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?

- If **> 1%** of the mycobacterial population grows on a culture which contains a drug at a certain specified concentration (critical concentration).
  - In comparison to amount which grows on a plate without the drug
- If treatment is given with that drug, eventually all the mycobacteria in that population will become resistant to it.

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 Terminology to Classify Drug Resistant TB

Note: No mention of the injectable agents by WHO

- **XDR-TB:**

Group A Drugs
Levofloxacin/Moxifloxacin
Bedaquiline
Linezolid

January 2021

- **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.**

Diagnosis of Drug-Resistant TB:

First step is to consider the possibility

WHEN Patient Notes:

- Prior TB treatment
- Inadequate prior treatment
  - Inadequate regimen
  - Drug shortage
  - Drug toxicity
  - DST not done to guide RX
  - EMB/PZA stopped without DST results and INH resistance noted later
  - Poor absorption
- Poor response to treatment

WHO?

- Those from areas where DR TB is common
- Those who relapse,
  - with history of poor adherence
- Those exposed to a person with possible DR TB

Molecular Diagnosis of Drug Resistance

MTB resistance unknown

- **First Step: GeneXpert**
  - Sputum specimen or culture

  - Gives **same day** information as to rifampin resistance
  - If positive for rifampin resistance further testing needed to confirm
    - False positive results can occur
    - Rarely false negative - rifampin resistance is missed

- **Whole genome sequencing (looks at more of the DNA)**

  - Many states preform on all isolates
    - Often is not a diagnostic tool, but rather an epidemiological tool
    - In Texas, isolates are batched.
      - Not able to test the initial specimen, only the isolate

  - Florida, New York
    - A diagnostic tool; results in one week

Xpert screens for rifampin resistance

Important considerations to quickly address:

Get the specimen to the CDC! Identify who will do this!

Laboratory:

Confirmation of rifampin resistance and ID of additional mutations

Work with medical consultant on treatment plan

Patient Assessment:

How ill is patient?

Co-morbid conditions

Treatment Plan:

Many patients will need to start a bridging regimen as it takes > two weeks to get specimen to CDC, report back, and start MDR regimen. That is too long to leave an individual with MDR TB untreated

Infection Control:

Where does patient live? Is patient hospitalized now?

Contact Investigation:

Who is at patient's home?

Molecular Diagnosis of Drug Resistance

MTB resistance reported by Xpert or DST

- Additional testing (CDC/other reference lab)
  - **Confirm** rifampin resistance

- If rifampin resistance is confirmed:
  - Molecular testing: INH, PZA, FQN, linezolid, BDQ, Clofazimine
    Molecular testing for Pretomanid only at NY State Lab

  - **THEN:** Culture based drug susceptibility studies for all first- and second-line drugs

  - MICs (Minimum Inhibitory Concentration) now at CDC
    - INH, Rifampin, Moxifloxacin, Linezolid, Bedaquiline and Pretomanid

What about Discrepancies in Rifampin Susceptibility?

Molecular tests and Culture Based DST

- **Rifampin?**
  - **Molecular testing** done by whole genome sequencing pyrosequencing, Sanger or targeted next genome sequencing (not Xpert) 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 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 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 patient started on RIPE**
  - **Confirm rifampin susceptibility before adding FQN**
  - **Confirm FQN susceptibility**
  - **Confirm ethambutol susceptibility (some cases have INH and EMB resistance)**

- 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 Prior to 2019

- 18-24 months of treatment
- 6-8 months of an injectable
- 4-6 second line drugs; all less effective than rifampin
- 50% cure, 10% mortality

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

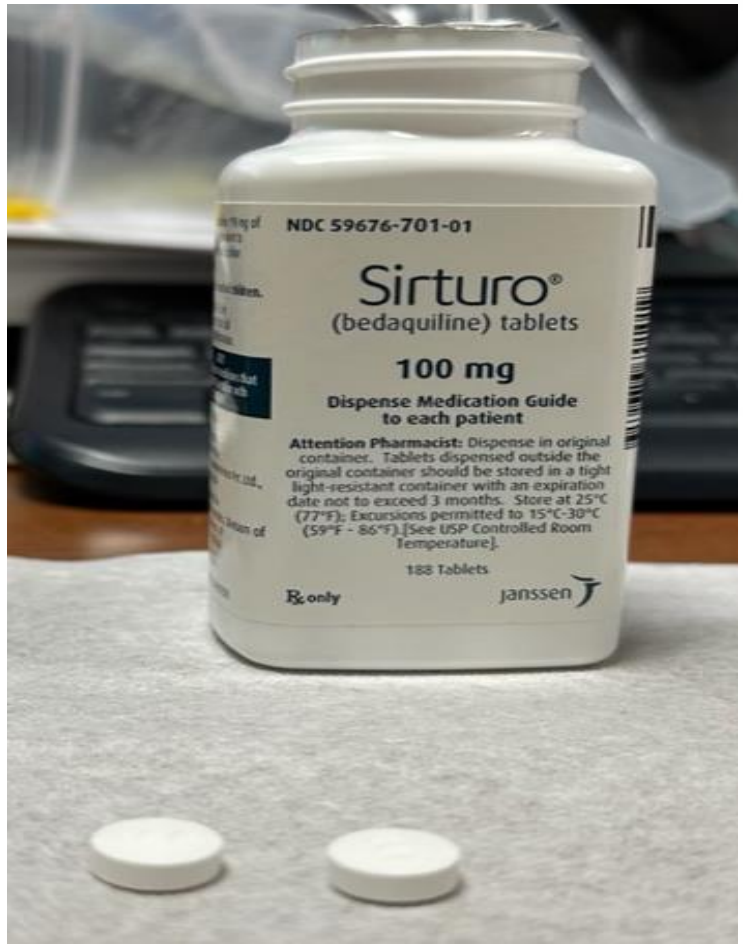
Agent	Class	Sponsor	Status	Indication	New Combination Study
delamanid (OPC-67683)	nitroimidazole*	Otsuka	Phase III	DR-TB	—
AZD5847	oxazolidinone	AstraZeneca	Phase IIa	TBA	—
sutezolid (PNU-100480)	oxazolidinone	Pfizer	Phase IIa	DR-TB	—
bedaquiline (TMC207)	diarylquinoline*	TB Alliance/ Janssen	Phase II	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

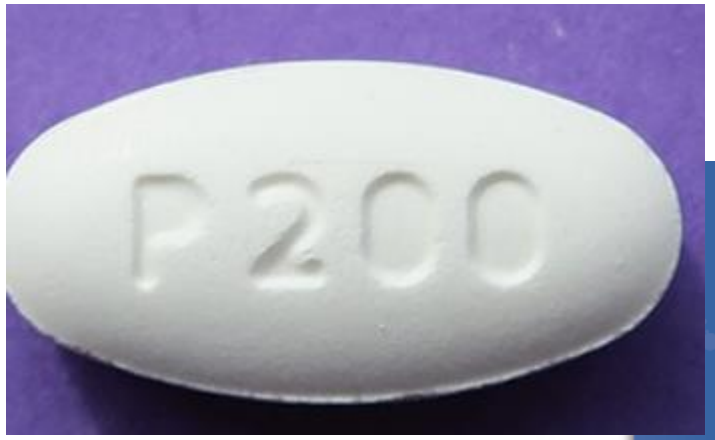
FDA Approves New Treatment for Highly Drug-Resistant Forms of Tuberculosis

Pretomanid (Pa)

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

Combinations
As "THE"
Regimen
BPaL
BPaLM
? …BPaMZ



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

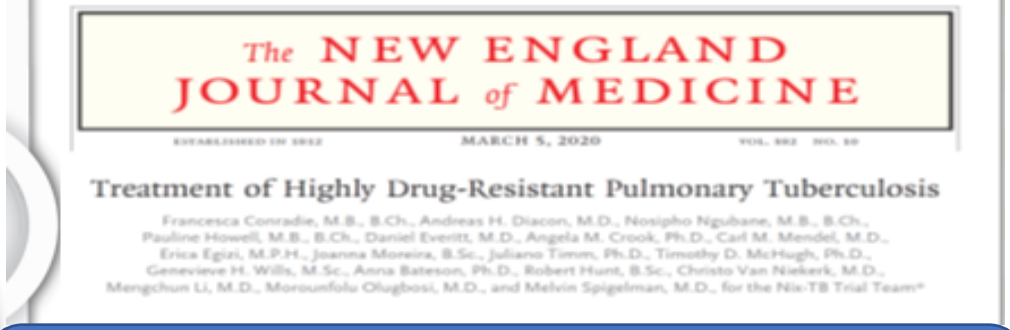
Am J Respir Crit Care Med Jan 2025

Two 6-month regimens

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

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

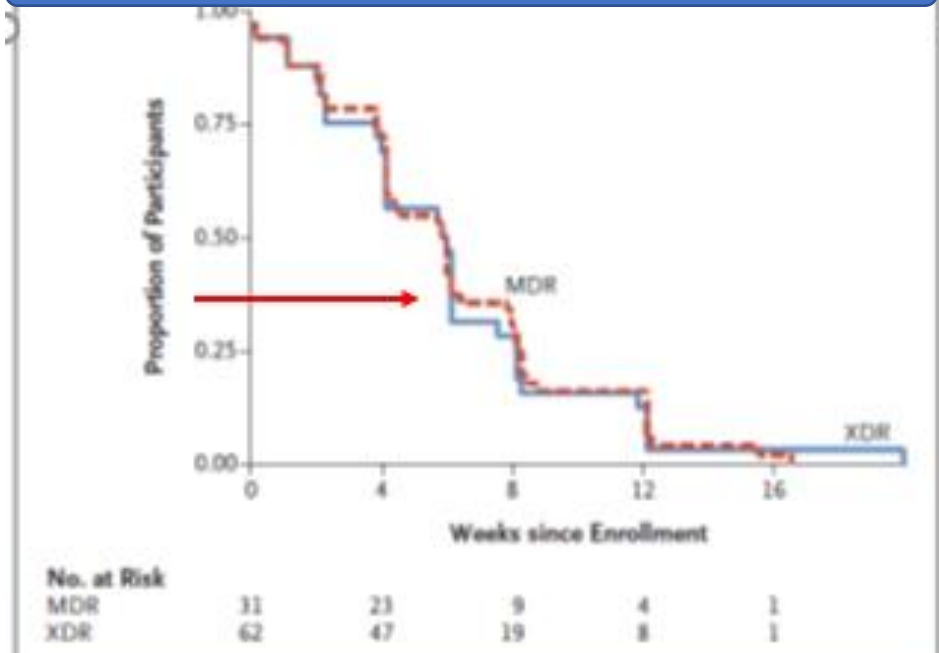


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

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

The NEW ENGLAND JOURNAL of MEDICINE
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

- Peripheral neuropathy
  24% (600 mg x26)
- Myelosuppression,
  2% (600 mg x 26)

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

Efficacy

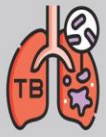
- LZD - 1200mg x 6 mo. - 93%
- LZD - 1200 mg x 9 wks. - 89%
- LZD - 600 mg x 6 mo. - 91%
- LZD - 600 mg x 9 wks. – 84%

Stopping linezolid early is associated with poorer outcomes with both high and low dose.

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 –

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

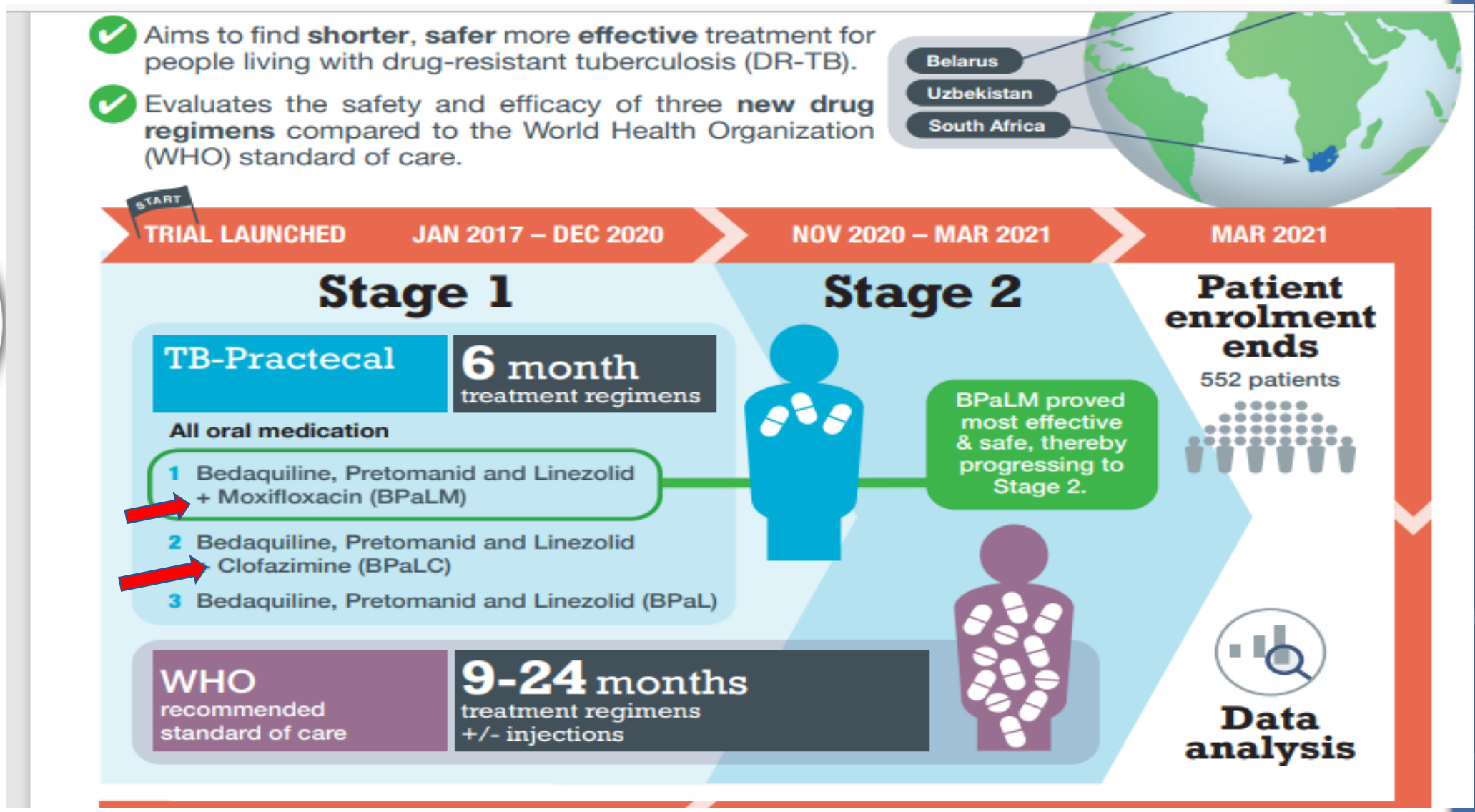
- Regimen 2:
- bedaquiline + pretomanid + linezolid + **clofazimine** for 26 weeks (**BPaL plus clofazimine**)

- Regimen 3:
- bedaquiline + pretomanid + linezolid for 24 weeks (**BPaL**)

- Standard of Care in Country at the time

TB-Practecal Clinical Trial

randomized, controlled

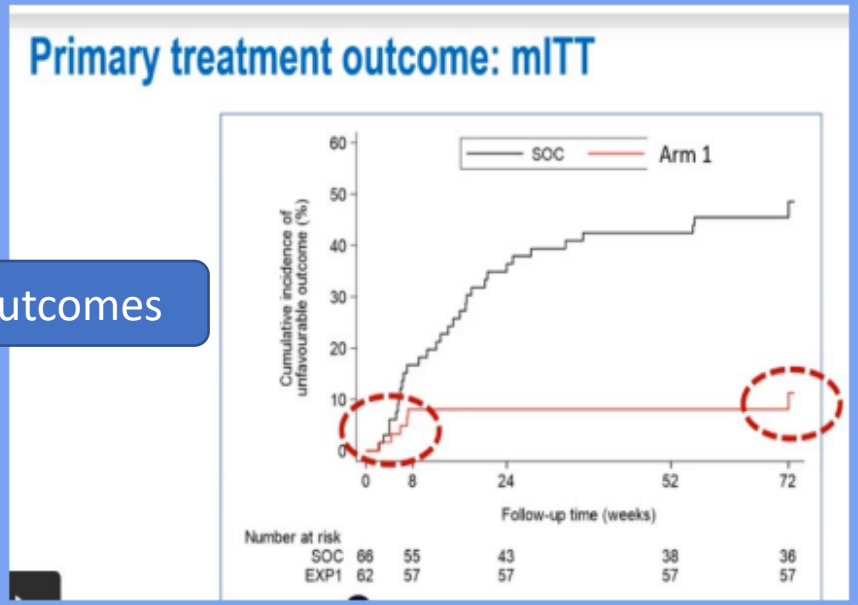


TB-PRACTECAL - Efficacy

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

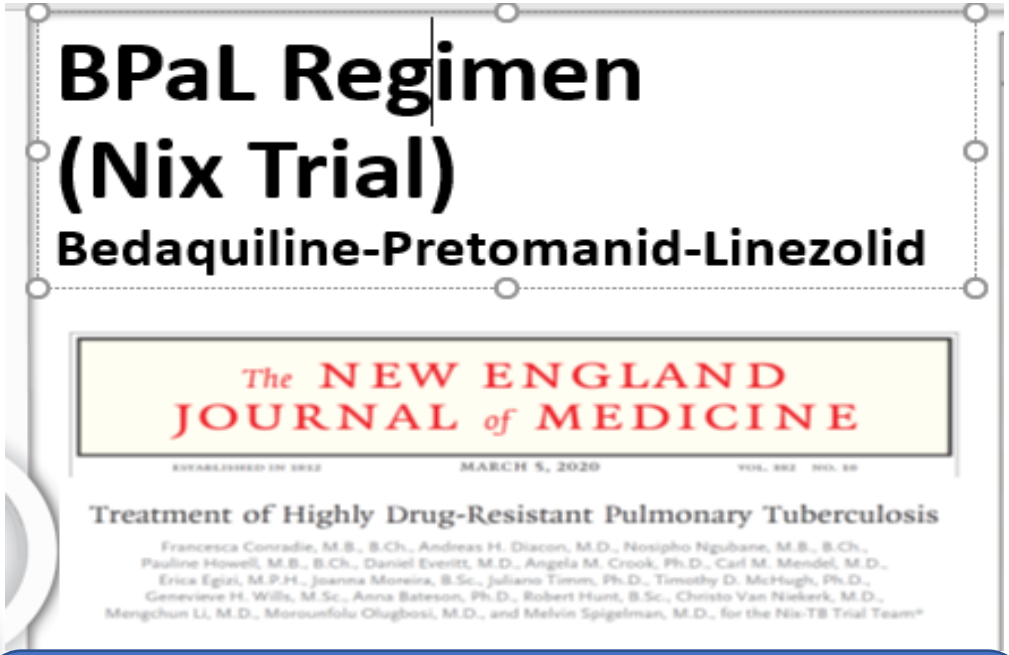
26% FQN resistant

Cumulative incidence of unfavorable outcomes



BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid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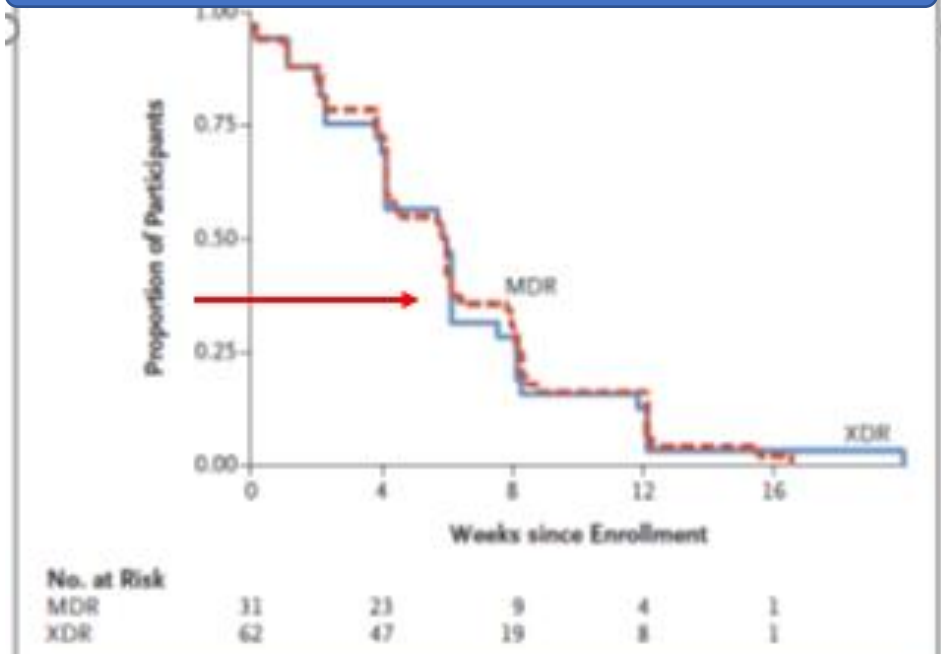


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

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

WHO Consolidated TB Guidelines 2025

- **BPaLM:** BDQ/Pretomanid/Linezolid/Moxifloxacin 26 wks (**TB-PRACTECAL**)
  - 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 if FQN resistant
  - Recommended when pretomanid cannot be used (children, pregnancy)
  - In U.S. Delamanid is compassionate use drug

Short course treatment options for drug resistant TB

6 – 9 months

All oral

Core drugs:

Bedaquiline

Pretomanid

Linezolid

Moxifloxacin

- **BPaL** 6 months; may extend to 9
- **BPaLM** 6 months; may extend to 9
- **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

Key Considerations for Selecting a Regimen

- For MDR TB (not FQN resistant) **BPaLM preferred**
- Pre-XDR TB (FQN resistant) **BPaL** recommended.
- Extensive or Extrapulmonary disease **BPaLM or BPaL**
  - Most likely need to extend therapy and/or add other drugs
- BPaLM and BPaL-not recommended/contraindicated:
  - CNS other Extra-pulmonary TB disease (minimal data on these patients and CNS penetration
    - Increasing observations suggest BPaLM +/- cycloserine may be good choice for CNS TB
  - Pregnancy (current study underway)
  - Age < 15 (study underway)

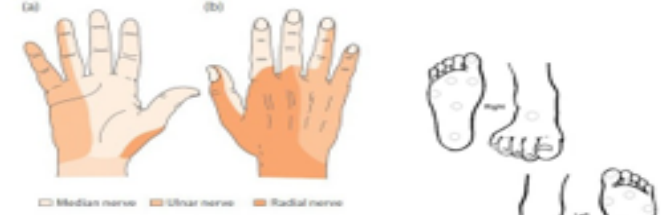
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

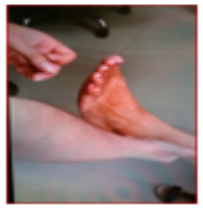
Additional information for selected nurse assessment (see complete toxicity assessment tool)

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





Baseline and Monthly Assessment

Early Identification of Toxicity

Patient Education

Early report 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.

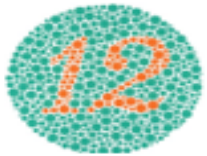
- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

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

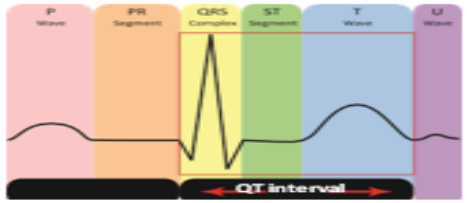
Monitoring for Adverse Effects

Cardiac Toxicity

QT interval prolongation: Fluoroquinolones, bedaquiline, pretomanid, clofazimine and delamanid may prolong the QT interval in the EKG(electrocardiogram) and may predispose patients to arrhythmias, torsade de pointes, and sudden death.

What is the QT Interval?

It is the portion of the EKG that begins at the start of the QRS complex and ends at the termination of the T wave. The QT is longer in women and those with lower heart rates. The QTc is a correction for extremes in heart rates.



Risk Factors for QTc Prolongation

Presence of multiple factors may increase the risk of QT prolongation.

What is the normal QTc value?

Normal QTC is < 450ms in men and < 470ms in women. It can vary by up to 75ms in the same individual at different times during the same day. Therefore, it is recommended that EKGs be done at approximately the same time of the day.

QTc > **450ms** **Asymptomatic**

QTc > **470ms**

- Draw blood for and correct if abnormal.
  - Electrolytes (Ca+, Mg+, K+)
  - TSH
  - Hgb
- Review other QTc prolonging drugs and stop these if possible.
- Get weekly EKG.

***Note: Many non-TB drugs may cause increased QTc prolongation. See www.challengetb.org/publications/tools/pmdt/Guidance_on_ECG_monitoring_in_NDR_v2.pdf**

QTc > **500ms** **Asymptomatic**

- Hospitalize patient, if possible.
- Draw blood for and correct if abnormal.
  - Electrolytes (Ca+, Mg+, K+)
  - TSH
  - Hgb (Blood transfusion if needed)
- Stop QTc prolongation drugs sequentially*.
- Repeat EKG 24-48 hours.
- Request cardiology consultation.
- Get weekly EKG until normal.

* Starting with ancillary drugs, then DR-TB drugs with moxifloxacin/levofloxacin, then pretomanid/clofazimine/delamanid, and then bedaquiline

QTc > **500ms**
Symptoms: Palpitations, tachycardia, fainting, headache, chest pain, syncope

- Hospitalize patient (intensive or cardiac unit monitoring).
- Draw blood for and correct if abnormal.
  - Electrolytes (Ca+, Mg+, K+)
  - TSH
  - Hgb (Blood transfusion if needed)
- Stop ALL QTc prolongation drugs
- Repeat EKG 24-48 hours
- Request cardiology consultation
- Get weekly EKG until normal

Monitoring During Therapy

- Monitor sputum culture monthly during treatment
  - 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.
- Monitor weight monthly
- Monitor toxicity monthly (neuropathy, vision, lab, EKG)
- CXR at baseline, 2 months and 6 months

Monitor After Treatment for 24 months

- Monitor **RR or MDR TB patients** at 6-month intervals
  - Sputum culture
  - CXR
  - Medical assessment
  - Weight

Therapeutic Serum Drug Level Monitoring

- No official absolute recommendation

- WHO and ATS/CDC/ERS/IDSA note may be helpful; especially a linezolid trough
  - **Goal** is to keep linezolid trough < 2 as this seems to correlate, at least imperfectly with 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

ZeNIX: Linezolid Optimization Trial

MDR or XDR TB Treatment Failure or Intolerant

Safety

- Peripheral neuropathy
  24% (600 mg x26)
- Myelosuppression,
  2% (600 mg x 26)

- 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%

Stopping linezolid early is associated with poorer outcomes with both high and low dose.

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?

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

Outcomes Non-inferior to SOC

Trial regimens		Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	89%	B			L	M	Z
9BCLLfxZ	90.4%	B		C	L	Lfx	Z
9BDLLfxZ	85.2%	B	D		L	Lfx	Z
9DCLLfxZ			D	C	L	Lfx	Z
9DCMZ			D	C		M	Z
Control	80.7%	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

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.

  - **BLMZ** > **BLLfxCZ** > **BDLLxZ**

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.

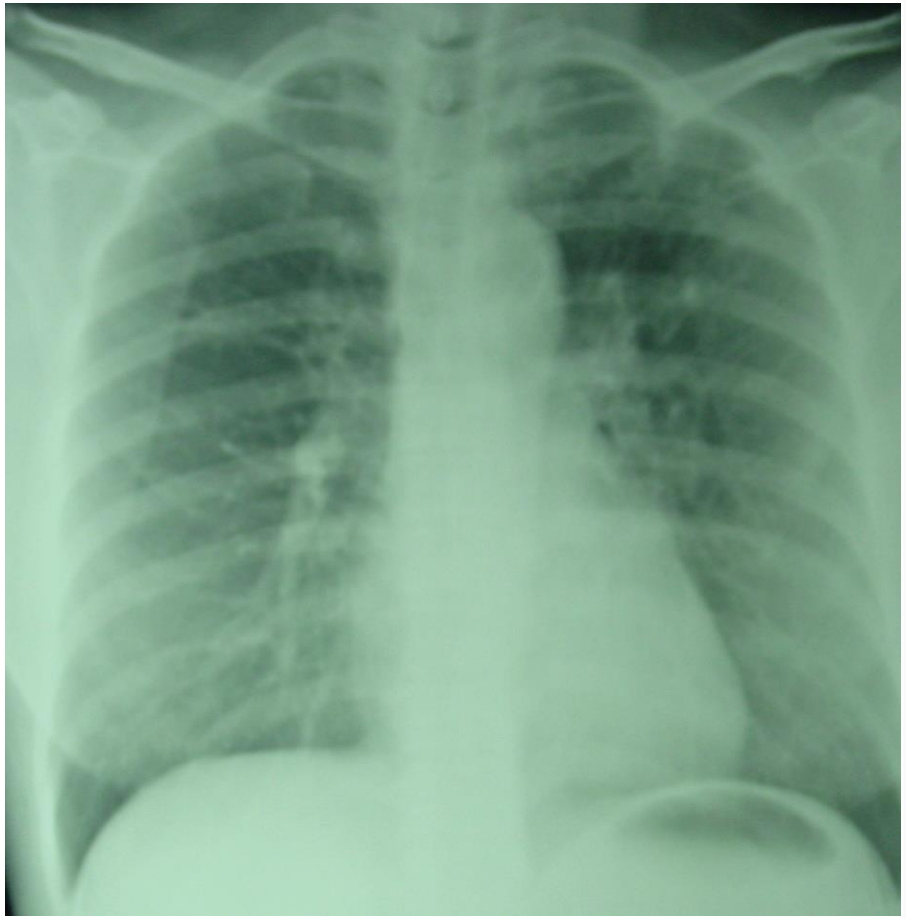
- AE = adverse event; DS-TB = drug-sensitive TB; mITT = modified intention to treat; MDR-TB = multidrug-resistant TB; N = sample size; NA = not applicable; NI = noninferiority; PP = per protocol; RR-TB = rifampicin-resistant TB; SOC = standard of care
- Numbers at the beginning of each regimen or after 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

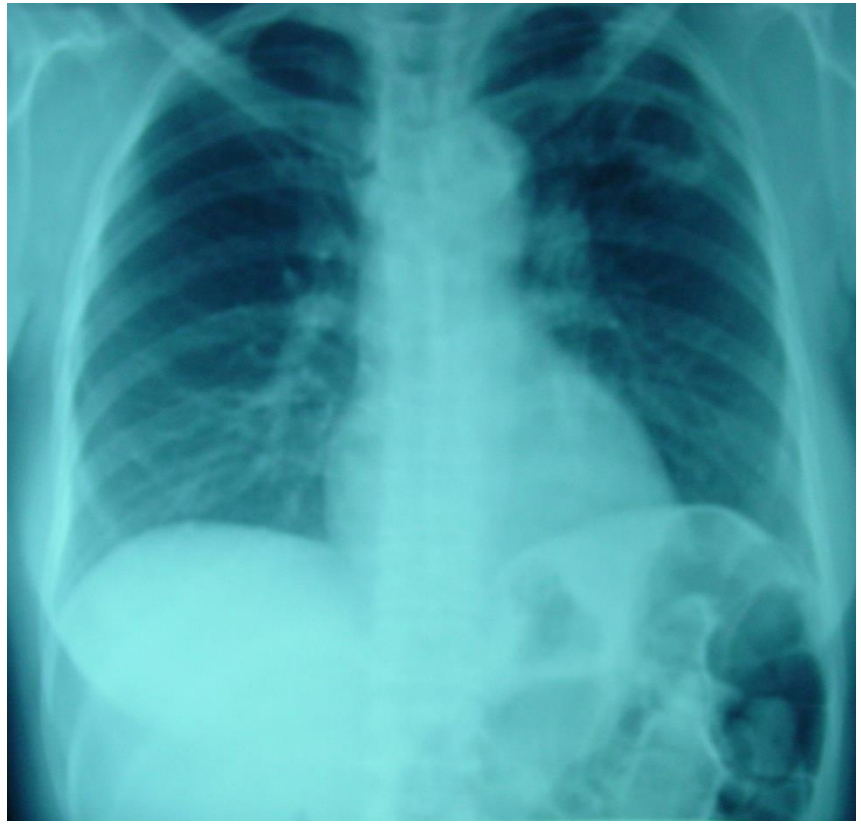
Case study new immigrant with abnormal CXR

- 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
    - **How long was treatment?**
    - **Was an Injectable drug used?**
    - **Possible FQN, linezolid or BDQ use?**
    - **DOT, ? Urine orange (rifampin) ? Adherence? Cured?**
  - What concerns are there?
    - **Non-standard regimen**
    - **Additional resistance?**
  - 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

- 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**
    - **Culture did not grow**
  - **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
    - 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 later cultures turn positive**

When do we worry about bedaquiline resistance?

BPaL and BPaLM Revolutionized Treatment of Rifampin Resistant (RR), MDR, pre-XDR & XDR TB But… reports of resistance, relapse, failure

Eight patients failed or relapsed

Two deaths

Decreased susceptibility to bedaquiline defined in consultation with laboratory and clinical TB co-authors as isolates where the minimum inhibitory concentration **(MIC) was lower than <1 ug/ml but higher than MIC distribution that would be expected for a drug sensitive wild type** in the presence of a mutation that may or may not confer resistance

Critical concentration for BDQ 1.0 ug/ml MGIT

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA OXFORD

Relapse and Emergent Resistance With Novel Short-Course Regimens for Multidrug-Resistant Tuberculosis, United States, 2022–2024

Rina Liang,[1,0] James C. M. Brust,[1,0] Caitlin Reed,[2] Vincent Escuyer,[3,0] Derek T. Armstrong,[4,0] Nicole Parrish,[4] Patrick Valois,[5,0] Marie-Claire Rowlinson,[5] Atanaska Marinova-Petkova,[5] Gregory P. Bisson,[7] Sarah M. Labuda,[2,0] Angel Colon-Semidey,[8] Connie A. Haley,[9,0] David Ashkin,[9] Charles A. Peloquin,[10,0] Alfred Lardizabal,[11,0] Amee Patrawalla,[11] Alice Cuenca,[12] Michelle K. Haas,[13,0] Richard Brostrom,[2] Chima Mbakwem,[12] Marcos C. Schechter,[14,15,0] Susan M. Ray,[14,15,0] Jason Cummins,[16,0] Barbara Cahill,[17,0] Katherine Arn,[17] Lisa L. Chen,[13] John W. Wilson,[18] and Neela D. Goswami[2,0]

BPaL and BPaLM Revolutionized Treatment of Rifampin Resistant (RR), MDR, pre-XDR & XDR TB but Emerging Concerns

- Increasing reports of treatment failure, relapse and resistance.
  - Lack of good data on the rates and spread of BDQ resistance
- Initial hope that BDQ resistance would be rare is inconsistent with current evidence as increased reports indicate a growing threat of both acquired and transmitted resistance.
- M TB has acquired resistance to every antibiotic used against it, and so the development of resistance to BDQ should not be a surprise.
- **Pharmacological vigilance was not implemented with release of BDQ (2012) or Pretomanid (2019)**
  - Molecular tests and DST limited availability and reliability U.S. and globally
  - Questions as to true critical concentration of BDQ
  - Variance in molecular tests and correlation with phenotypic results for BDQ poor

Bedaquiline Resistance is a Serious Concern

- Bedaquiline is cornerstone of all regimens for RR, MDR, pre-XDR and XDR TB
- It is the key to a good outcome, avoidance of injectable drugs and use of a short regimen
- Central component of most novel regimens proposed to shorten therapy for DST, DR TB and all pan TB
- New drugs are in pipeline, they are not here yet. But the patients are !

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

Lancet Inf Disease 2022

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 BDQ-based treatment had samples collected at baseline, month 2, month 6 in South Africa in a programmatic setting **2015-2019**
- Baseline BDQ resistance was **3.8%**
  - Prior BDQ or clofazimine 4/76, **5.3%**
- **BDQ resistance associated with previous exposure to BDQ or clofazimine (OR 7.1) and baseline isolate which was FQN resistant**
- Rv0678 mutations poorly predictive of resistance
- Resistance emerged in 12/695 (2.3%) of patients on treatment with median time to emergence of 90 days (range 21-654 days)

Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study

Lancet Microbe 2023

Brigitta Derendinger, Anzaan Dippenaar*, Margaretha de Vos*, Stella Huo, Rencia Alberts, Rebecca Tadokera, Jason Limberis, Frik Sirgel,*

- **Retrospective study of poorly responding extensive DR TB treated with BDQ (1/2016-11/2017)**
- 36 with baseline isolate and ≥ 4 month + culture
- 26/36 FQN resistant at baseline
- **Outcomes**
- Favorable 20%, Cured 10%, Unfavorable 63% Failed 13% Died 50%
- **BDQ Resistance**
- Phenotypic resistance at baseline **3/35 (8%)** and last positive culture after at least 4 month of treatment **22/40 (45)%**
- Resistance associated with baseline FQN resistance, (OR 7) clofazimine exposure (OR 5) four or less likely effective drugs (OR 12)
- **88% patients gained variants associated with resistance; 12% did not by WGS**
- 7 of 36 patients had variants that suggested **transmission rather than acquired resistance**

Transmission of Bedaquiline-resistant Mycobacterium tuberculosis in KwaZulu-Natal, South Africa

Sobel et al, Am J Respir Crit Care Med Jan 2026

- Prospective study of all patients with **TB resistant to FQN or second line injectable agents (IA) 2018-2022**

  - Enrolled 843 of the 1070 patients with resistance to FQNs or 2nd line IA
  - Of 639 with high quality WGS data **14 – 18 %** had baseline mutation c/w BDQ resistance
    - Variance due to varying stringencies for defining resistance conferring mutations
  - FQN resistant isolates more likely to be BDQ resistant
  - **% similar across linages**
  - **Multiple clones** of BDQ resistant isolates found;
  - 68% due to recent clustering; **Transmission of BDQ resistant strains main driver and more rapid as no fitness cost identified**.

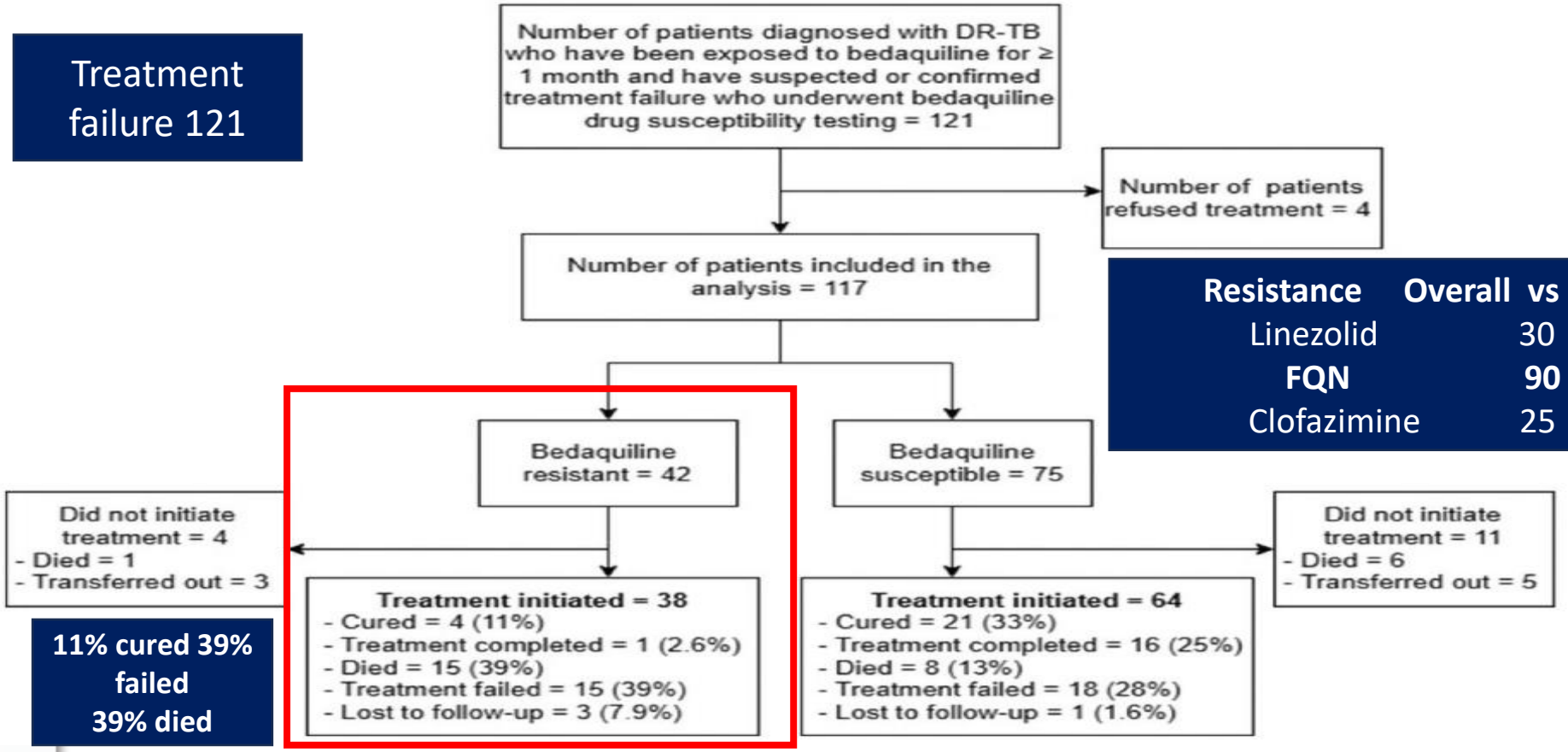
Clinical Infectious Diseases
MAJOR ARTICLE

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



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

11% cured 39% failed 39% died

Currently treating one person with relapse and new resistance to BDQ, pretomanid and increased MIC to linezolid.

- History of prior empyema, cause unknown, RX outside U.S.
- Baseline FQN resistance
- Extensive disease so given 9 months of BPaL (also a renal transplant)
- Relapsed with bilateral miliary infiltrates, strongly smear positive
  - New mutation to BDQ and clofazimine noted on molecular testing (rv0678)
  - New mutation to pretomanid
  - MIC BDQ 0.5 (MIC on baseline isolate pending), MIC linezolid 0.5
  - Finally converted culture to negative after 4 months of treatment
  - Perfusion scan shows significant bilateral perfusion defects
  - **Treatment:** IV amikacin, nebulized amikacin, tedizolid 200 mg, meropenem 2 gram IV q 8/125 mg clavulanic acid, cycloserine 500 mg, ethionamide 500mg/250, and BDQ (using but not counting as effective)
- **Surgery?**

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%)

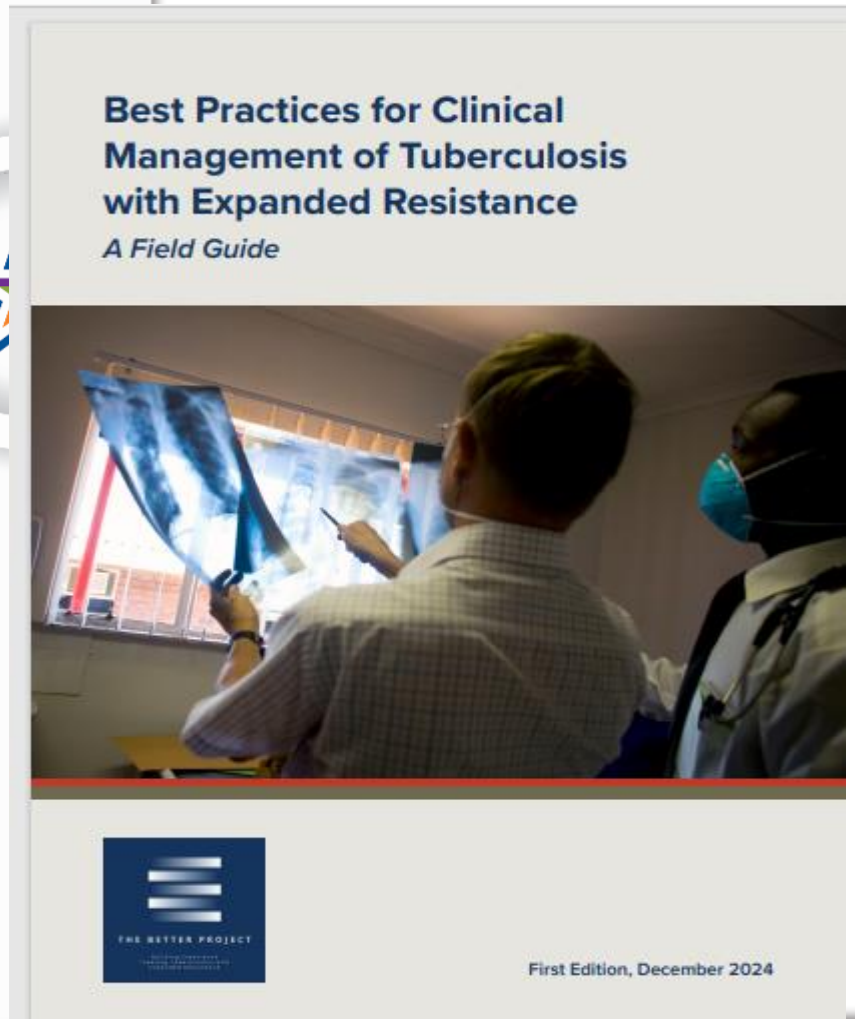
Non – inferior to SOC but longer regimen with IA Had a better outcome 75% versus 70.6%

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.

The Better Projec

Best Practices for Clinical Management of TB with Expanded Resistance

1st Edition December 2024



Back to Building Individualized Regimens

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

Choose as many as possible

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).

as many as possibl e

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).

Total of at least 5

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

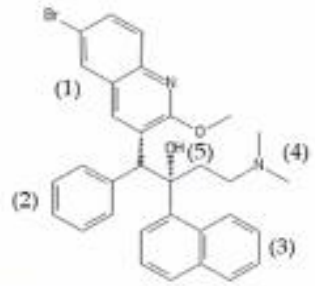
Please see the section on pre-approval access for more details. Some possible agents that have already completed at least phase 2b include quabodepistat, ganfeborole, and telacebec.

WHAT IS On Horizon?

- How are we going to treat these individuals?

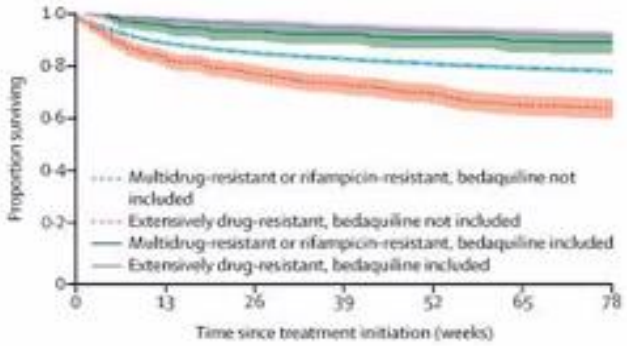
Sorfequiline - New Drug in the Diarylquinoline Class

BDQ



Bedaquiline (BDQ)

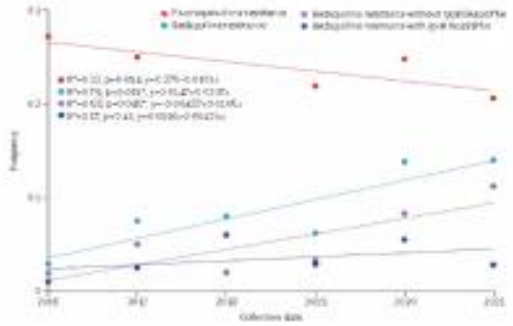
- First-in-class diarylquinoline (DARQ)
- Novel mechanism of action
- QT prolongation



SFQ

Sorfequiline (SFQ) design goals:

- Increase potency
- Reduce/eliminate QT effect



10x greater potency compared with BDQ

- Potential to shorter treatment duration
- Lower likelihood of resistance emerging
- Activity against BDQ-resistant strains

No QT prolongation observed in preclinical or clinical studies

Bedaquiline Resistance developing faster than initially projected; 10+ % in many areas

Drug Penetration into a Lesion is Critical to Overall Success
Lesional Liability

Stopped early due to lack of efficacy to shorten therapy

PAN-TB XBQU trial

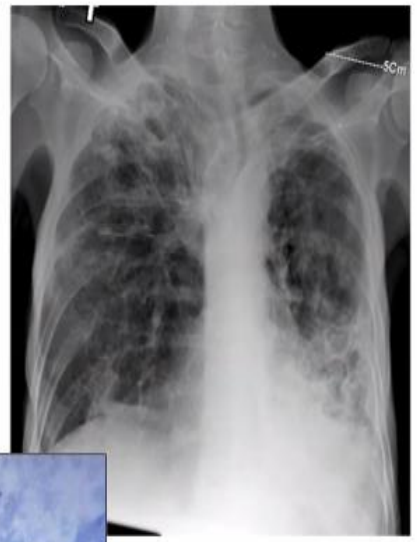
Hard-to-treat population

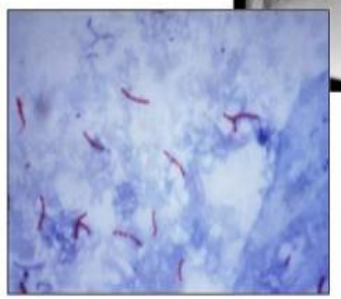
61% of mITT participants had:

- ≥2+ smear grade

  and

- Radiographically advanced disease
  - bilateral cavitation, cavity ≥4cm or ≥2 lung zones involved





Back-translation of XBQU

Why do regimens have varying lesional liability?

Lower liability — Higher liability

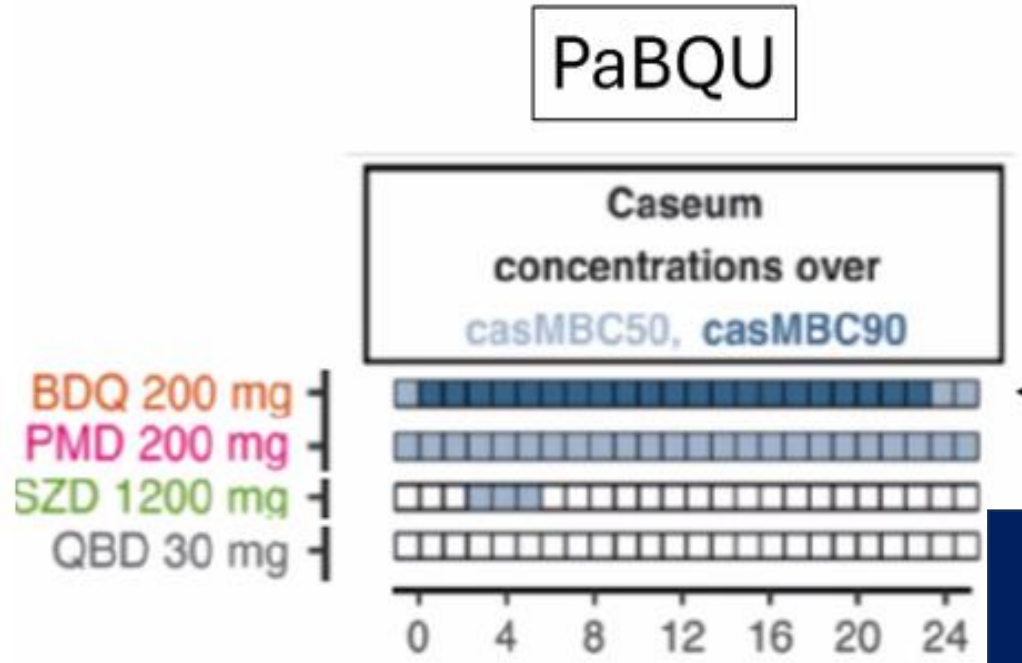
BPaMZ ← 2-drug substitution MZ vs QU → PaBQU

Adding DRIP plus sustezolid

Hypothesis is that limited efficacy in complex lesions due to inadequate lesion coverage leads to under performance of XBQU

Integrating PK

Lesion coverage at steady state



Nearly 24h above $cMBC_{90}$

Caseum Coverage

BDQ excellent coverage at MBC 90
Pretomanid good coverage but only at MBC 50
SZD limited coverage and only at MBC50
QBD no coverage

Conclusions

- Treatment regimens for TB are shortening
- Fluoroquinolones are playing a larger role in TB treatments
- TB regimens for DR TB in the US and worldwide increasingly contain BDQ, FQNs and linezolid.
- Baseline resistance to FQN associated with poorer outcomes
- Mechanisms for testing and surveillance need to grow in the direction the treatment regimens are taking us