects on death and treatment success. Additional details and other outcomes of interest are provided in the section on Drugs and Drug Classes, and in Appendix B: Evidence Profiles in the online supplement. Success is defined as end of treatment cure or treatment completion. aOR = adjusted odds ratio; CI = confidence interval; WHO = World Health Organization.

What else are we waiting for?

- **Expanded use of BPaLM or BPaL**
  - Children < 14 currently being studied
  - Pregnancy – currently being studied
  - CNS TB – no studies underway but some limited evidence that bedaquiline and pretomanid enter CNS
  - Other types of extra-pulmonary/ extensive TB disease
  - TB in special populations
    - Elderly
    - Transplants
    - Chemotherapy/Dialysis/Immunosuppressive medications
- **New drugs and regimens**
  - Reports of BDQ resistance and BPaL/BPaLM relapse

WHAT IS NEW?

TB Medication Soup Bowl



New MDR
FDA Approved

Repurposed Drug –
Essential Components

MDR - others

Investigational Drugs

22 new or investigational compounds
11 from new class or new mechanism
11 potentially advantage alterations to existing drugs

BDQ – bedaquiline CFZ – Clofazimine DLM – delaminid Levo – levofloxacin LZD – linezolid Moxi – moxifloxacin PA – pretomanid

BEAT Tuberculosis (South Africa)

6BDLz (Lx, C or both) no pretomanid

Allows treatment during pregnancy and for children < 14

Study Name (Type of TB; Sample Size)	Study Arms Experimental Regimens [Control Regimen]	Key Findings
BEAT Tuberculosis NCT04062201 (RR-/MDR-TB, Pre-XDR; 374 enrolled, 199 included in interim analysis)	**87% favorable outcome** (a) 6BDLz (Lx, C, or both) (b) [9–12mo SOC]	**Primary Efficacy Outcome:** **The six-month bedaquiline- and delamanid-based regimen had similar efficacy to the standard-of-care regimen (ITT).** The NI margin was 10%.

Unfavorable outcomes:		Risk difference, experimental-control (95% confidence interval)
(a)	13 (13%)	-1.4 (-10.9 to 8.1)
(b)	14 (14%)	NA

Primary Safety Outcome:
The six-month bedaquiline- and delamanid-based regimen had similar safety to the standard-of-care regimen.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	49 (25.7%)	33 (17.3%)	7 (3.7%)
(b)	51 (27.9%)	31 (16.9%)	6 (3.3%)

Similar safety and efficacy
But compared to newer SOC

BDQ & Delamanid no increase cardiac toxicity

Conradie F, Phillips P, Badet T, et al. High rate of successful outcomes treating RR-TB with a delamanid-bedaquiline regimen in BEAT Tuberculosis: an interim analysis. Presented at the Union World Conference on Lung health during LBTB The Union/CDC late-breaker session on TB. 2022 November

end TB

Non-inferior to SOC

Trial regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	B			L	M	Z
9BCLLfxZ	B		C	L	Lfx	Z
9BDLLfxZ	B	D		L	Lfx	Z
9DCLLfxZ		D	C	L	Lfx	Z
9DCMZ		D	C		M	Z
Control	Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis. Composed according to latest World Health Organization guidelines, as they evolved during the trial. This group included mostly participants treated with the 18-month conventional regimen.					

Figure **1**. *Composition of endTB trial regimens*

B denotes bedaquiline, L linezolid, M moxifloxacin, Z pyrazinamide, C clofazimine, Lfx levofloxacin, D delamanid

endTB

PIPELINE REPORT 2023

BDQ or Delamanid – no pretomanid

Table 1. Key Findings from Recently Completed Treatment-Shortening Trials

Study Name [Type of TB; Sample Size]	Study Arms Experimental Regimens [Control Regimen]	Key Findings
endTB NCT02754765 (MDR-TB, N=754)	[a] 9BLzMZ [b] 9BLzLxCZ [c] 9BDLzLxZ [d] 9DLzLxCZ [e] 9DMCZ [f] [9–20mo local SOC]	**Primary Efficacy Outcome:** **Three of the five nine-month endTB regimens (a, b, c) demonstrated noninferiority to the SOC (mITT and PP analyses). Regimen b also demonstrated superiority.** The NI margin was 12%.

Met margin of non-inferiority

89
90.4
85.2
78.8

	Favorable outcomes (mITT):	Risk difference, experimental - control (95% confidence interval)
(a)	105/118 (89.0%)	8.3 (-0.8 to 17.4)
(b)	104/115 (90.4%)	9.8 (0.9 to 18.7)
(c)	104/122 (85.2%)	4.6 (-4.9 to 14.1)
(d)	93/118 (78.8%)	-1.9 (-12.1 to 8.4)
(e)	89/104 (85.6%)	4.9 (-4.9 to 14.7)
(f)	96/119 (80.7%)	NA

Primary Safety Outcome:

The nine-month regimens had similar safety to the SOC regimen.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	69 (54.8%)	18 (14.3%)	3 (2.4%)
(b)	68 (55.7%)	16 (13.1%)	1 (0.8%)
(c)	78 (61.4%)	20 (15.8%)	3 (2.4%)
(d)	75 (60.5%)	18 (14.5%)	4 (3.2%)
(e)	72 (60.0%)	20 (16.7%)	2 (1.7%)
(f)	79 (62.7%)	21 (16.7%)	2 (1.6%)

Similar safety

Mitnick C, Khan U, Guglielmetti L, et al. SP01 Innovation to guide practice in MDR/RR-TB treatment: efficacy and safety results of the endTB trial. Presented at: Union World Conference on Lung Health. 2023 November 15. https://theunion.floq.live/event/worldconf2023/symposia?objectClass=timeslot&objectId=64ef5819e0400915b209e22f&type=detail.

81.5% of control regimen conformed to WHO guidance

Modified 9 month all oral regimens for MDR/RR TB

WHO Consolidated TB Guidelines 2025

- **WHO suggests using** the 9-month all oral regimens (**B**LMZ, **B**LLfxCZ, and **B**DLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR TB and in whom resistance to FQN has been excluded.
  - Among these regimens using **BLMZ is suggested over BLLfxCZ**
  - **BLLfxCZ is suggested over BDLLfxZ**

- **Who suggests against** using 9-month DCLLfxZ or DCMZ regimens with currently recommended longer (>18 mo.) regimens in patients with FQN susceptible MDR/RR TB

Treatment Options for RR/MDR TB
All oral longer regimens

WHO Consolidated TB Guidelines 2025

- **All oral modified 9-month regimens for FQN susceptible TB**
  - **BLMZ > BLLfxCZ > BDLLxZ**
- **All oral 9-month regimen**
  - 4-6 months of:
    - BDQ (4-6 mo.), Levofloxacin/Moxifloxacin (throughout RX), Linezolid (2 mo.), EMB, PZA, INH (high dose) and Clofazimine (6 mo.)
    - Can increase duration of initial phase to 6 months if slow response
  - 5 months Levofloxacin/moxifloxacin, EMB, PZA, and Clofazimine
- **Longer all oral** individualized regimen (18 months)
  - Use injectable drug only when no other options

Modified 9 month all oral regimens for MDR/RR TB

WHO Consolidated TB Guidelines 2025

- **Who suggests against** using 9-month DCLLfxZ or DCMZ regimens over currently recommended longer (>18 mo.) regimens in patients with FQN susceptible MDR/RR TB
  - Higher levels of failure or recurrence 11.2 % vs 2.5%
  - Higher levels of amplified resistance 6.7% vs 0%
  - Lower levels of death 2.8% vs 3.4%
  - Lower levels of adverse effects
- *Perhaps these regimens would be **helpful if longer?***

SimpliciTB - RIPE versus 4 months (drug susceptible) or 6 months BPaMZ(drug resistant)

Study Name (Type of TB; Sample Size)	Study Arms Experimental Regimens [Control Regimen]	Key Findings
SimpliciTB NCT03338621 (DS-TB; N=303) *Arm c was enrolled as an exploratory cohort (MDR-TB; N=152)	(a) 4BPaMZ (b) [2HRZE/4HR] (c) 6BPaMZ*	**Efficacy Outcomes:** **The four-month BPaMZ regimen failed to demonstrate noninferiority to the six-month SOC for DS-TB (mITT).** The NI margin was 12%.

Did not meet non-inferiority compared to HREZ

Highly potent but unfavorable outcomes
Hope when LZD not tolerated

Favorable outcomes:			Risk difference, experimental - control (95% confidence interval)
(a)	118/144 (81.9%)	81.9	10.27 (3.06 to 17.48)
(b)	134/144 (93.1%)	93.1	NA
(c)	111/133 (83.5%)	83.5	NA

Primary Safety Outcome:

The incidence of AEs was higher with 4BPaMZ compared to the 6-month standard of care regimen for DS-TB. A higher proportion of participants withdrew from treatment due to AEs (predominantly hepatotoxicity) in the 4BPaMZ arm.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	68 (45.3%)	17 (11.3%)	3 (2.0%)
(b)	61 (39.9%)	7 (4.6%)	1 (0.6%)
(c)	47 (31.5%)	16 (10.7%)	2 (1.3%)

Eristavi M, Variava E, Haraka F, et al. SimpliciTB Results and Hepatic Safety of Pretomanid Regimens +/1 Pyrazinamide [OA-109]. Presented at: 2023 Conference on Retroviruses and Opportunistic Infections during Oral Abstracts Session-02 TB and Hepatitis. 2023 February 20; Seattle, Washington.

- AE = adverse event; DS-TB = drug-sensitive TB; mITT = modified intention to treat; MDR-TB = multidrug-resistant TB; N = sample size; NA = not applicable; NI = noninferiority; PP = per protocol; RR-TB = rifampicin-resistant TB; SOC = standard of care
- Numbers at the beginning of each regimen or after the forward slash (for regimens with intensive and continuation phases) represent the duration of treatment in months, unless otherwise specified
- Letters represent the individual drugs comprising each regimen: B = bedaquiline, C = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, Pa = pretomanid, R = rifampicin, Z = pyrazinamide

SimpliciTB - RIPE versus 4 months (drug susceptible) or 6 months BPaMZ(drug resistant)

- Method was to study in drug susceptible TB to get initial information and to look for alternative 4 month regimen
  - Regimen **highly potent - 2.93 x more likely to reach culture conversion at 56 days but….**
  - Failed to meet non-inferiority due to unfavorable outcomes
    - 10% withdrew
    - Hepatotoxicity – likely due to combination of PZA and Pretomanid
      - **Stand Trial** Pretomanid/Moxifloxacin/PZA stopped due to safety. Restart allowed but TB Alliance decided to move forward with **NIX Trial** instead (BPaL).
- Drug resistant group added for safety analysis
  - Not powered for efficacy

CRUSH TB (CDC TB Trial Consortium)

drug sensitive TB but MDR type regimens

TBTC Study 38 / CRUSH-TB NCT05766267	4BMZRb 4BMZD [2HRZE/4HR]	DS-TB	288	IIc	Recruiting [Dec 2026]

Figure 1. Global Pipeline of Medicines in Clinical Development for TB

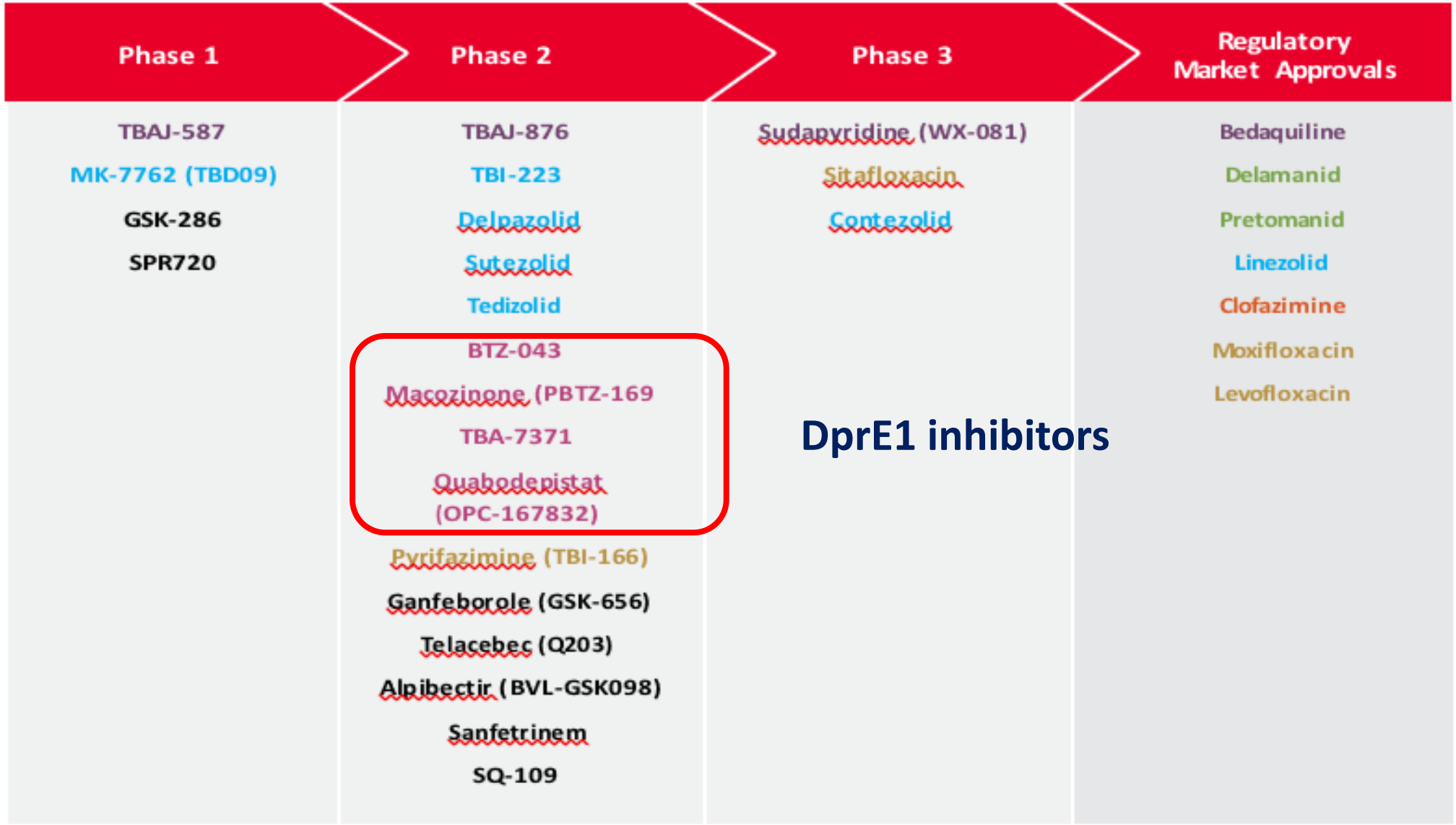


Figure adapted from Stop TB Partnership Working Group on New Drugs.
Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine Nitroimidazole; Fluroquinolone.
Drugs that appear in black font are from classes and/or with mechanisms of action not otherwise represented by the other colors.

Pipeline Report 2023

Table 8. Monitoring Plan for Patients Treated with BPaL or BPaLM*

ATS, CDC, ERS, IDSA Jan 2025

Activity	Month of Treatment										Post-Treatment†				
	0 (Baseline)	1‡	2	3	4	5	6	7	8	9	3	6	12	18	24
Sputum smear and culture§	●	● ● ●	●	●	●	●	●	○	○	○	●	●	●	●	●
Imaging (CXR, CT, other)‖	●			●			●			○	○	○	○	○	○
Weight¶	●	●	●	●	●	●	●	○	○	○	●	●	●	●	●
Symptom review**	●	●	●	●	●	●	●	○	○	○	●	●	●	●	●
DST††	●			○											
CBC‡‡	●	● ● ● ●	● ●	●	●	●	●	○	○	○					
Creatinine§§	●	●	●	●	●	●	●	○	○	○					
ALT/AST, alkaline phosphatase, bilirubin‖‖	●	●	●	●	●	●	●	○	○	○					
K^+, Ca^{2+}, Mg^{2+}, bicarbonate¶¶	●	●	●	●	●	●	●	○	○	○					
Serum drug concentration***		○													
HIV†††	●														
Pregnancy‡‡‡	○	○	○	○	○	○	○	○	○	○					
EKG§§§	●	● ○	○	●	○	○	●	○	○	○					
Vision exam‖‖‖	●	●	●	●	●	●	●	○	○	○					
Peripheral neuropathy¶¶¶	●	●	●	●	●	●	●	○	○	○					
Arthralgias****	●	○	○	○	○	○	○	○	○	○					
Amylase, lipase, TSH††††	○														

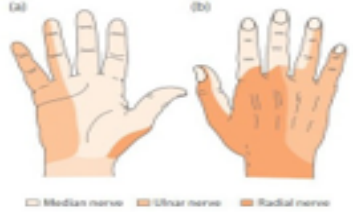
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

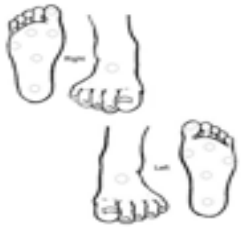
Additional information for selected nurse assessment (see complete toxicity assessment tool)

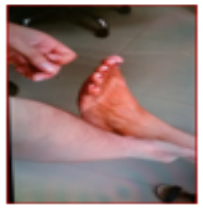
Peripheral Neuropathy

Peripheral neuropathy may be painful and is often non-reversible. Neuropathy usually manifests initially in the lower extremities, with sensory disturbances, but may also involve the upper extremities. Disturbances are often bilateral. Assess for:

- numbness (using a monofilament) or tingling
- burning, pain
- temperature sensation
- difficulty walking (unsteady gait/balance)
- decreased or absent deep tendon reflexes







Monthly assessment
Early Identification of Toxicity

Patient Education
Report early if symptoms occur

Behavior and Mood

Some TB medications may contribute to depression and in rare cases, suicidal ideation. Depressive symptoms may fluctuate during therapy. Although the risk may be increased in those with a history of depression, it is not an absolute contraindication to the use of cycloserine. Some patients with depression at baseline improve on cycloserine, as they respond to treatment.

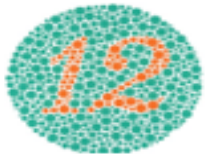
- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

Vision

Optic neuritis may exhibit as change in color vision or visual acuity. Loss of red-green color distinction may be detected first, however, a decrease in visual acuity is more common. Changes are usually reversible if detected early and medication is discontinued.

- Educate patients to report any vision changes.
- Screen patients using the Ishihara vision test and Snellen eye chart during monthly exams.

If either change is detected, hold linezolid and ethambutol, notify provider, and request referral to an ophthalmologist.



Ishihara Vision Test

Snellen Eye Chart

How long can the culture stay positive?

- Monitor culture monthly during treatment

- Drug susceptible TB or older MDR therapy
  - **Failure** identified if positive culture at **4 months or later**
  - Evaluation after 3 months of positive cultures recommended

- Unclear as to when failure is identified with shorter regimens

- Recommendation to extend therapy for 6-month regimens when response delayed.

- I often consider extending if positive at 3 months especially if clinical or radiographic response is delayed.

Therapeutic Serum Drug Level Monitoring

- No official absolute recommendation
- WHO and ATS/CDC/ERS/IDSA note may be helpful; especially a linezolid through
  - **Goal** is to keep linezolid trough < 2 as this seems to correlate, at least imperfectly with less toxicity
  - **Goal** also is to keep linezolid at 600 mg daily for initial 2 months if possible; WHO recommends this approach unless toxicity
  - Linezolid levels often not reproducible – be cautious with to change in dose

Preserved Efficacy and Reduced Toxicity with Intermittent Linezolid Dosing in Combination with Bedaquiline and Pretomanid in a Murine Tuberculosis Model

Bigelow et al : Antimicrobial Agents and Chemotherapy Oct 2020

- Compared C3HeB/FeJ and BALBC mouse models of TB
- Daily versus thrice weekly
  - Intermittent dosing introduced:
    - 1) from treatment start
    - 2) after initial period of daily dosing

- Daily dosing of linezolid for 1 – 2 months had greatest efficacy but after that results similar if intermittent dosing or drug stopped

Management of Treatment Interruptions and substitutions

Restarting bedaquiline depends on prior duration of treatment and duration of interruption

INT J TUBERC LUNG DIS 26(7):671–677

http://dx.doi.org/10.5588/ijtld.21.0678

Addressing bedaquiline treatment interruptions in the treatment of drug-resistant TB

C. Kambili,[1] S. Rossenu,[2] R. M. W. Hoetelmans,[2] E. Birmingham,[3] N. Bakare[4]

[1]Johnson & Johnson Global Public Health, New Brunswick, NJ, USA, [2]Janssen Pharmaceutica, Beerse, Belgium, [3]Janssen Research & Development, Titusville, NJ, USA; [4]Johnson & Johnson Global Public Health, Janssen Research & Development, Titusville, NJ, USA

SUMMARY

SETTING: The recommended dosing regimen for bedaquiline (BDQ), consisting of a 2-week loading phase (400 mg/day), followed by a maintenance phase (200 mg three times/week), might pose challenges when treatment is interrupted and needs to be reinitiated. Guidance on BDQ treatment re-initiation is, therefore, needed.

OBJECTIVE: This pharmacokinetic-based simulation study aimed to provide recommendations for re-initiating BDQ following treatment interruptions.

DESIGN: Simulations of treatment interruptions, defined as any time a patient misses ≥2 consecutive BDQ doses for up to 56 consecutive days (2 months), were assessed using the BDQ population-pharmacokinetic model.

RESULTS: Any treatment interruption lasting ≤28 days prior to completing the 14-day loading phase can be managed by completing the remaining loading doses. Scenarios when it is sufficient to simply restart maintenance dosing are discussed. In some scenarios, treatment interruptions require reloading for 1 week prior to restarting maintenance dosing.

CONCLUSIONS: This simulation study provided recommendations for managing BDQ treatment interruptions and underscores the importance of having a robust population-pharmacokinetic model for TB drugs to inform clinical guidance. Such recommendations are valuable to help ensure optimal treatment with BDQ for treating multidrug-resistant TB.

KEY WORDS: MDR-TB treatment; BDQ; pharmacokinetics; modelling; dosing

Treatment interruption with bedaquiline can be with restart of maintenance dose if

After completion of loading dose

Restart maintenance RX after interruption of	When prior exposure was
•20 days	•2 weeks
•20 days	•3 weeks
•21 days	•4 weeks
•22 days	•5 weeks
•24 days	•6 weeks
•26 days	•7 weeks
•≤ 28 days	•≥8 weeks
•≤39 days	•≥12 weeks

Int J Tuber and Lung Dis: Kambili et al, July 2022

Case study - new immigrant with abnormal CXR

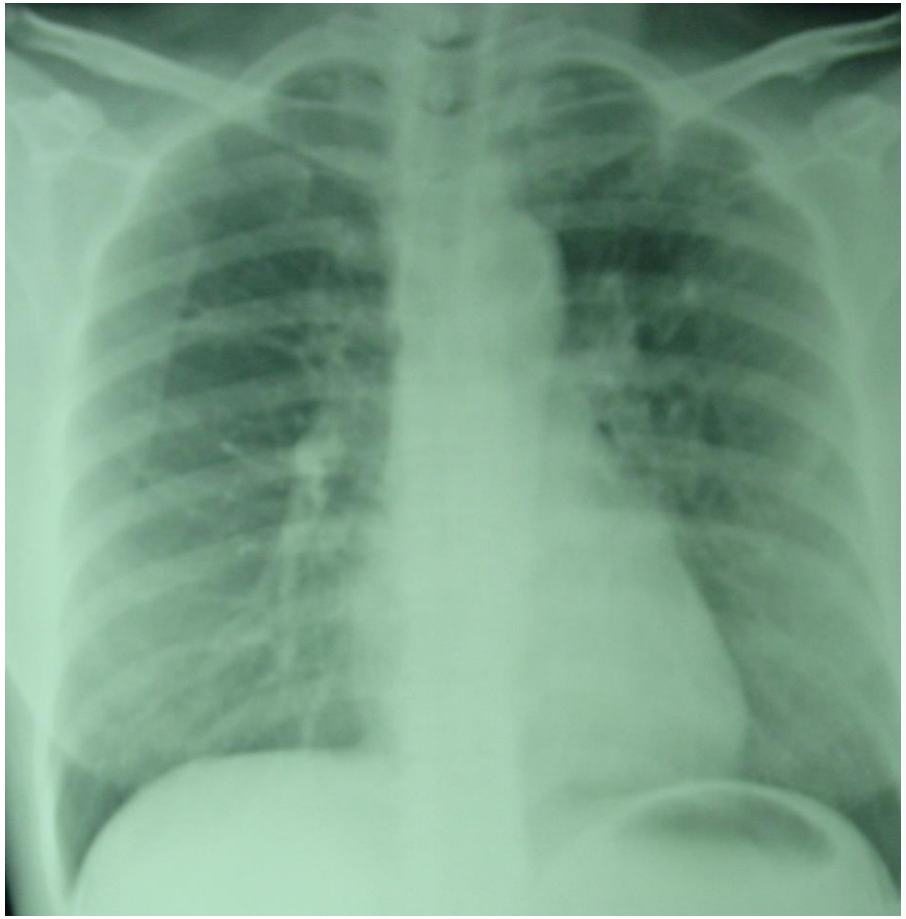
- 62-year-old Asian male enters U.S. Sept 2022
  - Rx TB in Viet Nam 2004-2005
  - Screened overseas prior to entry
  - Evaluation in U.S.
    - Smear negative, **Xpert positive, rifampin resistance detected**
  - What additional information do we need?
  - What is the diagnosis?

Case Study new immigrant with abnormal CXR

- 62-year-old Asian male enters U.S. Sept 2022
  - Rx TB in Viet Nam 2004-2005
    - **9 months including Injectable**
    - **DOT, ? Urine orange (rifampin) ? Adherence? Cured?**
  - What concerns are there?
    - **Non-standard regimen**
    - **INH, ethambutol and PZA compromised as well as streptomycin**
    - **Additional resistance?**
      - **Moxifloxacin – probably not but possible**
      - **Linezolid - very likely isolate is susceptible**
      - **Bedaquiline - very likely isolate is susceptible**
      - **Pretomanid - very likely isolate is susceptible**
  - Screened overseas prior to entry
    - **Results of CXR and sputum smears/cultures**
  - Evaluation in U.S.
    - **Smear negative, Xpert positive, rifampin resistance detected**

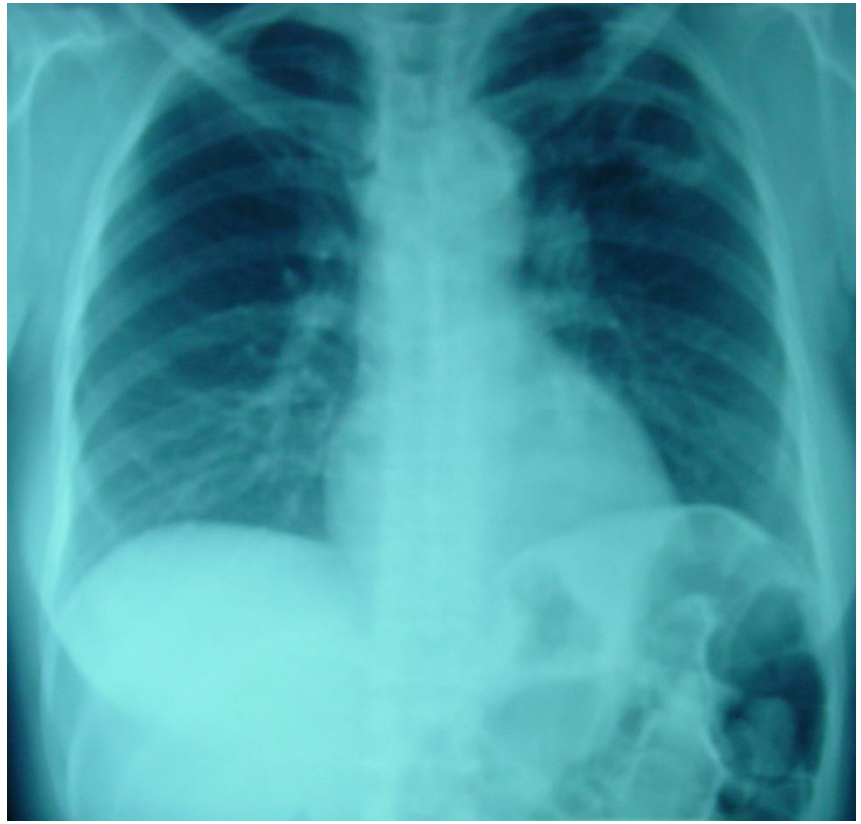
Case study new immigrant with abnormal CXR

- Overseas screen
  - CXR May 2022
    - Linear opacity LUL
  - Sputum x 3 smear and culture negative
  - Asymptomatic
- Plan: follow up in U.S. on arrival



Case study new immigrant with abnormal CXR

- CXR September 2022
  - Smear negative x 3
  - Xpert + MTB, + rifampin **R**
    - **Probe E dropout –**
    - **not sent for MDDR (Quest Lab)**
  - **New cavity LUL**



Case Study new immigrant with abnormal CXR

- 62-year-old Asian male enters U.S. Sept 2022
  - Rx TB in Viet Nam 2004-2005 - **9 months including Injectable**
  - What concerns are there?
    - **Non-standard regimen**
    - **INH, ethambutol and PZA compromised as well as streptomycin**
    - **Additional resistance?**
      - **Moxifloxacin – probably not but possible**
      - **Linezolid - very likely isolate is susceptible**
      - **Bedaquiline - very likely isolate is susceptible**
      - **Pretomanid - very likely isolate is susceptible**
  - Evaluation in U.S.: **Smear negative, Xpert positive, rifampin resistance detected**
    - **New CXR with cavity**
  - **What is diagnosis?**

Case Study new immigrant with abnormal CXR

- **What is diagnosis?**
  - Active TB disease
    - New radiographic change (cavity) and positive Xpert
    - With smears negative x 6 and only one of two + Xpert very likely low numbers of mycobacteria in sputum
    - Very possible that all cultures will be negative

- **What should we treat with?**
  - Drugs unlikely that mycobacteria are resistant to
    - **Best option: BPaLM**

- **Follow for CXR improvement, clinical improvement (may be subtle), and to see if cultures turn positive**

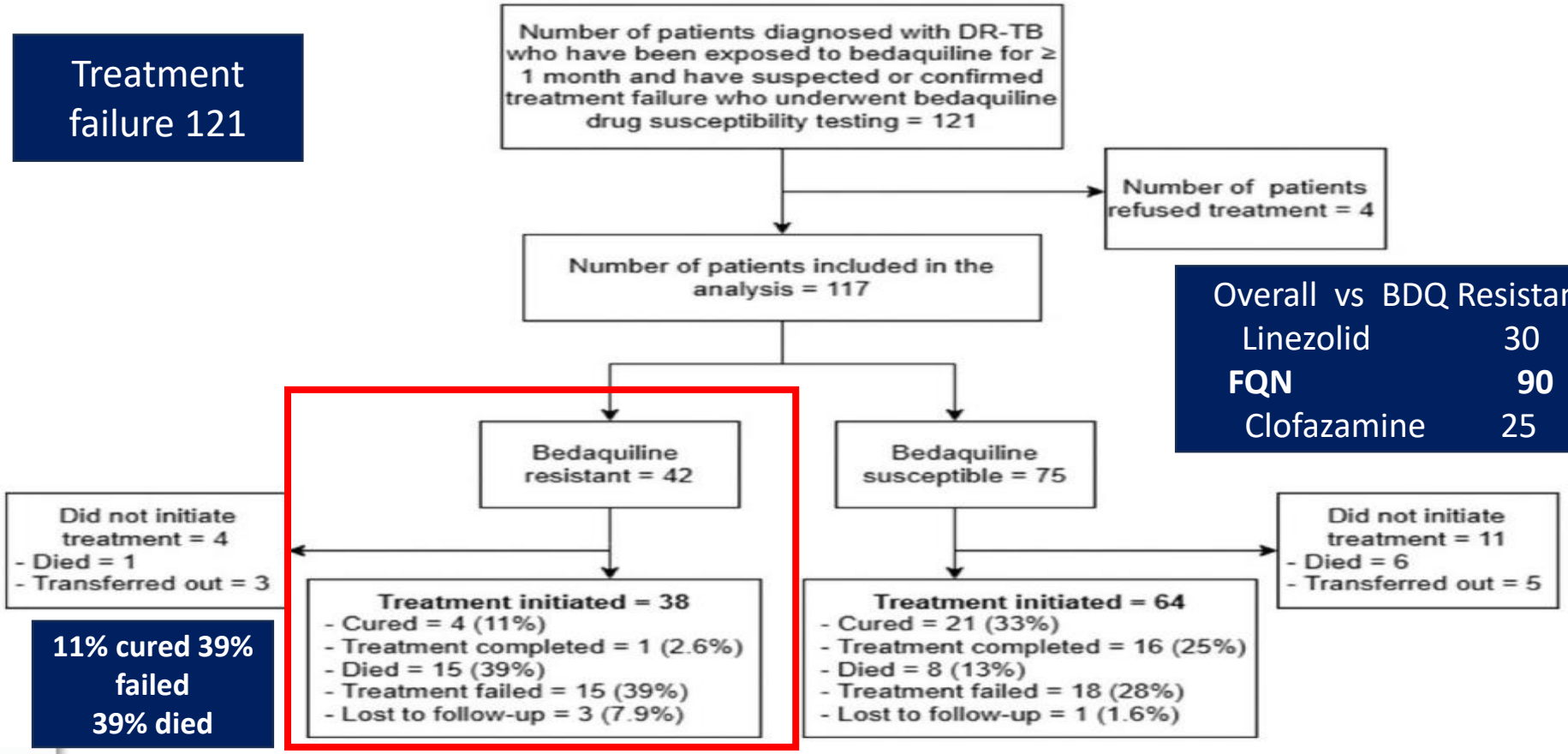
Clinical Infectious Diseases
MAJOR ARTICLE

Bedaquiline Resistance and Treatment Outcomes Among Patients With Tuberculosis Previously Exposed to Bedaquiline in India: A Multicentric Retrospective Cohort Study

July 2024

Rupak Singla,[1] Samsuddin Khan,[2,a] Arunima Silsarma,[2,a] Vijay Chavan,[2,a] Raman Mahajan,[2,a] Homa Mansoor,[2] Ravindra Kumar Devan,[1] Neeta Singla,[1] Manpreet Bhalla,[1] Gavish Kumar,[1] Pramila Singh,[2] Aparna Iyer,[2] Mabel Morales,[2,b] Satish Chandra Devkota,[2] Alpa Dalal,[3] Hannah Spencer,[4,a] and Petros Isaakidis[4,5,a]

Treatment failure 121



Overall vs BDQ Resistance %		
Linezolid	30	37
FQN	**90**	**93**
Clofazamine	25	44

11% cured 39% failed 39% died

Bedaquiline resistance
Now What?

- Current Treatment Options
- BPaLM
- BPaL
- BPaMZ - not advised due to liver toxicity

end TB (9 month regimens)

WHO now recommends #1-3 and if BDQ resistance #4

Non-inferior to SOC

Trial regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	B			L	M	Z
9BCLLfxZ	B		C	L	Lfx	Z
9BDLLfxZ	B	D		L	Lfx	Z
9DCLLfxZ		D	C	L	Lfx	Z
9DCMZ		D	C		M	Z
Control	Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis. Composed according to latest World Health Organization guidelines, as they evolved during the trial. This group included mostly participants treated with the 18-month conventional regimen.					

Superior

Figure **1**. *Composition of endTB trial regimens*

B denotes bedaquiline, L linezolid, M moxifloxacin, Z pyrazinamide, C clofazimine, Lfx levofloxacin, D delamanid

Higher failure & acquired drug resistance

9mo D-C-Lzd-Lfx-Z may give an option other than older individualized regimen when isolate is resistant to or patient is intolerant to Bedaquiline –

MDR-END 9 D-Lfx-Lzd-Z No BDQ or Pretomanid (Korea)

MDR-END NCT02619994 (MDR-TB; 214; PLHIV not included)	(a) 9DLzLxZ (b) [20mo IA-containing regimen]	**Primary Efficacy Outcome:** **The nine-month delamanid-based regimen demonstrated non-inferiority to a 20-month injectable-containing regimen–the standard of care in 2014 (mITT).** The NI margin was -10%.

Unfavorable outcomes:		**Risk difference, experimental-control (95% confidence interval)**
(a)	25 (29.4%)	4.4 (-9.5 to ∞)
(b)	18 (25%)	NA

Primary Safety Outcome:
No statistically significant differences in safety were detected between arms.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	29 (36.7%)	20 (25.3%)	5 (6%)
(b)	26 (29.2%)	19 (21.3%)	2 (2%)

Non – inferior to SOC but longer regimen with IA Had a better outcome 75% versus 70.6%

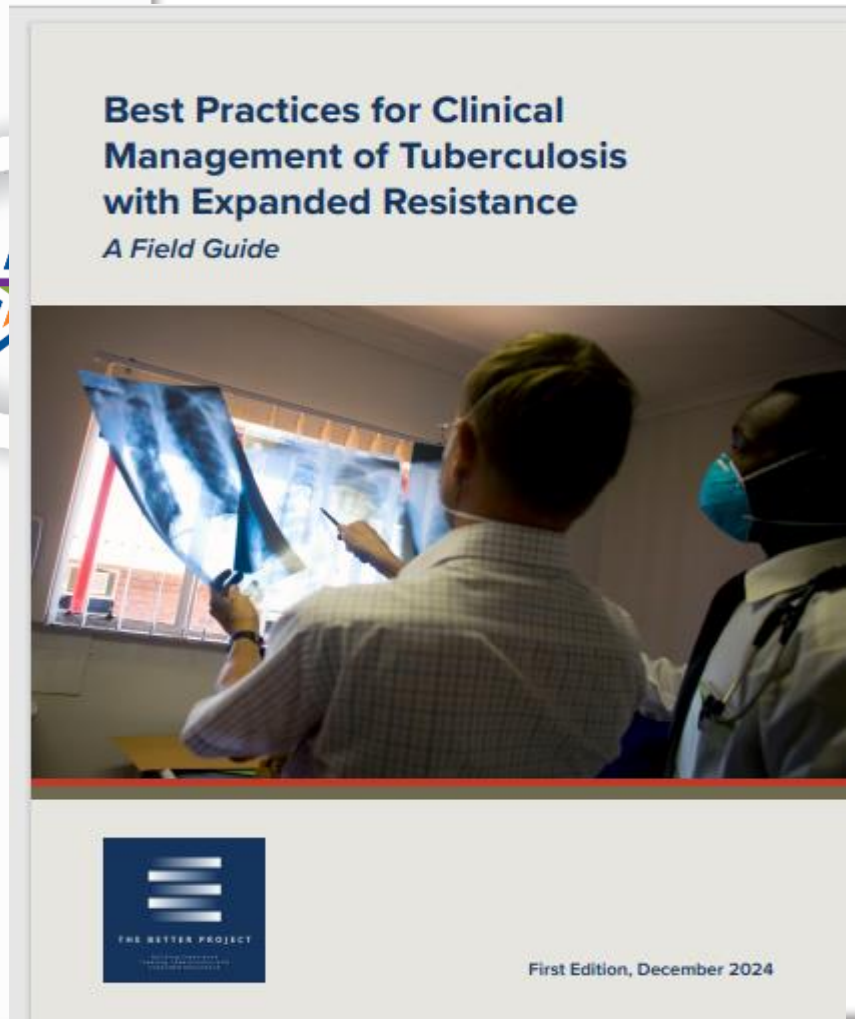
Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet. 2022 Oct 29;400(10362):1522–1530. doi: 10.1016/S0140-6736(22)01883-9.

Back to Buidling Individualized Regimens

The Better Projec

Best Practices for Clinical Management of TB with Expanded Resistance

1st Edition December 2024



When designing an individualized regimen for a person with TB who has possible or known expanded resistance, consideration should be given to both the WHO groupings and the bactericidal/sterilizing activity. Regimens need to include a combination of drugs that are bactericidal and drugs that are sterilizing. We suggest the following steps below:

Step 1: Choose as many core drugs as you can

Core drugs are group A drugs that are both sterilizing and bactericidal and include Bdq, Lzd and the third-generation Flqs.

These drugs should be included if susceptibility is documented or uncertain. If low-level resistance has been demonstrated, the third-generation Flqs can be given at higher doses. High-dose Bdq could also be considered. Of note, for high-dose Bdq, there are no clinical studies that demonstrate the effectiveness of this approach. Rather, it is based on modeling data. If high-dose Bdq is given, it should be only done so when there are no other options and when there is close monitoring for toxicity.

Step 2: Choose as many oral agents as you can for their bactericidal activity, including a nitroimidazole (Pa or Dlm) and/or Cs. Depending on the resistance mutations detected, then either high-dose Inh could be given (if only an *inhA* mutation) or Eto (if only a *katG* mutation).

Step 3: Choose from the following oral agents for their sterilizing activity as you need to construct a 5-drug regimen:

Sterilizing: Pza (if susceptible), Cfz

Step 4: Choose as many injectable agents for their bactericidal activity as you need to construct a 5-drug regimen including Am and the carbapenems + clavulanic acid. It is essential that regimens have sufficient numbers of bactericidal agents, especially in the first weeks/months of treatment and thus many individualized regimens will need to have one of these injectable drugs. Of note, some experts would place step 4 above step 3 in the regimen design process to ensure there are adequate bactericidal drugs.

Step 5: Choose other drugs if more are needed to reach a total of at least 5 effective drugs in the regimen

Bactericidal: PAS, Emb (if susceptible), rifabutin (if there is susceptibility to rifabutin demonstrated, although in most settings, testing to this drug is not available nor is the drug).

Step 6: Consider pre-approval access/compassionate use drugs

Please see the section on pre-approval access for more details. Some possible agents that have already completed at least phase 2b include quabodepistat, ganfeborole, and telacebec.

Where should research be going? What does the TB Community Want?

- **Safety**

Efficacy

- **Tolerability**
  - Pill burden, side effects

Time

Duration, **home time**

One Size Does Not Fit All

Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study

Lancet Infect Dis 2022; 22: 496–506

Nazir Ahmed Ismail, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsaolo, Gary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okozi, Xavier Padanilam, Anja Reuter, Rodolf Romero, Simon Schaaf, Julian te Riele, Ebrahim Variava, Minty van der Meulen, Farzana Ismail†, Norbert Ndjeka†*

- 8041 patients starting bedaquiline-based treatment had samples collected at baseline, month 2, month 6
- Baseline BDQ resistance was 3.8%
  - BDQ naïve 72/2023, 3.6%
  - Prior BDQ or clofazimine, 4/19, 21.1%
- BDQ resistance was associated with previous exposure to bedaquiline or clofazimine (OR 7.1)
- Rv0678 mutations were associated with resistance
- Resistance emerged in 12/695 (2.3%) of patients on treatment with median time to emergence of 90 days (range 21-654 days)
- Successful treatment outcomes were lower in patients with bedaquiline resistance