Drug Resistant Tuberculosis

Barbara J. Seaworth, MD

July 17, 2024

TB Intensive
July 16 – 18, 2024
San Antonio, Texas

Barbara J. Seaworth, MD has the following disclosures to make:

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

Drug Resistant Tuberculosis

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Heartland National TB Center of Excellence

When is a specimen identified as having resistance?

- If **> 1%** 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
  - **WHY?**
    - If treatment is given with the drug eventually all the mycobacteria in that population will become resistant

How Do we Classify Drug Resistant TB?

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

- **Rifampin Resistant (RR)/MDR** (INH and rifampin resistant)
  - Grouped together

Group A Drugs
Levofloxacin/Moxifloxacin
Bedaquiline
Linezolid

Note: No mention of the injectable agents by WHO

- **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
- Poor response to 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 When MDR/RR TB is Suspected/Identified

- **Stop** RIPE treatment

- Submit specimen to CDC for Molecular Detection of Drug Resistance (MDDR – sequencing) to confirm rifampin resistance testing once Xpert identifies rifampin resistance

- 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
  - Other medical comorbidities/medications

- Strongly consider a bridging regimen unless likely patient will get specific treatment within a week.

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 is:

    "Gold Standard"

    - Culture may miss rifampin resistance
      - **MGIT misses more of these 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

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

From this to ----

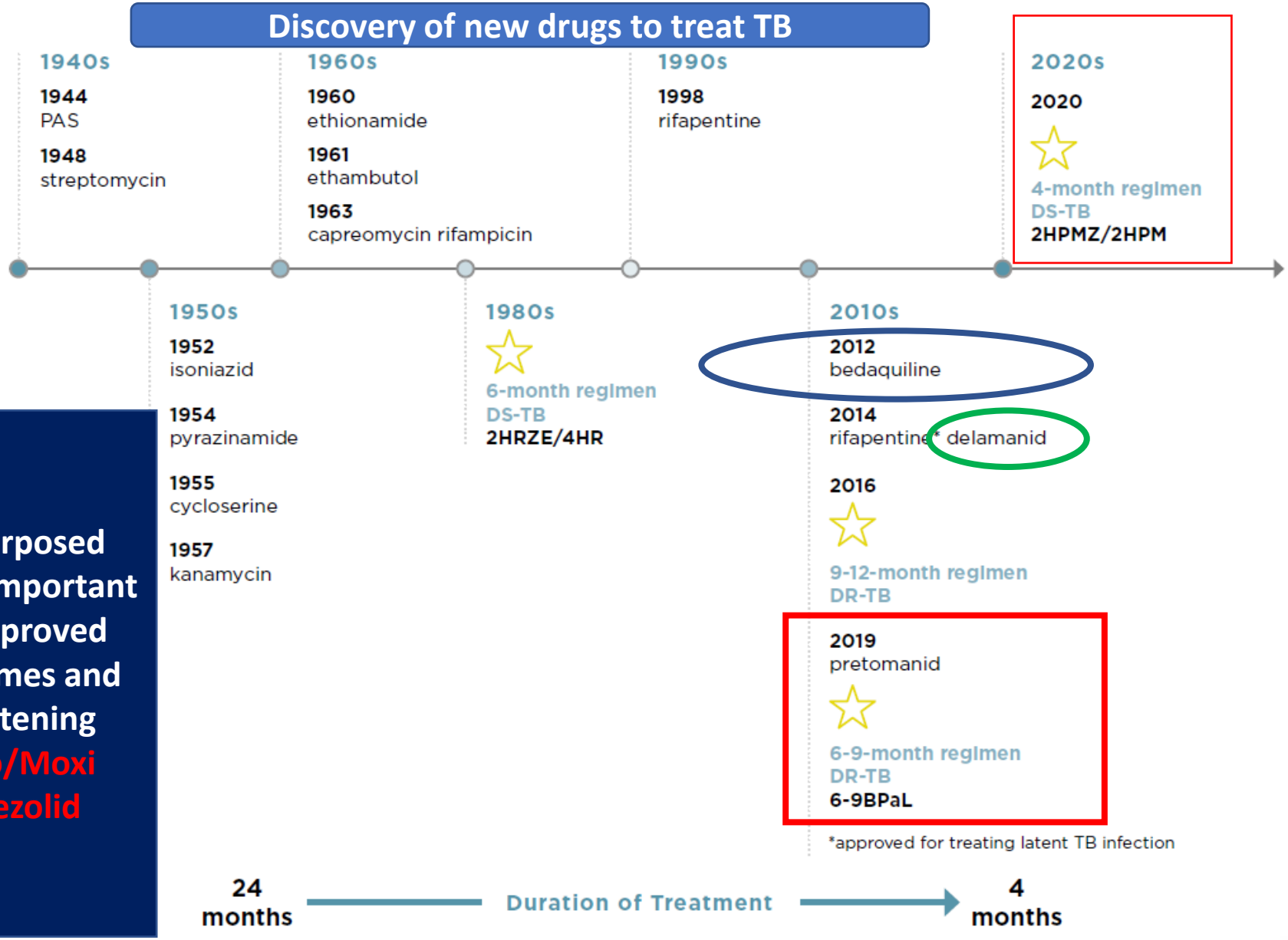
The medicine and syringes to treat one MDR-TB patient for one year.

Patients need treatment for 18–24 months

IDSA fact sheet 2013

- **Staggering Medication Burden**

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



Repurposed drugs important to improved outcomes and shortening
Levo/Moxi
Linezolid

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

TB Alliance

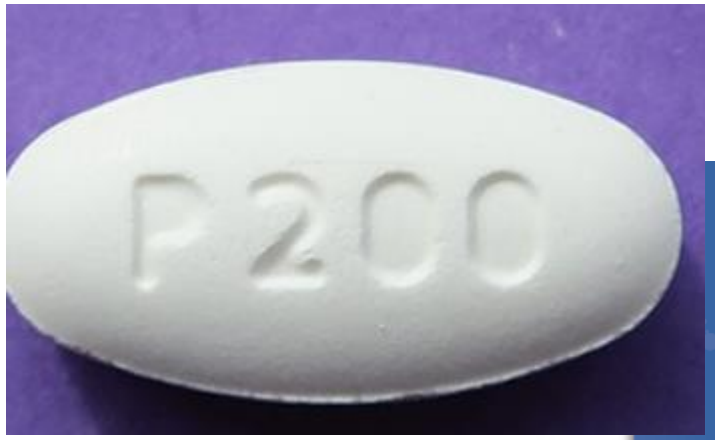
ABOUT WHY NEW TB DRUGS? R&D ACCESS NEWS DONATE

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

Combinations
As "THE"
Regimen
BPaL
later - BPaLM
?...BPaMZ



Treatment Options for RR/MDR TB – WHO

- **BPaLM: BDQ**/Pretomanid/Linezolid/Moxifloxacin 26 weeks (9mo.)
  - Linezolid dose 600 mg once daily
- **BPaL: BDQ**/Pretomanid/Linezolid 26 weeks (9 mo.)
  - Linezolid dose 600 mg once daily as identified by ZeNix study
- **All oral 9-month regimen - updated (WHO)**
  - 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 of:
    - Levofloxacin/moxifloxacin, EMB, PZA and clofazimine
- **Longer all oral** individualized regimen (18 months)
  - Use injectable drug only when no other options

TAG PIPELINE REPORT 2012

Novel Compounds to Treat Active TB Disease

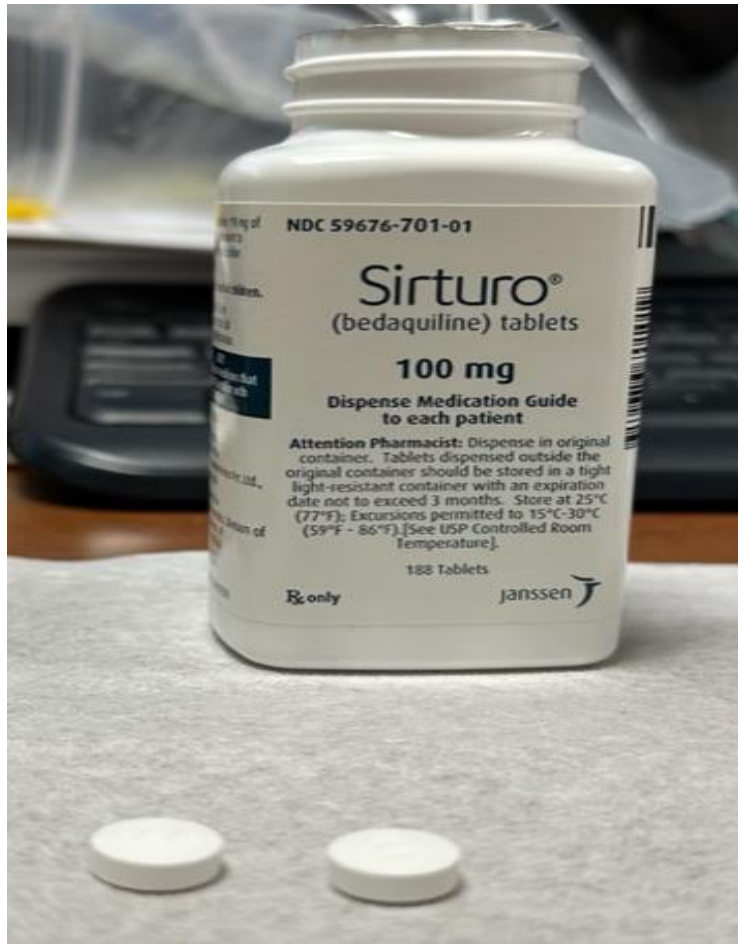
TABLE 3. Novel and Second-Generation Compounds in Late-Stage Clinical Studies for Active TB as of June 2012

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

2022: Bedaquiline - Core Drug for MDR/XDR TB



BPaLM (BPaL plus Moxifloxacin - 5 tablets)

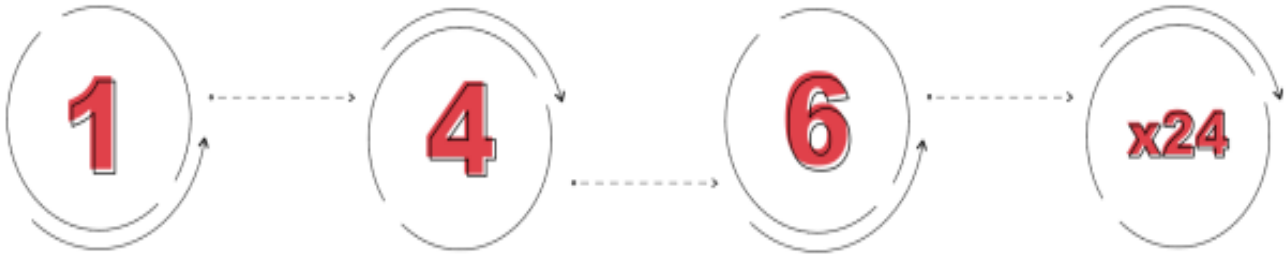
BDQ/Pretomanid/Linezolid/Moxifloxacin

1/4/6x24

A Campaign to Rally Energy, Political Will & Funding to End TB

The 1/4/6x24 Campaign's name comes from its central demand:

that countries and other duty bearers take action to implement the shortest available regimens – one month or once-weekly for TB prevention, four months for drug-sensitive TB, and six months for drug-resistant TB — by the end of 2024.



one-month or once weekly treatment regimens for TB prevention.

four-month treatment regimens for drug-sensitive TB.

six-month treatment regimens for drug-resistant TB.

by the end of 2024.

A deadline for having in place the "staff, stuff, space, systems, and support" needed for shorter TB regimens to be made accessible to everyone, everywhere as a human right.

& priority research to extend the benefits of short treatment and prevention regimens to any groups who cannot currently use them due to data gaps or research exclusions.

TAG (Treatment Action Group)
TB CAG (Global TB Community Advisory Group)

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

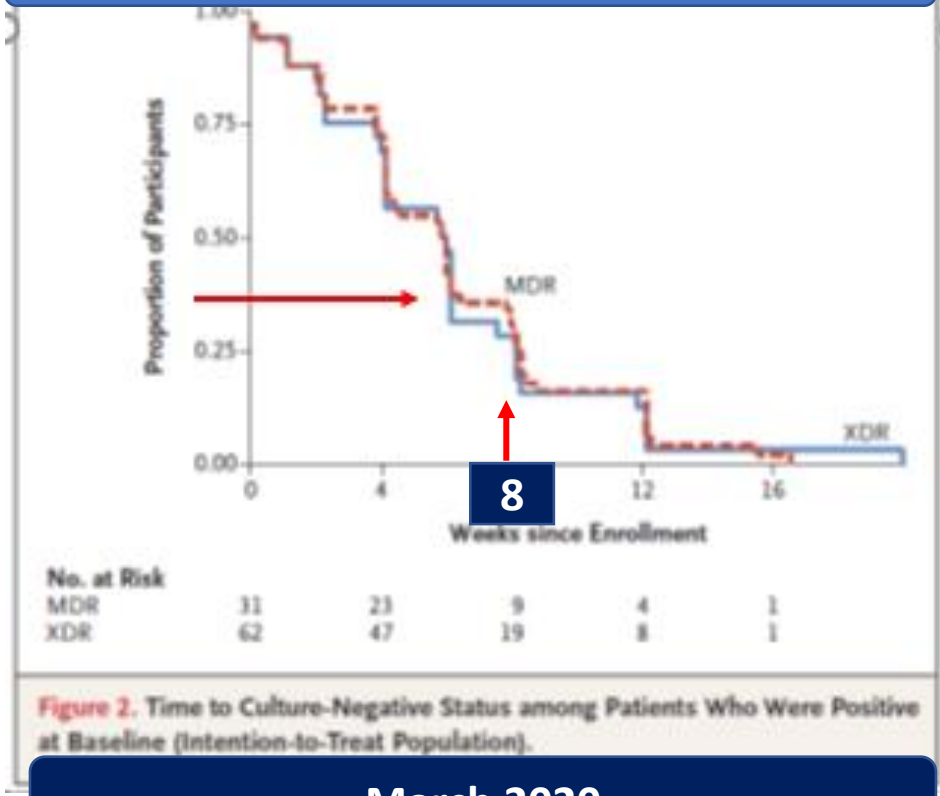


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

March 2020

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
Patients with MDR or XDR TB
Treatment Failure or Intolerant

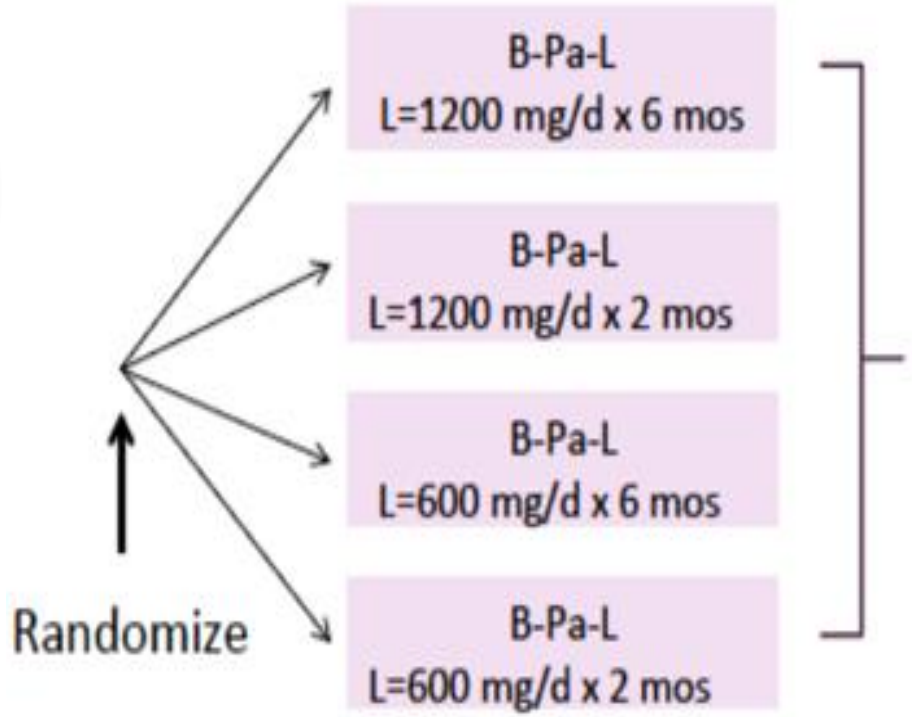
NEJM September 2022

The NEW ENGLAND JOURNAL of MEDICINE

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*



6 months of treatment

30 XDR TB/group and up to 15 pre-XDR or treatment non-response or intolerant MDR TB
45 -46 patients/group

Bedaquiline dose
200 mg daily x 8 weeks
100 mg daily 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

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%

Linezolid dose modified in 23/45 **(51%)** dose with LZD 1200 x 26 wks.
Only 6/45 **(13%)** required dose modification when LZD 600 mg x 26 wks.

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

Implementation of Bedaquiline, Pretomanid, and Linezolid in the United States: Experience Using a Novel All-Oral Treatment Regimen for Treatment of Rifampin-Resistant or Rifampin-Intolerant Tuberculosis Disease

Connie A Haley ✉, Marcos C Schechter, David Ashkin, Charles A Peloquin, J Peter Cegielski, Barbara B Andrino, Marcos Burgos, Lori A Caloia, Lisa Chen, Angel Colon-Semidey ... Show more

Author Notes

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

Published: 30 May 2023 **Article history** ▾

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

Linezolid Dosing in U.S. Cohort

Linezolid dosing adjustments before or during BPaL (n = 68)[c]	
Serum drug concentrations obtained for TDM, any reason	66 (97.1)
Dose or frequency adjusted, any reason	42 (61.8)
Adjusted based on TDM	36 (52.9)
Adjusted based on provider decision followed by TDM	6 (8.8)
Trough >2 µg/mL with 600 mg daily	20 (29.4)
Dose or frequency adjusted without symptoms	14 (20.6)
Dose or frequency adjusted with symptoms	4 (5.7)
Dose or frequency not adjusted with symptoms	2 (2.9)
Dose >600 mg required to reach therapeutic range (12–26 µg/mL)	20 (30.9)
Final linezolid dose used during BPaL (n = 68)[d]	
600 mg daily	27 (39.7)
600 mg TIW	21 (30.9)
900 mg daily	8 (11.8)
900 mg TIW	10 (14.7)
1200 mg TIW alternating with 600 mg QIW	1 (1.5)
1200 mg daily	0
1200 mg TIW	1 (1.5)

Abbreviations: BPaL, bedaquiline, pretomanid, and linezolid; QIW, 4 times weekly (on Tuesday, Thursday, Saturday, and Sunday); TDM, therapeutic drug monitoring; TIW, thrice weekly (on Monday, Wednesday, and Friday).

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
  - Some possible antagonism so strain to strain difference investigated
  - Daily dosing of linezolid for 1 – 2 months had greatest efficacy but after that results similar if intermittent dosing or drug stopped

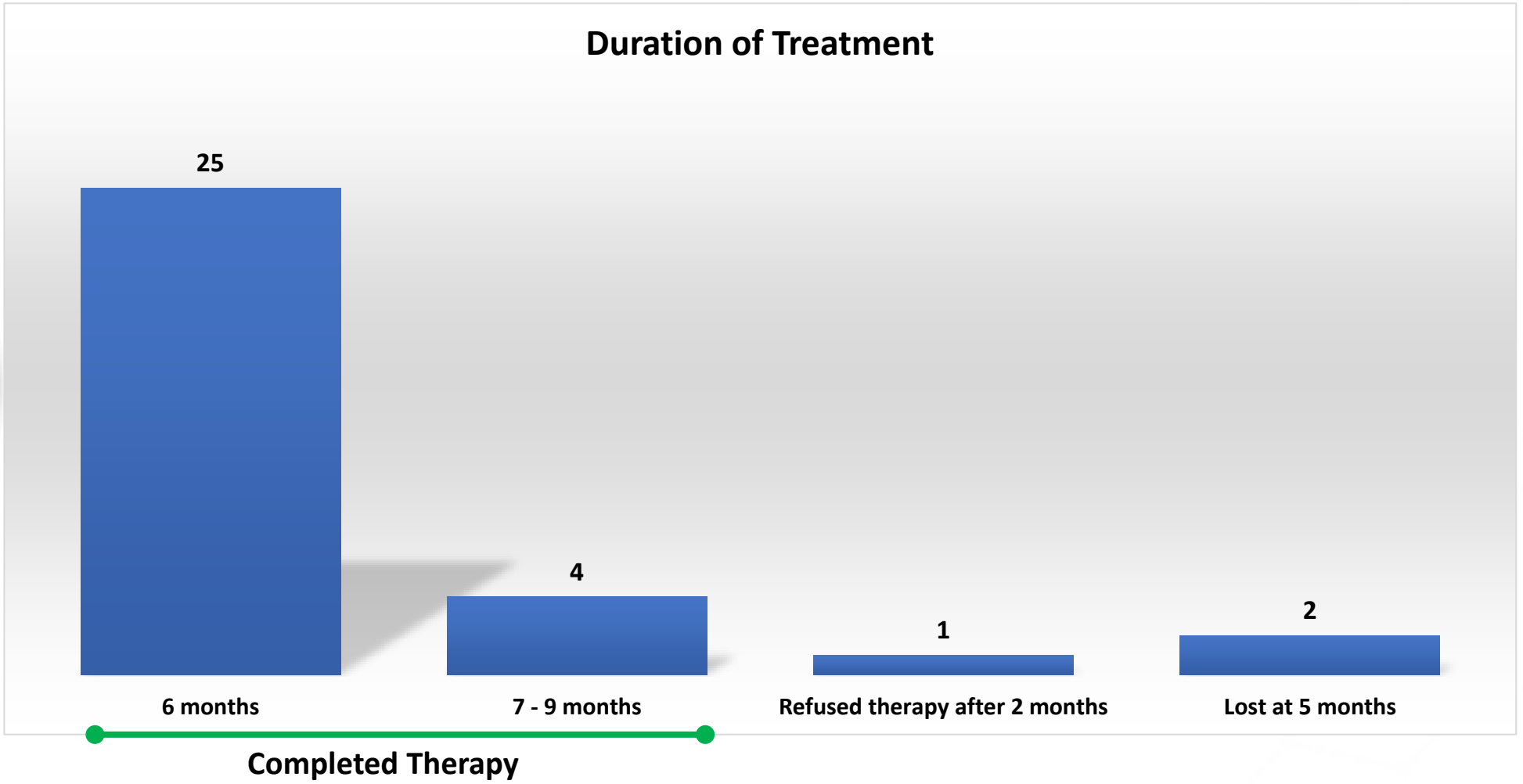
Characteristics of Drug-Resistant TB treated in Texas with BPaL and BPaLM 2021 – 6/2023

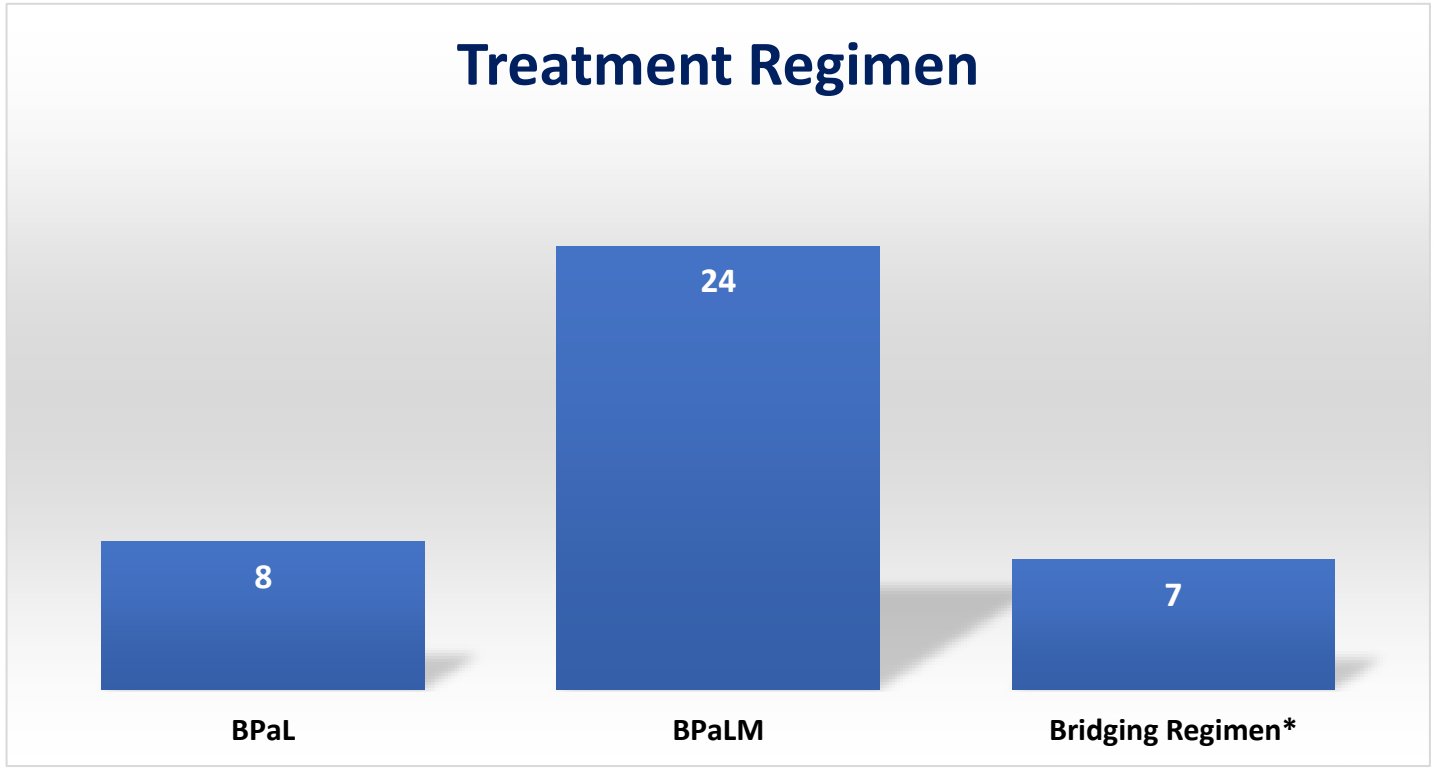
Diagnosis	
Pulmonary TB (PTB)	23
PTB + Extra Pulmonary TB*	9

First Case 8/3/2021

 # starting treatment
2021 (5)
2022 (16)
2023 (11)-
who finished treatment in 2023

Age at Diagnosis	
0 – 17	1
18 – 39	14
40 – 59	6
60 – 70	5
70 or greater	6

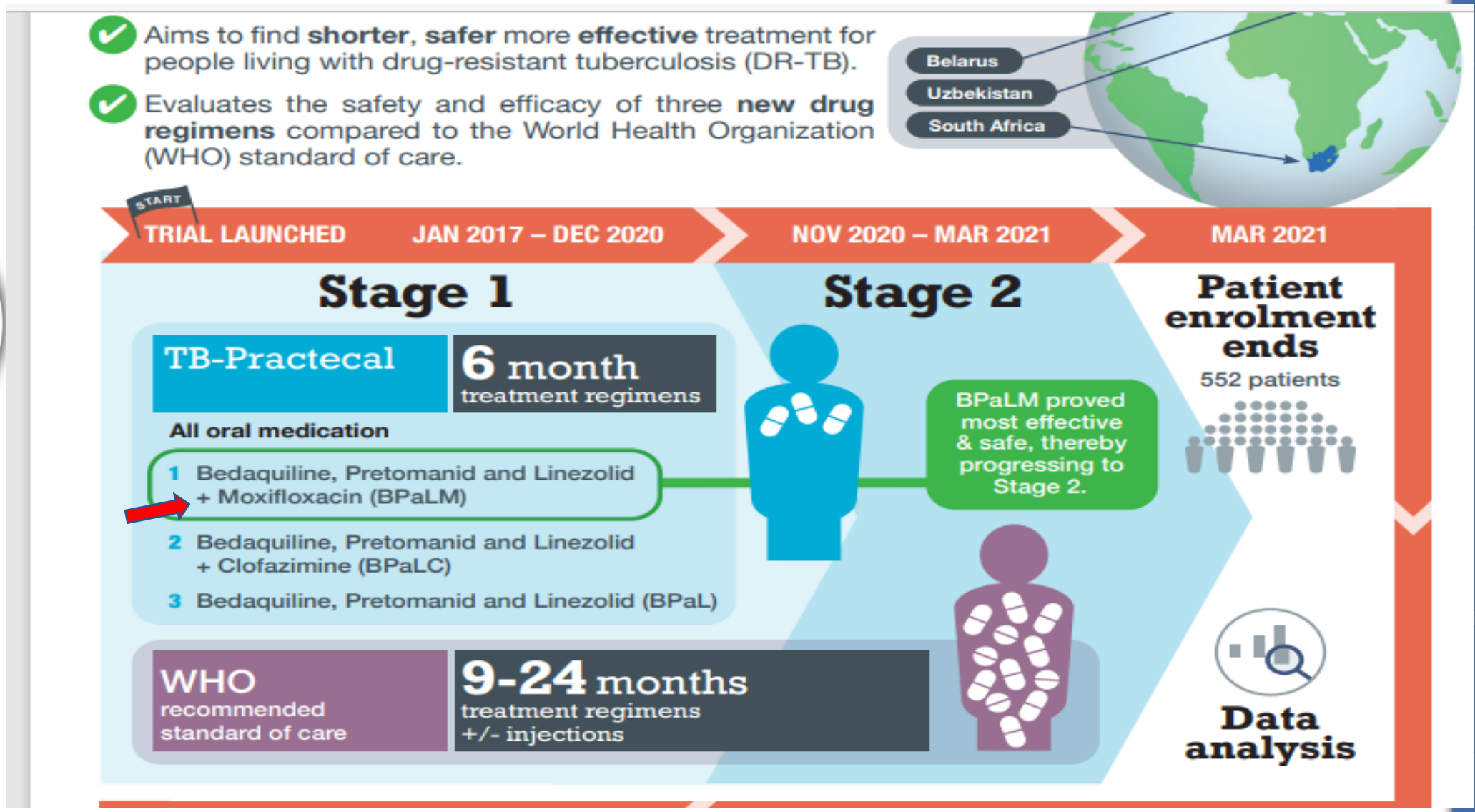

Duration of Treatment
25
4
1
2
6 months
7 - 9 months
Refused therapy after 2 months
Lost at 5 months
Completed Therapy



- **Bridging regimen** – Adequate treatment regimen for RR or MDR/pre-XDR or XDR TB prior to start of BPaL or BPaLM
- **BPaLM** (Bedaquiline, Pretomanid, Linezolid and Moxifloxacin)
- **BPaL** (Bedaquiline, Pretomanid, Linezolid)

TB-Practecal Clinical Trial

randomized, controlled



TB PRACTECAL –

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

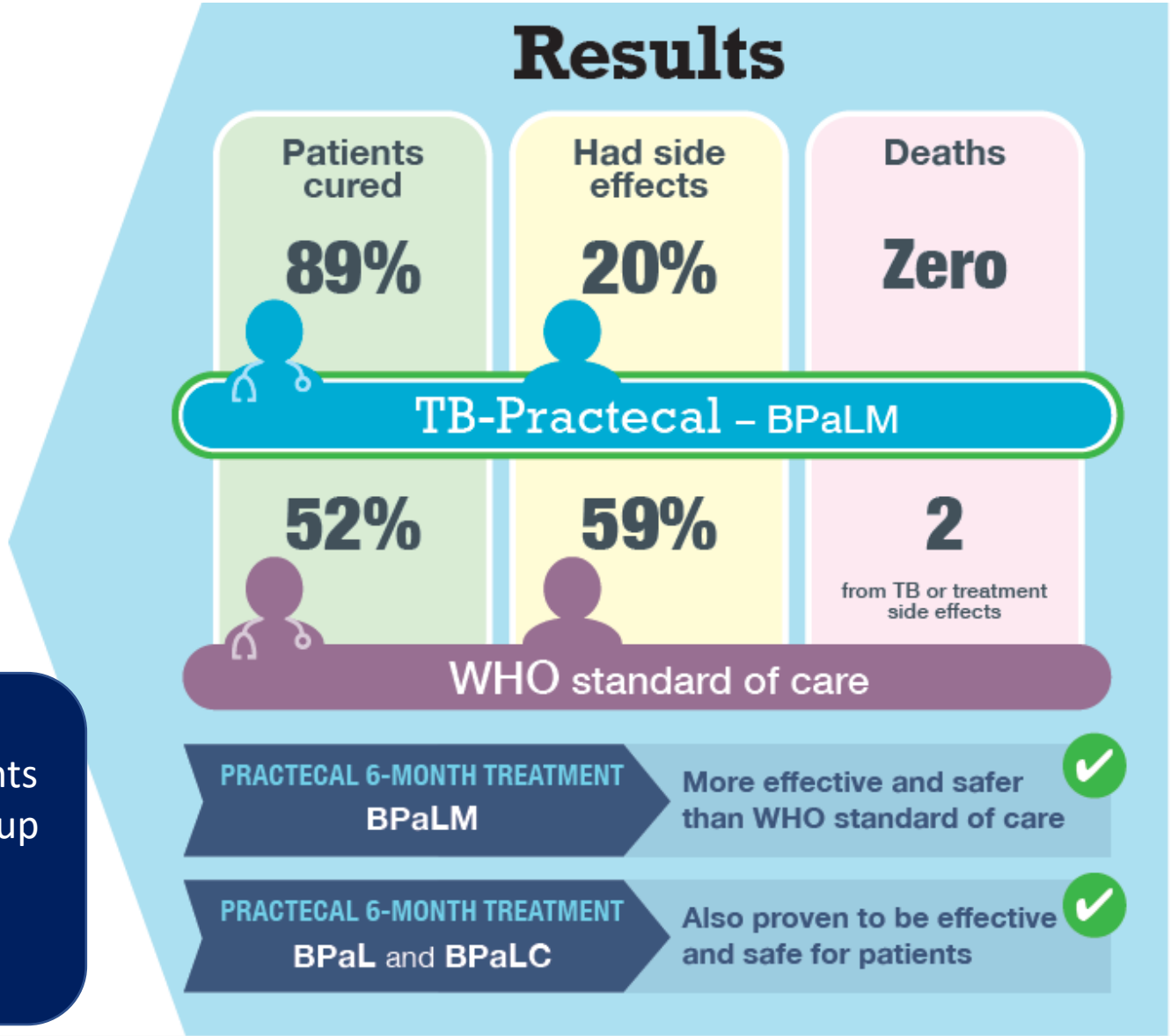
- Regimen 2:
- bedaquiline + pretomanid + linezolid + **clofazimine** for 26 weeks

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

- Standard of Care in Country at the time

Linezolid 600 mg daily x months, then 300 mg daily

TB PRACTECAL



26% of patients in BPaLM group were FQN resistant

Outcomes in Per Protocol Population (completers) in TB-PRACTICAL Trial

Outcome	BPaLM	BPaLC	BPaL	Standard of Care (SOC)
Primary Efficacy – Culture Conversion at 8 weeks	77%	67%	46%	
Favorable	**96%**	**88%**	**90%**	**88%**
Unfavorable	4%	10%	12%	12%
Death	0	1	3	2
Failure				
Relapse	0	1	0	0
Adverse events at 108 weeks post randomization				
Patients with ≥ 1 SAE	10/40 (**25%**)	18/43/(**42%**)	11/43 (**26%**)	25/43 (**60%**)
Number of events	11	22	21	48

Key Considerations for Selecting a Regimen

- DST: Fluoroquinolone resistant? - BPaL preferred
- For other patients BPaLM may be more active based on preliminary information from TB Practecal study and early WHO guidance
- BPaLM and BPaL-not recommended/contraindicated:
  - CNS disease (lacking good data on CNS penetration)
  - Pregnancy
  - Age < 15
  - Extensive disease or Extrapulmonary disease
    - may need RX extended or drugs added

When the patient with MDR/XDR doesn't fit the advised options for BPaLM or BPaL

Treatment in special situations:

- **CNS TB**
- **Children < 14**
- **Pregnancy**

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

Pretomanid for Central Nervous System Infections?

Six healthy volunteers

F-pretomanid PET shows excellent CNS penetration of pretomanid

Significantly higher levels in brain parenchyma than in CSF.

nature communications

Article

https://doi.org/10.1038/s41467-022-35730-3

Dynamic ^{18}F-Pretomanid PET imaging in animal models of TB meningitis and human studies

Received: 25 August 2022

Accepted: 20 December 2022

Published online: 29 December 2022

Check for updates

Filipa Mota[1,2,3,7], Camilo A. Ruiz-Bedoya[1,2,3,7], Elizabeth W. Tucker[1,2,4,7], Daniel P. Holt[5,7], Patricia De Jesus[1,2,3], Martin A. Lodge[5], Clara Erice[1,2,4], Xueyi Chen[1,2,3], Melissa Bahr[1,2,3], Kelly Flavahan[1,2,3], John Kim[1,2,4], Mary Katherine Brosnan[5], Alvaro A. Ordonez[1,2,3], Charles A. Peloquin[6], Robert F. Dannals[5] & Sanjay K. Jain[1,2,3,5]

Pretomanid is a nitroimidazole antimicrobial active against drug-resistant *Mycobacterium tuberculosis* and approved in combination with bedaquiline and linezolid (BPaL) to treat multidrug-resistant (MDR) pulmonary tuberculosis (TB). However, the penetration of these antibiotics into the central nervous system (CNS), and the efficacy of the BPaL regimen for TB meningitis, are not well established. Importantly, there is a lack of efficacious treatments for TB meningitis due to MDR strains, resulting in high mortality. We have developed new methods to synthesize ^{18}F-pretomanid (chemically identical to the antibiotic) and performed cross-species positron emission tomography (PET) imaging to noninvasively measure pretomanid concentration-time profiles. Dynamic PET in mouse and rabbit models of TB meningitis demonstrates excellent CNS penetration of pretomanid but cerebrospinal fluid (CSF) levels does not correlate with those in the brain parenchyma. The bactericidal activity of the BPaL regimen in the mouse model of TB meningitis is substantially inferior to the standard TB regimen, likely due to restricted penetration of bedaquiline and linezolid into the brain parenchyma. Finally, first-in-human dynamic ^{18}F-pretomanid PET in six healthy volunteers demonstrates excellent CNS penetration of pretomanid, with significantly higher levels in the brain parenchyma than in CSF. These data have important implications for developing new antibiotic treatments for TB meningitis.

J Antimicrob Chemother 2022; 77: 1720–1724
https://doi.org/10.1093/jac/dkac067 Advance Access publication 8 March 2022

Journal of Antimicrobial Chemotherapy

Pharmacokinetics of bedaquiline in cerebrospinal fluid (CSF) in patients with pulmonary tuberculosis (TB)

Caryn M. Upton [1]*†, Chanel I. Steele[2]†, Gary Maartens [2], Andreas H. Diacon[1], Lubbe Wiesner [2]‡ and Kelly E. Dooley[3]‡

[1]TASK, Cape Town, South Africa; [2]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA

- 7 males with rifampin resistant TB but no CNS disease
- CNS sampling for concentration of BDQ and M2 in CSF
  - BDQ and M2 present in CSF of all
  - Lower levels than plasma; **similar** to estimated plasma unbound fraction of BDQ and M2 **suggesting free CSF penetration**
  - Human experience minimal
  - No studies

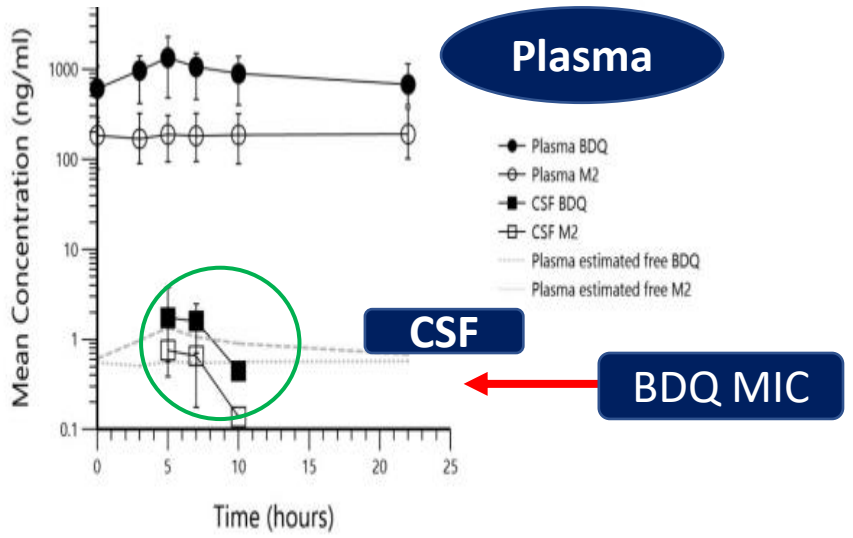
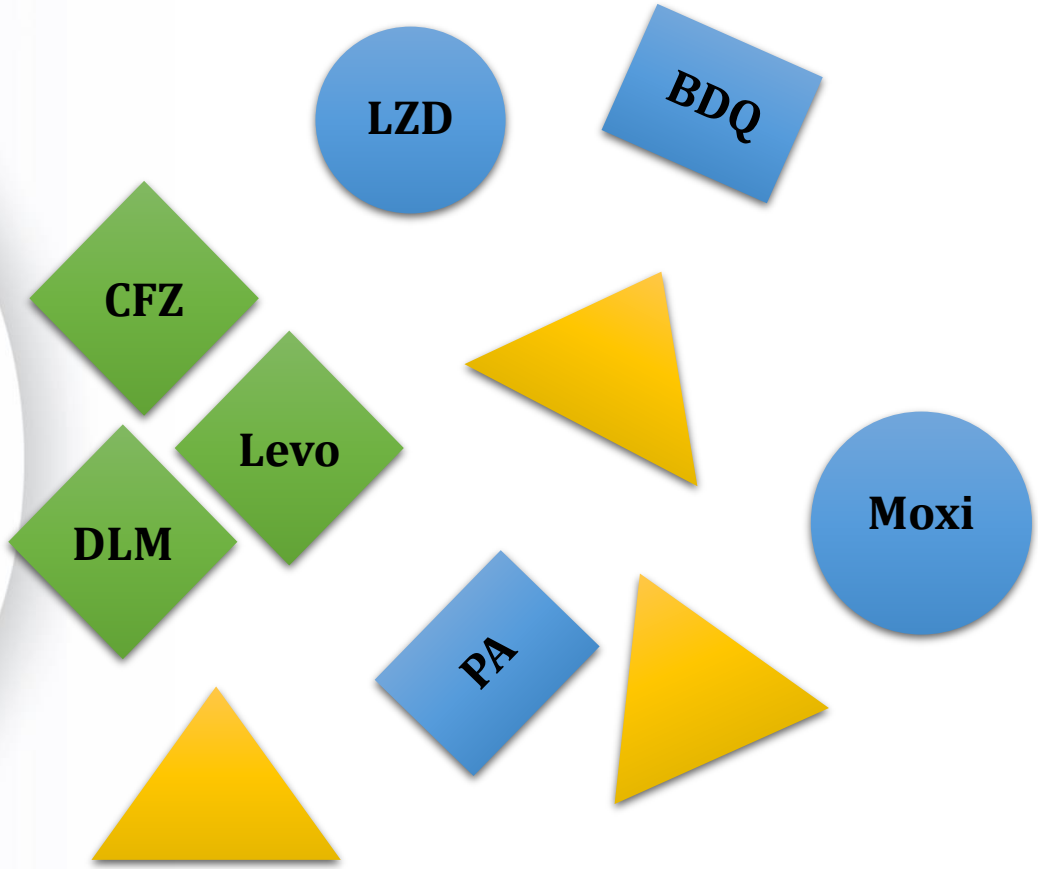


Figure 1. Mean (range) total plasma and CSF concentration profiles of bedaquiline and M2. The mean concentration and range of bedaquiline and M2 in plasma (filled and open circles, respectively) and CSF (filled and open squares, respectively) are shown for the seven participants. Estimated plasma free fractions of each analyte are displayed with pale broken lines. BDQ, bedaquiline.

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

Ongoing Trials of 6-month Oral Regimens

- SimpliciTB – BDQ+PTM+MFX+PZA, no control
- BEAT-Tuberculosis – BDQ+DLM+LZD*+LFX/CF vs SOC
- DRAMATIC – BDQ+DLM+LZD(1200_{2MOS})+LFX+CF x 16, 24,32, 40 weeks, no control
- BEAT-TB – BDQ+DLM+LZD(600)+CF, no control
- TB-TRUST Trial – LFX+LZD(600) +CS+PZA/CF vs SOC
- A5356 – BDQ+DLM+LZD($600/1200_{TIW}$)+CF, no control

*Weight based, 600 or 300

DLM = Delamanid

endTB

evaluates safety of treatment regimens containing both BDQ and Delamanid

Clinical Infectious Diseases

MAJOR ARTICLE

Safety of Treatment Regimens Containing Bedaquiline and Delamanid in the endTB Cohort

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Background. Safety of treatment for multidrug-resistant tuberculosis (MDR/RR-TB) can be an obstacle to treatment completion. Evaluate safety of longer MDR/RR-TB regimens containing bedaquiline and/or delamanid.

Methods. Multicentre (16 countries), prospective, observational study reporting incidence and frequency of clinically relevant adverse events of special interest (AESIs) among patients who received MDR/RR-TB treatment containing bedaquiline and/or delamanid. The AESIs were defined a priori as important events caused by bedaquiline, delamanid, linezolid, injectables, and other commonly used drugs. Occurrence of these events was also reported by exposure to the likely causative agent.

Results. Among 2296 patients, the most common clinically relevant AESIs were peripheral neuropathy (26.4%), electrolyte depletion (26.0%), and hearing loss (13.2%) with an incidence per 1000 person months of treatment, 1000 person-months of treatment 21.5 (95% confidence interval [CI]: 19.8–23.2), 20.7 (95% CI: 19.1–22.4), and 9.7 (95% CI: 8.6–10.8), respectively. QT interval was prolonged in 2.7% or 1.8 (95% CI: 1.4–2.3)/1000 person-months of treatment. Patients receiving injectables (N = 925) and linezolid (N = 1826) were most likely to experience events during exposure. Hearing loss, acute renal failure, or electrolyte depletion occurred in 36.8% or 72.8 (95% CI: 66.0–80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis, and/or myelosuppression occurred in 27.8% or 22.8 (95% CI: 20.9–24.8) times/1000 patient-months of linezolid exposure.

Conclusions. AEs often related to linezolid and injectable drugs were more common than those frequently attributed to bedaquiline and delamanid. MDR-TB treatment monitoring and drug durations should reflect expected safety profiles of drug combinations.

Clinical Trials Registration. NCT03259269.

Keywords. MDR-TB; adverse events; new drugs; QT prolongation; linezolid.

The treatment for multidrug-resistant/rifampin-resistant tu- events (AEs) experienced by patients receiving these mul-

end TB (9 month regimens)

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

This give may give an option other than older individualized regimen when isolate is resistant to or patient is intolerant to Bedaquiline - 9CLLfxZ

endTB

PIPELINE REPORT 2023

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%.

Favorable outcomes (mITT):			Risk difference, experimental - control (95% confidence interval)
(a)	105/118 (89.0%)	89	8.3 (-0.8 to 17.4)
(b)	104/115 (90.4%)	90.4	9.8 (0.9 to 18.7)
(c)	104/122 (85.2%)	85.2	4.6 (-4.9 to 14.1)
(d)	93/118 (78.8%)	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%)

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.

Met margin of non-inferiority

superior

endTB
9 month

Similar safety

81.5% of control regimen conformed to WHO guidance

BEAT-TB India 6 BDLzC (no Pretomanid or FQN)

BEAT-TB India
CTRI/2019/01/017310

(Pre-XDR-TB; 165; PLHIV not included)

(a) 6BDLzC

(b) [none]

Favorable outcome 91%

Primary Efficacy Outcome:
The six-month bedaquiline- and delamanid-containing regimen was efficacious, producing a favorable outcome among 91% of participants at treatment completion and 86% of participants six months later (mITT).

Unfavorable outcomes:		Risk difference, experimental-control (95% confidence interval)
(a)	14 (9%)	NA
(b)	NA	NA

Primary Safety Outcome:
The six-month bedaquiline- and delamanid-containing regimen was generally safe with most AEs easily identified and managed (e.g., anemia, neuropathy, skin hyperpigmentation).

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	47 events	33 events	4 deaths
(b)	NA	NA	NA

Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. Clin Infect Dis. 2022 Jun 29:ciac528. doi: 10.1093/cid/ciac528.

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)	(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%.

87% favorable outcome

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

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

BEAT TUBERCULOSIS: A STRATEGY TRIAL OF 6 MONTH ORAL REGIMEN FOR RR TB IN SOUTH AFRICA

BDQ, Delamanid, Linezolid with Levofloxacin and Clofazamine

EFFICACY ENDPOINT: END OF TREATMENT OUTCOME

Successful	Unsuccessful
Cured	Treatment failed ○ lack of sputum culture conversion by the end of treatment OR ○ bacteriological reversion after sputum culture conversion to negative OR ○ if two or more anti-TB drugs are substituted due to Adverse Drug Reactions (ADRs)
Treatment completed	Death during the treatment from any cause
	Lost to follow-up
	Not evaluated

MDR-END 9 DLzLxZ No BDQ or Pretomanid (Korea)

MDR-END
NCT02619994
(MDR-TB; 214; PLHIV not included)

(a) 9DLzLxZ
(b) [20mo IA-containing regimen]

Non – inferior to SOC but longer regimen with IA Favorable outcome 70.6%

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%)

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.

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

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

CRUSH TB (CDC TBTC study #38)

- Drug susceptible TB but MDR type regimens
  - 4 months **BDQ**, Moxi, PZA Rifabutin
  - 4 months **BDQ**, Moxi, PZA, Delamanid

- Control: @HRZE/4HR

- Plan to enroll 288 participants
  - First participants enrolled in Uganda in early April 2024
  - U.S./Canada pending resolution involving supply of BDQ

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

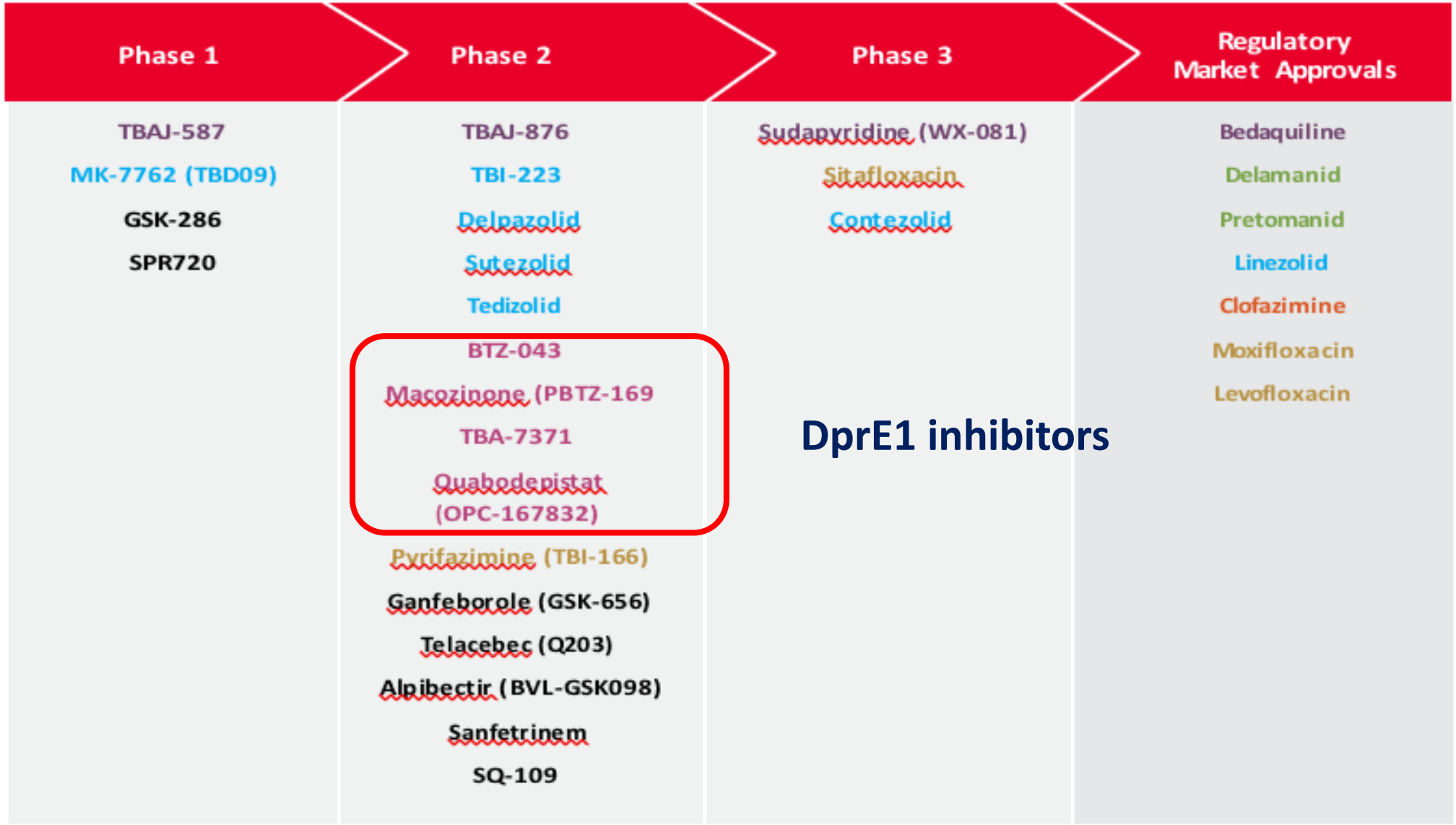


Figure adapted from Stop TB Partnership Working Group on New Drugs.
Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine Nitroimidazole; Fluroquinolone.
Drugs that appear in black font are from classes and/or with mechanisms of action not otherwise represented by the other colors.

Pipeline Report 2023

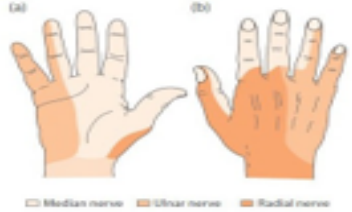
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

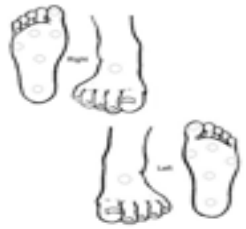
Additional information for selected nurse assessment (see complete toxicity assessment tool)

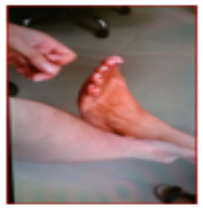
Peripheral Neuropathy

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

If newly identified discuss need for treatment change

Risk vs Benefit

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.

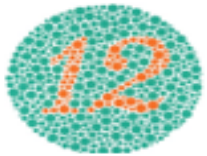
- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

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

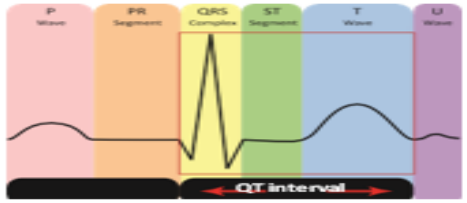
Monitoring for Adverse Effects

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

endTB Interim Analysis Report (EN / ES / RUS)

May 14th, 2020

Executive Summary

Each year, there are an estimated 600,000 new cases of rifampicin-resistant (RR) or multidrug resistant tuberculosis (MDR-TB) patients. Globally, the cure rate for MDR-TB is only 54%. Bedaquiline and delamanid were approved for use in MDR-TB patients in 2012 and 2013 respectively, the first two new drugs for TB developed in 50 years.

1,244 RR-TB patients initiating BDQ or Delamanid or both included in safety analysis.

No evidence of any major safety issue with either delamanid or bedaquiline
QT prolongation is known to be associated with both drugs
But clinically relevant prolongation uncommon and no deaths or SAEs

“While clearly there is a role for EKG screening , more resources and energy should be allocated to screening for more common” toxicities.

What substitutions are allowed?

- BPaLM

- BPaL

Management of Treatment Interruptions and substitutions

Restarting bedaquiline depends on duration of treatment to date 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

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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.

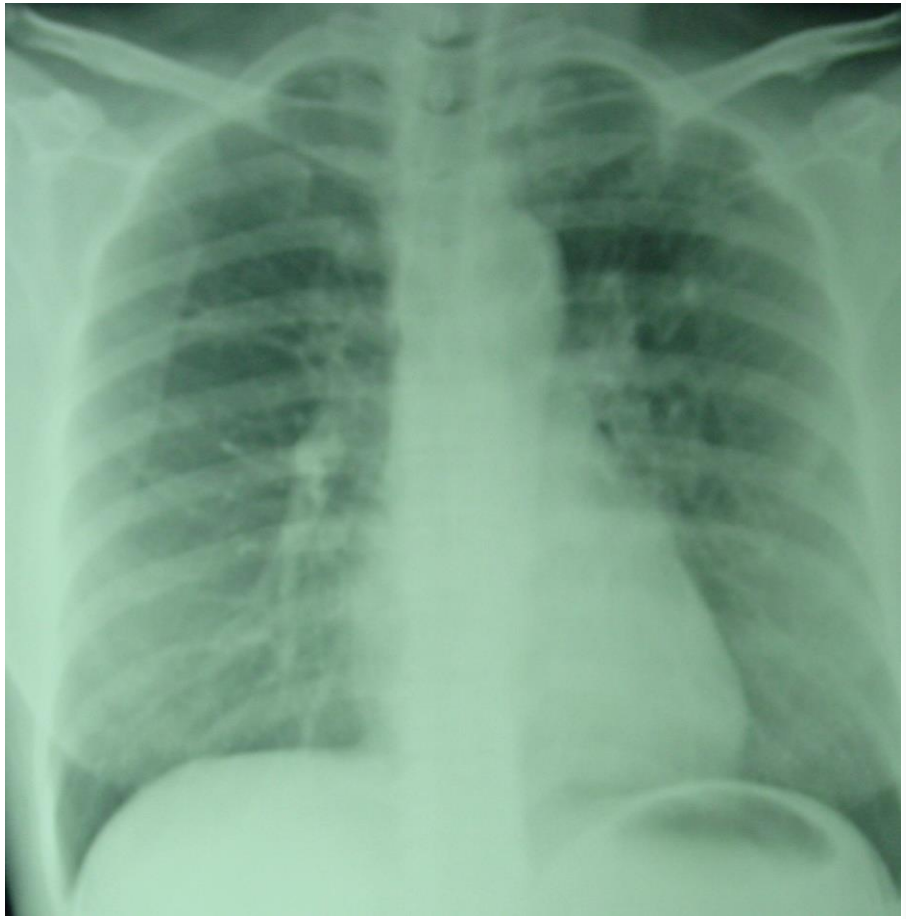
KEY WORDS: MDR-TB treatment; BDQ; pharmacokinetics; modelling; dosing

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

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

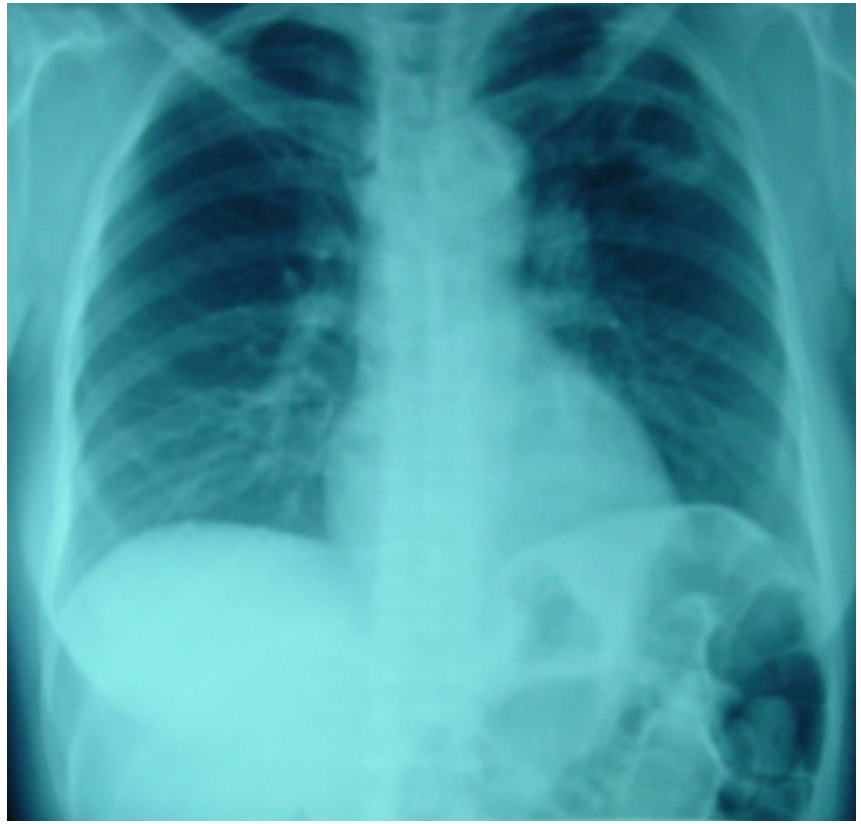


Case Study new immigrant with abnormal CXR

- 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 reported negative**
  - Evaluation in U.S.
    - **Smear negative, Xpert positive, rifampin resistance detected**

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

- **What is diagnosis?**
  - **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
    - Likely will diagnosis at least as culture negative TB
- **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**

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

- **Safety**

Efficacy

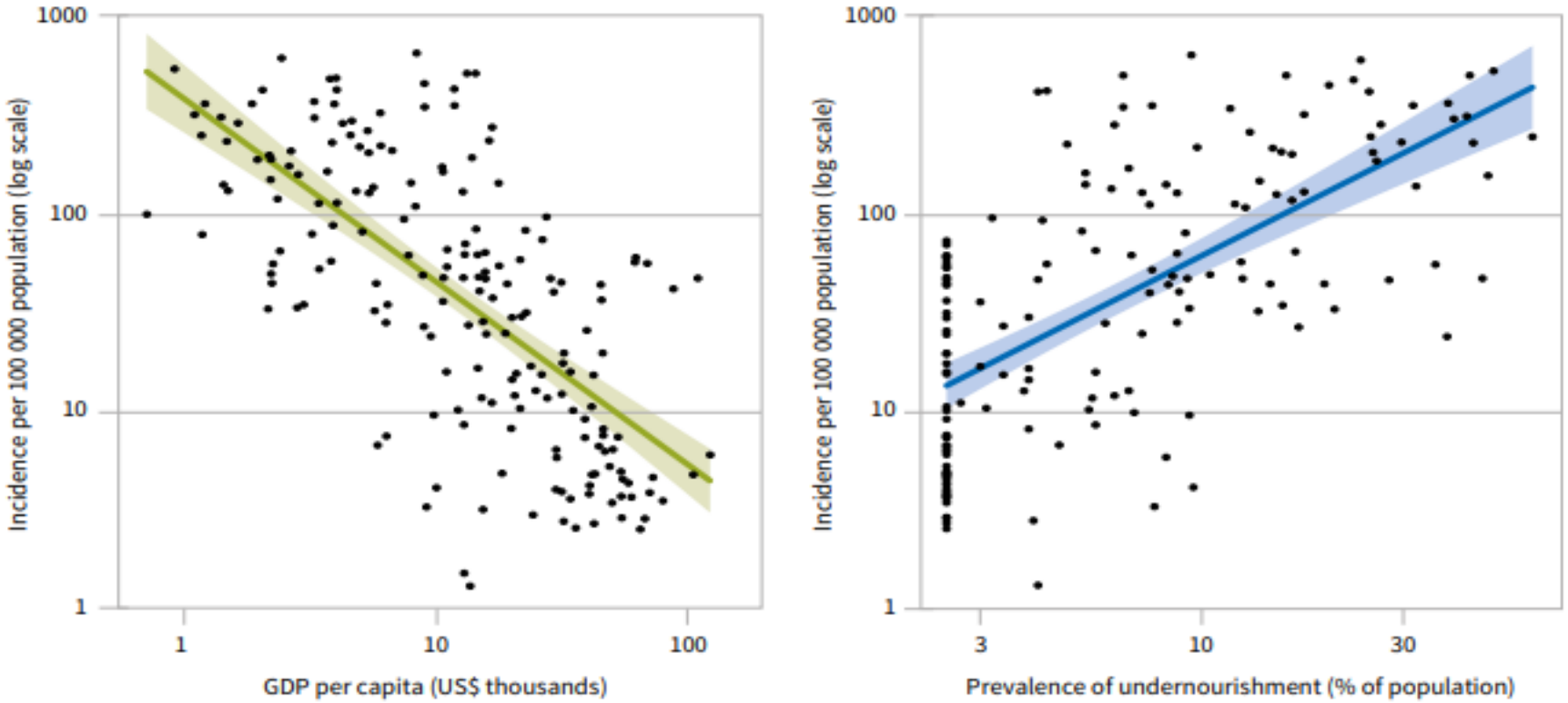
- **Tolerability**
  - Pill burden, side effects

Time

Duration, **home time**

One Size Does Not Fit All

The relationship between GDP per capita and the prevalence of undernourishment, and TB incidence per 100 000 population, 2021[a]



[a] The year of data used for GDP per capita and undernourishment is the latest year for which data are available in the World Bank (https://data.worldbank.org/) and SDG (https://unstats.un.org/sdgs/dataportal) databases, respectively.

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