MDR/XDR-TB

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September 14, 2023

TB Intensive
September 13 – 15, 2023
Richmond, TX

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Barbara Seaworth, BS, MD, FIDSA, FACP has the following disclosures to make:

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

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Drug Resistant Tuberculosis

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Barbara Seaworth, MD

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

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CDC Terminology to Classify Drug Resistant TB

OLD Terminology

- **rifampin mono-resistant TB (RR TB):** no designation
- **Pre-XDR TB:** no formal designation

Updated Terminology - January 2022

- **rifampin mono-resistant TB (RR TB):** no designation
- **Pre-XDR TB:** caused by an organism that is resistant to at least INH, rifampin, and a **Fluoroquinolone OR a 2nd line injectable (amikacin, capreomycin and kanamycin)**

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CDC Terminology to Classify Drug Resistant TB

OLD Terminology

- **XDR-TB:** caused by an organism that is resistant to INH, rifampin, a **Fluoroquinolone and a 2nd line injectable** (amikacin, capreomycin and kanamycin)

Updated Terminology - January 2022

- **XDR-TB:** caused by an organism that is resistant to INH, rifampin, a **Fluoroquinolone and a 2nd line injectable OR** by an organism that is resistant to INH, rifampin, **a FQN and BDQ or linezolid**

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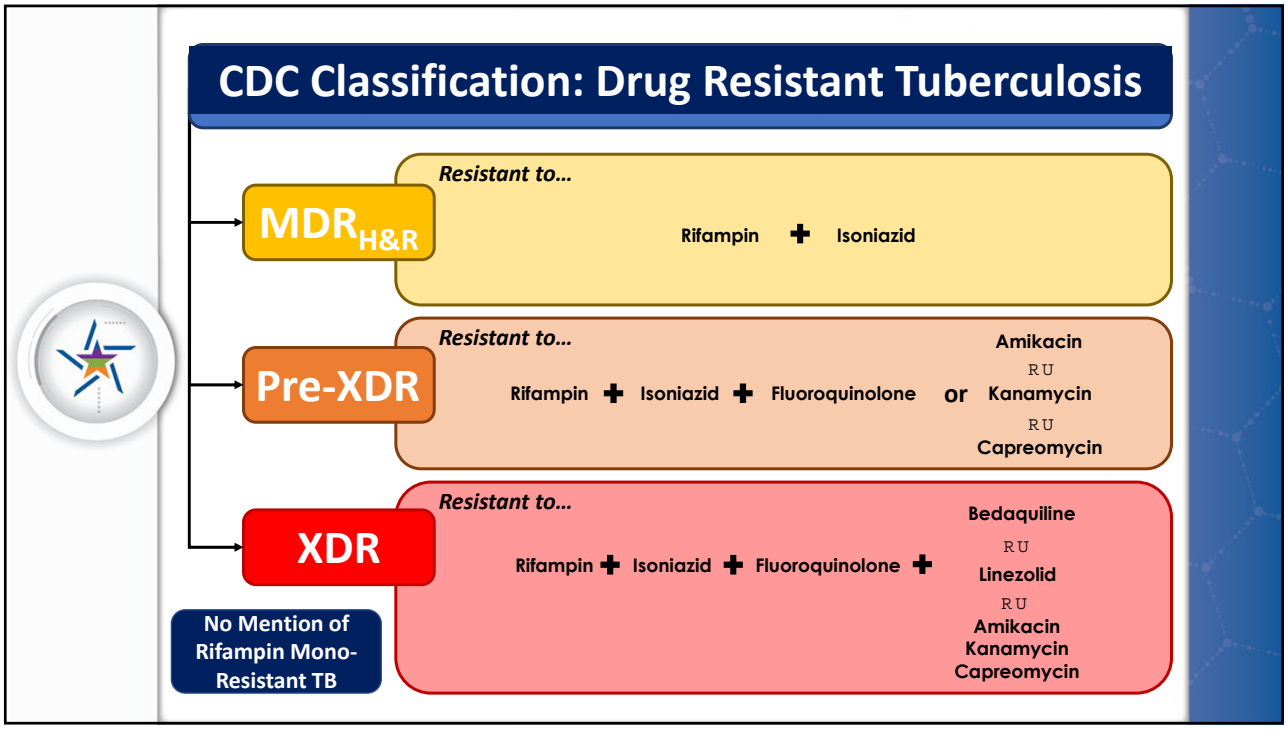

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WHO Classification: Drug Resistant TB

January 2021

Group A Drugs
Levofloxacin/Moxifloxacin
Bedaquiline
Linezolid

Note: No mention of the injectable agents by WHO

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

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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

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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
  - Possibility of poor absorption
- 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

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Diagnosis of Drug Resistant TB

Initial specimen

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

If Xpert is positive for MTB and rifampin resistance

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

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Management of Patient When MDR/RR TB is Suspected/Identified

- Stop RIPE treatment
  - If patient seriously ill contact a consultant to help with an empiric regimen pending more information
- 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

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What about Discrepancies in Rifampin Susceptibility – Molecular Tests and DST (culture)

- **Molecular testing** done by whole genome sequencing pyrosequencing, Sanger or next generation 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 rifampin resistance but these are clinically significant – cannot be treated with standard regimen

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Treatment of Drug Resistant TB

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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

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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**

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FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES

Discovery of new drugs to treat TB

1940s
1944 PAS
1948 streptomycin

1950s
1952 isoniazid
1954 pyrazinamide
1955 cycloserine
1957 kanamycin

1960s
1960 ethionamide
1961 ethambutol
1963 capreomycin rifampicin

1980s
6-month regimen DS-TB
2HRZE/4HR

1990s
1998 rifapentine

2010s
2012 bedaquiline
2014 rifapentine* delamanid
2016
9-12-month regimen DR-TB
2019 pretomanid
6-9-month regimen DR-TB
6-9BPaL

2020s
2020
4-month regimen DS-TB
2HPMZ/2HPM

*approved for treating latent TB infection

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

24 months — Duration of Treatment → 4 months

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

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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 now available for compassionate use
Pa-824 - Pretomanid

2022: Bedaquiline - Core Drug for MDR/XDR TB

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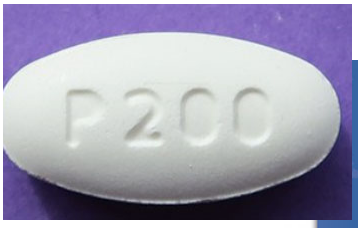
TB Alliance ABOUT WHY NEW TB DRUGS? R&D ACCESS NEWS DONATE

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

Combination As "THE" Regimen
BPaL
later - BPaLM
? Coming…BPaMZ



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BPaLM (BPaL plus Moxifloxacin - 5 tablets)

BDQ/Pretomanid/Linezolid/Moxifloxacin

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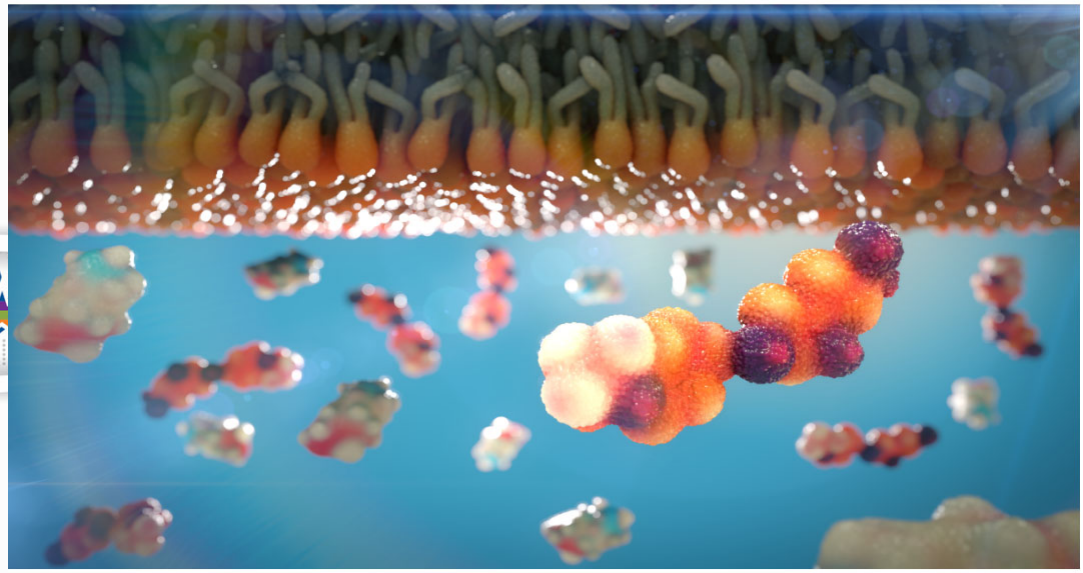

Artist's rendering of the pretomanid compound.

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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

    7 drugs
  - 5 months of:
    - Levofloxacin/moxifloxacin, EMB, PZA and clofazimine
- **Longer all oral** individualized regimen (18 months)
  - Use injectable drug only when no other options

December 2022

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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?

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Case Study new immigrant with abnormal CXR

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

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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

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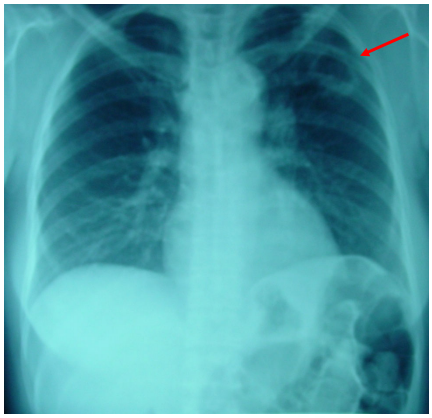
Case study new immigrant with abnormal CXR

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



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Case Study new immigrant with abnormal CXR

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

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Case Study new immigrant with abnormal CXR

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

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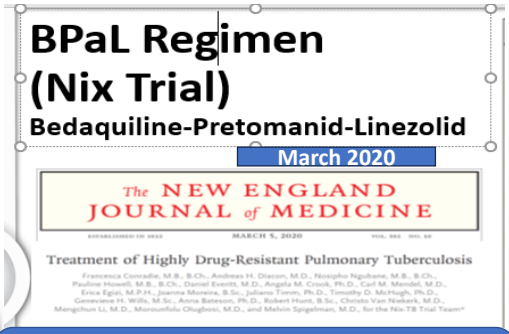
BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid

March 2020


The NEW ENGLAND JOURNAL of MEDICINE

MARCH 5, 2020

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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

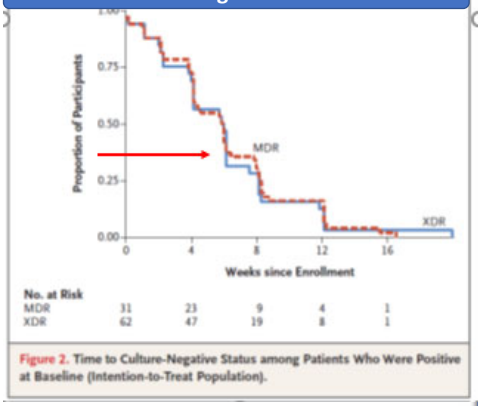


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

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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%

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ZeNIX: Linezolid Optimization Trial
Patients with MDR or XDR TB Treatment Failure or Intolerant

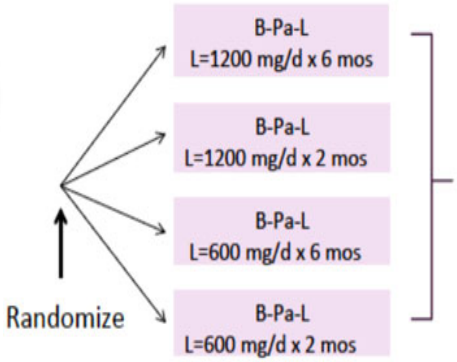
NEJM September 2022

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

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ZeNIX: Linezolid Optimization Trial
MDR or XDR TB Treatment Failure or Intolerant

Safety 600 mg x 26 wk.

24% Peripheral neuropathy

2% Myelosuppression

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

Efficacy

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

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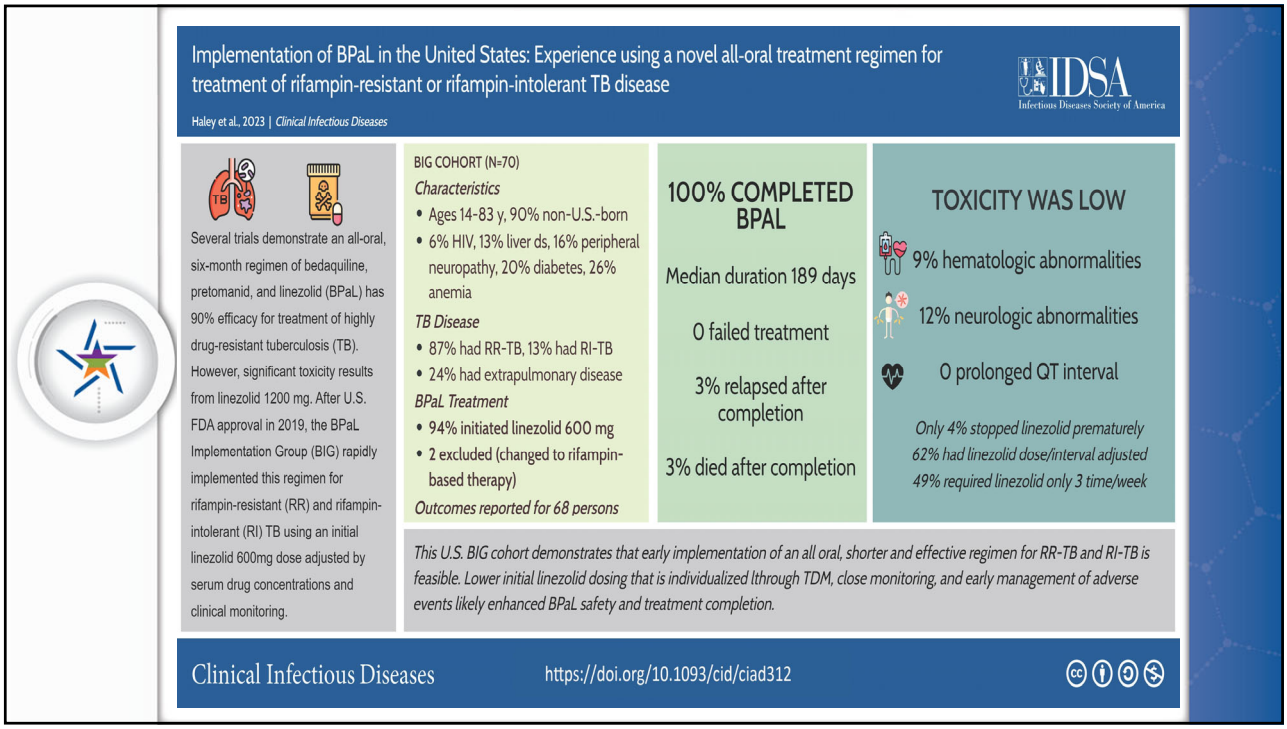
Implementation of BPaL in the United States: Experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant TB disease
Haley et al., 2023 | Clinical Infectious Diseases
IDSA
Infectious Diseases Society of America
Several trials demonstrate an all-oral, 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

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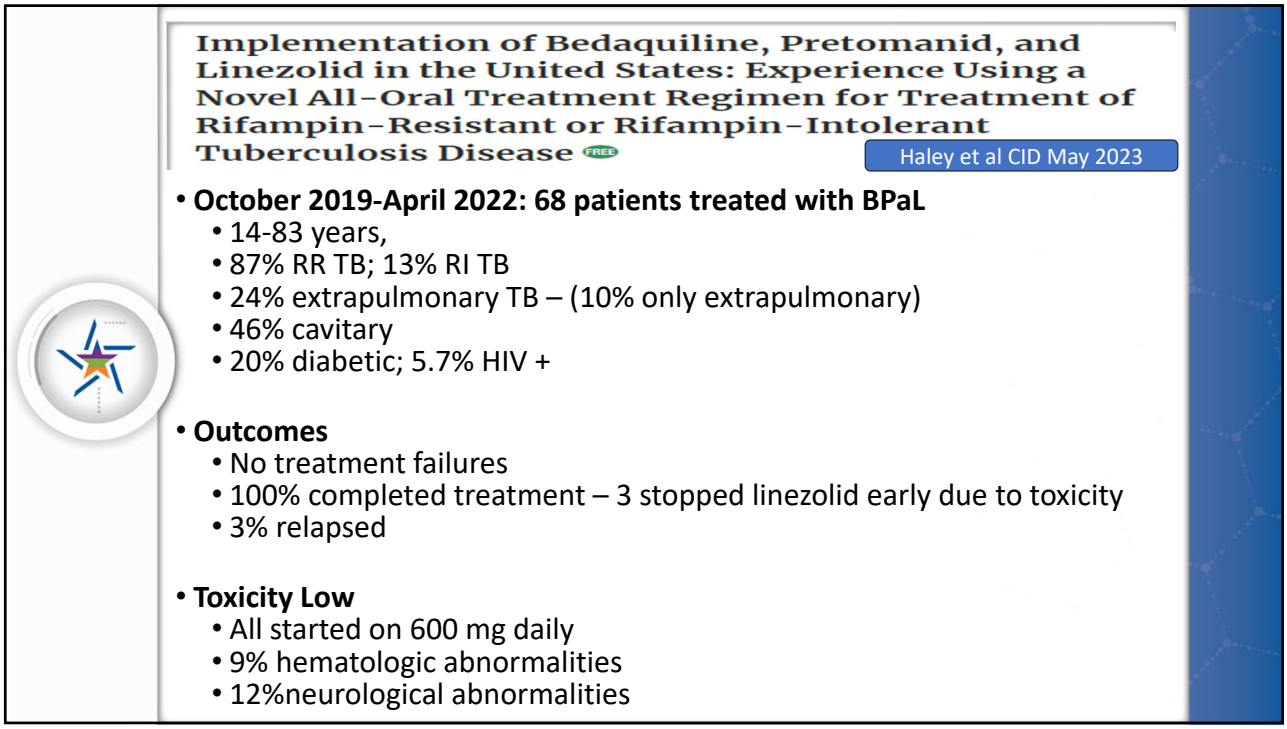
Implementation of Bedaquiline, Pretomanid, and Linezolid in the United States: Experience Using a Novel All-Oral Treatment Regimen for Treatment of Rifampin-Resistant or Rifampin-Intolerant Tuberculosis Disease
FREE
Haley et al CID May 2023
• October 2019-April 2022: 68 patients treated with BPaL
• 14-83 years,
• 87% RR TB; 13% RI TB
• 24% extrapulmonary TB – (10% only extrapulmonary)
• 46% cavitary
• 20% diabetic; 5.7% HIV +
• Outcomes
• No treatment failures
• 100% completed treatment – 3 stopped linezolid early due to toxicity
• 3% relapsed
• Toxicity Low
• All started on 600 mg daily
• 9% hematologic abnormalities
• 12%neurological abnormalities

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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)

32/68 TIW

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TB PRACTECAL –

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

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

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

- Standard of Care in Country at the time

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TB-Practecal Clinical Trial

randomized, controlled

- Aims to find **shorter**, **safer** more **effective** treatment for people living with drug-resistant tuberculosis (DR-TB).
- Evaluates the safety and efficacy of three **new drug regimens** compared to the World Health Organization (WHO) standard of care.

START
TRIAL LAUNCHED | JAN 2017 – DEC 2020 | NOV 2020 – MAR 2021 | MAR 2021

Stage 1

TB-Practecal — 6 month treatment regimens

All oral medication

1. Bedaquiline, Pretomanid and Linezolid + Moxifloxacin (BPaLM)
2. Bedaquiline, Pretomanid and Linezolid + Clofazimine (BPaLC)
3. Bedaquiline, Pretomanid and Linezolid (BPaL)

WHO recommended standard of care — 9-24 months treatment regimens +/- injections

Stage 2

BPaLM proved most effective & safe, thereby progressing to Stage 2.

Patient enrolment ends

552 patients

Data analysis

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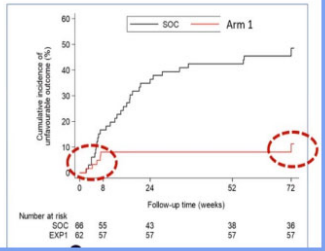
TB-PRACTECAL - Efficacy

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

BPaLM - Superior and Non-Inferior

Cumulative incidence unfavorable outcome 72 wks.

Primary treatment outcome: mITT



2022 RESIST-TB Webinar

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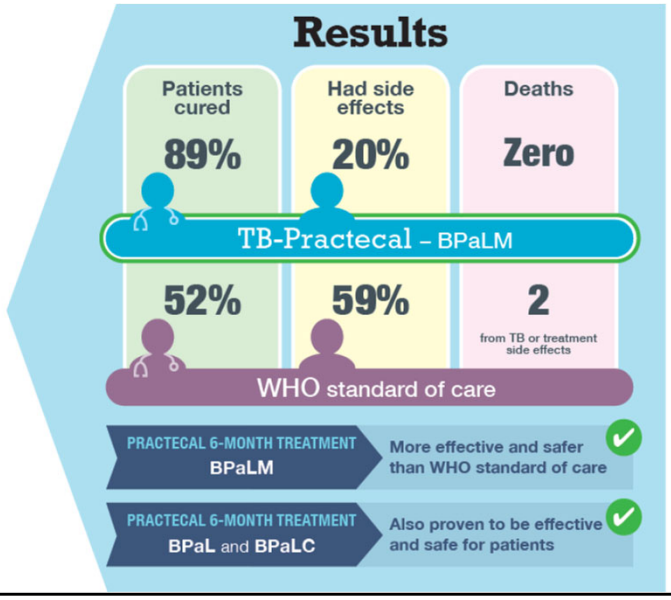
TB PRACTECAL



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

Outcome percent (#)	BPaLM	BPaLC	BPaL	Standard of Care (SOC)
Culture Conversion at 8 wks.	77%	67%	46%	
Culture Conversion at 12 wks.	88%			79%
Favorable 72 weeks F/U	**96%**	**88%**	**90%**	**88%**
Unfavorable 72 weeks F/U	4%	10%	12%	12%
Death	0	2% (1)	0	6% (2)
Failure	0	2% (1)	0	0
Relapse	0	2% (1)	6% (3)	0
Adverse events at 108 weeks post randomization				
Patients with ≥ 1 SAE	**25% (10/40)**	**42% (18/43)**	**26% (11/43)**	**60% (26/43)**
Number of events	11	22	21	48

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WHO Consolidated Guidelines – Drug Resistant TB 2022

- WHO suggests the use of the new 6-month treatment regimen composed of Bedaquiline, Pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR TB and pre-XDT TB rather than 9-month or longer regimens
- WHO suggests the use of the new 9-month **all-oral** regimen rather than longer (18-month) regimens in patients with MDR/RR-TB in whom resistance to fluoroquinolones has been excluded.
- In RR/MDR TB on longer regimens (18 –month) three Group A drugs and at least one Group B drug should be included to ensure that treatment starts with at least 4 effective drugs and at least three are present throughout therapy after the initial period with 4 drugs.

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Section 1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)

1.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.

WHO 2022

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Provisional CDC Guidance for Use of Pretomanid as part of a Regimen (BPaL) to treat Drug-Resistant TB –May 2023

- CDC recommends use of BPaL regimen in adults with pulmonary TB resistant to INH, rifampin and at least one fluoroquinolone (levo/moxi) or injectable drug or pulmonary TB that is resistant to INH and rifampin among patients who are treatment intolerant or nonresponse.
- Recommends treatment x 26 weeks; may extend to 39 weeks if slow bacteriological, clinical or radiographic response
- Linezolid dose should be 600 mg daily; may adjust dose
- Only definite contra-indication HIV/ART on efavirenz or cobistat
- Pretomanid does not have an approved indication for: pregnancy, children < 14

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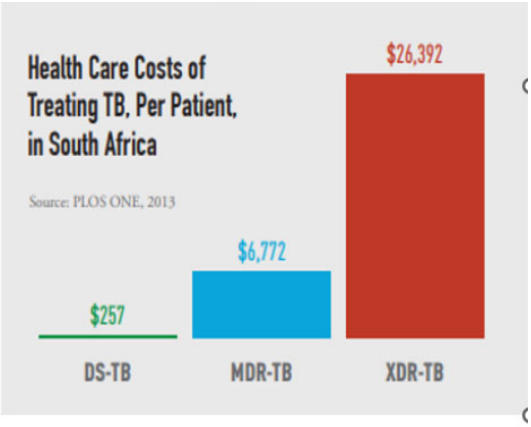
Cost effectiveness of short, oral treatment regimens fo RR-TB

Cost Savings with change from SOC to:

BPaL: $1,173/person in South Africa to $112 in India

BPaLM: would save $80-$904

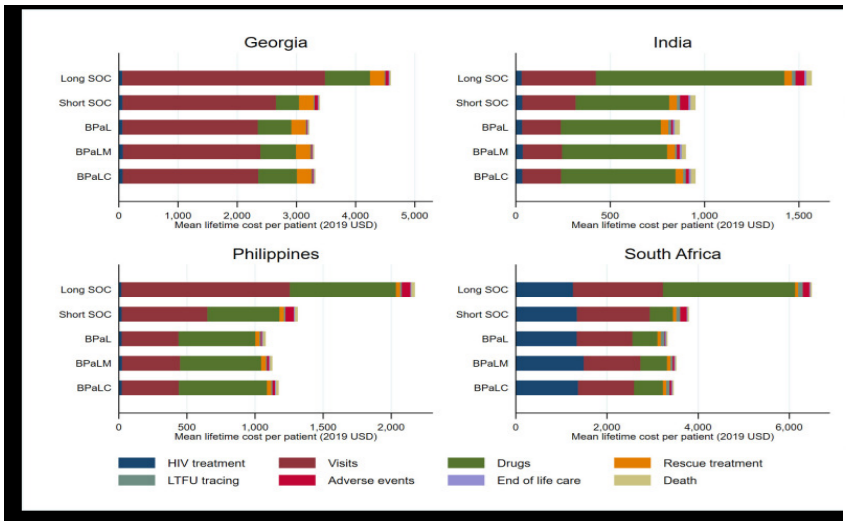
PLOS Global Public Health December 2022



PLOS ONE 2013

44

Average Lifetime Costs by Country and Regimen



PLOS Global Public Health December 2022

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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

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

6 – 9 months
All oral
Core drugs:
Bedaquiline
Pretomanid
Linezolid
Moxifloxacin

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

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

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When do we worry about bedaquiline resistance?

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

Lancet Infect Dis 2022; 22: 496-506

Nazir Ahmed Ismail*, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsoalo, 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†

- 8023 surveillance samples screened 2015-2019 (South Africa)
- Patients starting Bedaquiline-based treatment had samples collected at baseline, month 2, month 6
- Baseline BDQ resistance was **3.8%** **(**76/2023)
  - **BDQ naïve 72/2023, 3.6%**
  - **Prior BDQ or clofazimine, 4/19, 21.1%**
- BDQ resistance was associated with previous exposure to Bedaquiline or clofazimine (OR 7.1)
- Rv0678 mutations were associated with resistance
- **Resistance emerged in 12/695 (2.3%) of patients on treatment** with median time to emergence of 90 days (range 21-654 days)
- Successful treatment outcomes were lower in patients with Bedaquiline resistance

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Linezolid Resistance in patients with drug-resistant TB

- Meta analysis of clinical isolates of MDR TB
  - Azimi et al, Front. Pharmacol 2022
  - Pooled frequency of **Linezolid resistance 4.2%**
  - Majority of studies were from China and Turkey; only one study from India included
- Isaakidis, Letter to the Editor Int J Tuberc Lung Dis 2023 The Union reported linezolid resistance from a retrospective, cohort study of routinely collected clinical data from Mumbai, India
  - 365 patients registered 2016-202 – **Linezolid resistance 19.7%** (72/365)
  - Cohort of patients who had failed DR TB treatment regimen who were being retreated in MSF Clinic
  - 78% prior treatment with linezolid - 22% no prior history of linezolid treatment
  - 36% unfavorable outcome despite use of Bedaquiline and Delamanid in 64/72

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Characteristics of Commonly Used Second-Line Drugs for DR-TB

For complete information on these and other drugs for MDR-TB, consult medication package inserts or medication fact sheets in *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd edition* available at: currytbcenter.ucsf.edu/product/view/drugresistant-tuberculosis-a-survival-guide-for-clinicians-3rd-edition

Drug	Standard Adult Dosing*	Considerations	Side Effects
Bedaquiline	400 mg once daily for 14 consecutive days; then 200 mg 3 times/wk for 22 wks (may give longer); 26 wks total duration as part of BPaL regimen	CNS penetration unproven. can be safely used with moderate chronic kidney disease (CKD) or moderate liver disease; give with meal to increase bioavailability	QTc prolongation, decreased appetite, nausea, hepatitis, headaches, arthralgias, elevated amylases
Moxifloxacin	400 mg once daily, PO or IV	Good CNS penetration.	GI upset, dizziness, hypersensitivity, photosensitivity, headaches, arthralgias, tendonitis, tendon rupture (rare), CNS irritability, QTc prolongation, thrush, peripheral neuropathy, elevated liver enzymes (rare hepatotoxicity with moxifloxacin)
Levofloxacin	750-1,000 mg once daily, PO or IV	Good CNS penetration; adjust dose with creatine clearance < 30; avoid caffeine, milk-based products, antacids, or mineral supplements within 2 hrs of medication	
Linezolid	600 mg once daily, PO or IV	Good CNS penetration; trough < 2 µg/ml is associated with lower toxicity	Peripheral and optic neuropathy, reversible with early recognition), anemia, thrombocytopenia, neutropenia, headache, GI upset, rash, serotonin syndrome, lactic acidosis, acute pancreatitis, black hairy tongue
Pretomanid (As part of BPaL or BPaLM regimen)	200 mg once daily for 26 wks	No dose adjustment in patients with mild to moderate renal impairment; use with caution with severe renal impairment; should be taken with food	Hepatotoxicity, myelosuppression, peripheral and optic neuropathy, lactic acidosis, QTc prolongation, pancreatitis, [AEs listed are for entire BPaL regimen]
Delamanid	100 mg twice daily for 24 wks (longer is possible)	CNS penetration unknown; can be safely used with moderate CKD or moderate liver disease; should be taken with food	GI upset, dizziness, insomnia, upper abdominal pain, QTc prolongation

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AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis
An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

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

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

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

All Oral Regimen!

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

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

www.thelancet.com **Vol 393 April 20, 2019**

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

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

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What substitutions are allowed?

- BPaLM
- BPaL

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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

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Clinical Trial > Lancet Infect Dis. 2021 Jul;21(7):975-983. doi: 10.1016/S1473-3099(20)30770-2. Epub 2021 Feb 12.

QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial

Kelly E Dooley [1], Susan L Rosenkranz [2], Francesca Conradie [3], Laura Moran [4], Richard Hafner [5], Florian von Groote-Bidlingmaier [6], Javier R Lama [7], Justin Shenje [8], Jorge De Los Rios [7], Kyla Comins [6], Joel Morganroth [9], Andreas H Diacon [10], Yoninah S Cramer [2], Kathleen Donahue [11], Gary Maartens [12]; AIDS Clinical Trials Group (ACTG) A5343 DELIBERATE Study Team

Collaborators, Affiliations + expand

PMID: 33587897 PMCID: PMC8312310 DOI: 10.1016/S1473-3099(20)30770-2

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BDQ & Delamanid – EKG and Culture Conversion

- **Mean change in QTc from baseline was:**
- **12·3 ms Bedaquiline**
- 8·6 ms delamanid
- 20·7 ms bedaquiline plus Delamanid

- There were no grade 3 or 4 adverse QTc prolongation events
- No deaths during study treatment.

- **Cumulative culture conversion by week 8** was:
- 21 (88%) of 24 Bedaquiline
- 20 (83%) of 24 Delamanid
- 19 (95%) of 20 bedaquiline plus delamanid

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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

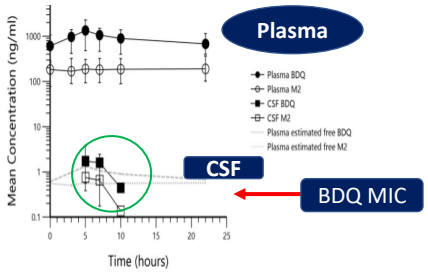

Figure 1. Mean (range) total plasma and CSF concentration profiles of bedaquiline and M2. The mean concentration and range of bedaquiline and M2 in plasma (filled and open circles, respectively) and CSF (filled and open squares, respectively) are shown for the seven participants. Estimated plasma free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

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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.

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Delamanid

- Animal studies show penetration into CNS
- Children treated with Delamanid can have "night terrors:
- Adults may have headache
- Participants in the "Deliberate" trial of BDQ and Delamanid combination were evaluated for CNS penetration of Delamanid - substudy

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Case Management II

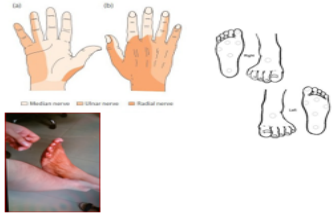
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

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

Peripheral Neuropathy

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

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



Monthly assessment
Early Identification of Toxicity

Patient Education
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

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Monitoring for Adverse Effects

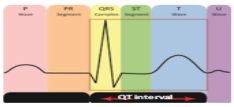
Monitoring for Adverse Effects

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?

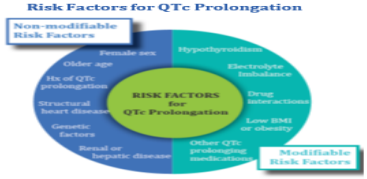
It is the portion of the EKG that begins at the start of the QRS complex and ends at the termination of the T wave. The QT is longer in women and those with lower heart rates. The QTc is a correction for extremes in heart rates.



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.

Risk Factors for QTc Prolongation



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

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

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Management of Treatment Interruptions and substitutions

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

INT J TUBERC LUNG DIS 26(7):671–677

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

After completion of loading dose

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

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

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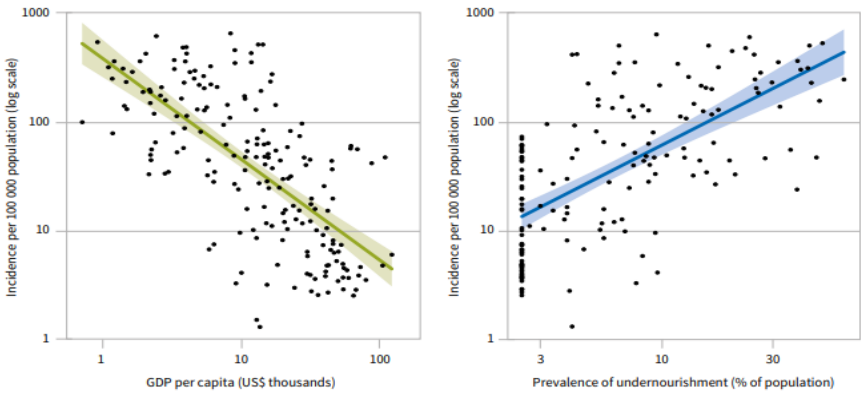
What about contacts to persons with MDR TB?

- Only good option: levofloxacin or moxifloxacin qd x 6mo.
- If source case is FQN resistant, check to see if resistant to all FQNs, especially moxifloxacin.
  - The MDDR result can identify MTB likely to be moxi susceptible
  - And can also identify MTB likely to have high level moxi
    - Dose increase of moxifloxacin won't be helpful
    - When this occurs request moxifloxacin MIC – DSHS lab will assist
    - Moxifloxacin MIC> 1.0 fully resistant
- At this time no option other that FQN but I think Delamanid will likely be option in future; study is over and pending results.

65

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.

Food: the tuberculosis vaccine we already have thelancet.com 402 Aug19 2023

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Conclusions

- Treatment regimens for TB are shortening
- TB treatment regimens for drug resistant TB in the US and worldwide increasingly contain bedaquiline, fluoroquinolones and linezolid.
- Mechanisms for testing and surveillance need to grow in the direction the treatment regimens are taking us

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