Drug-Resistant Tuberculosis

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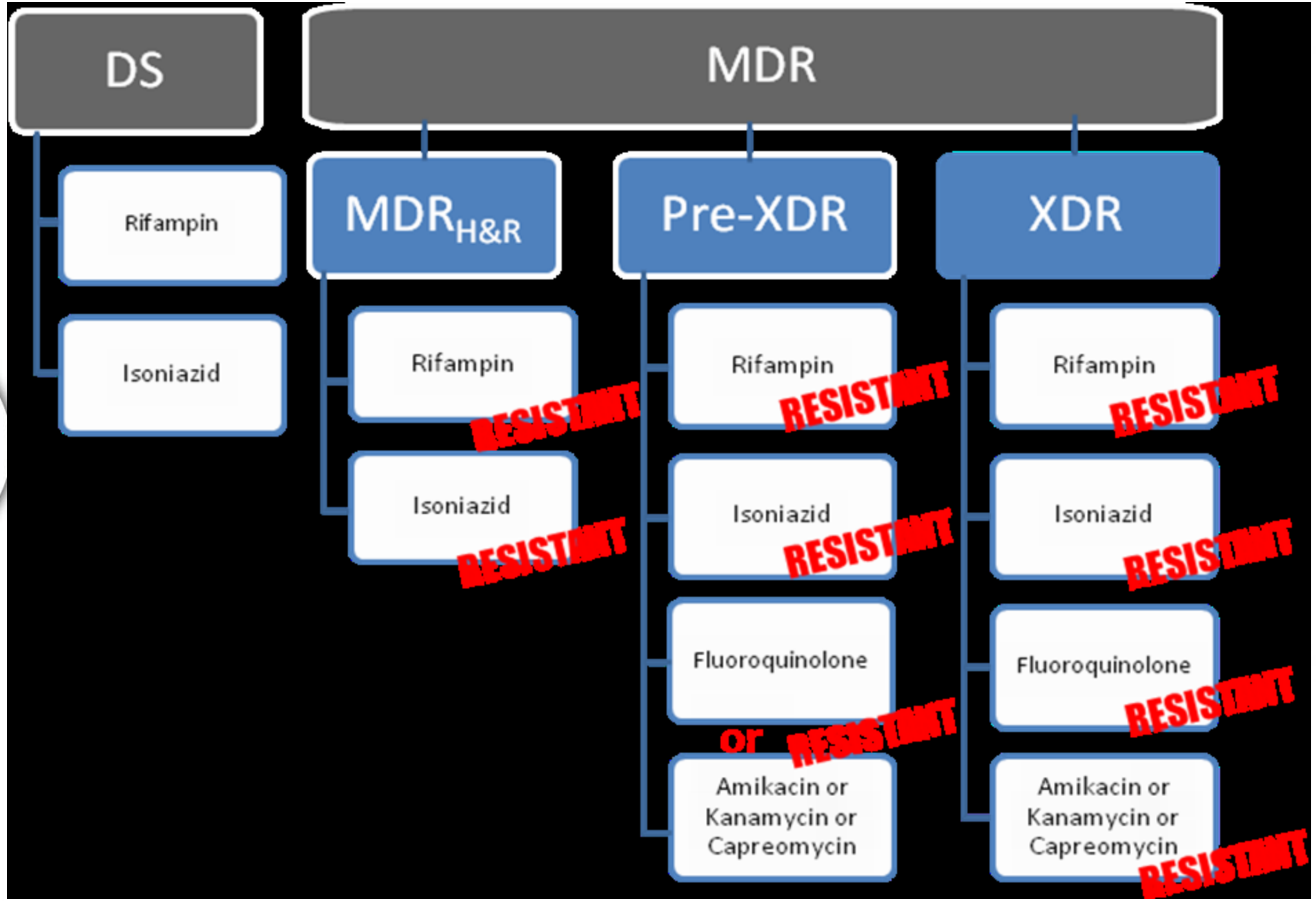

DS
MDR
Rifampin
Isoniazid
MDR H&R
Rifampin
RESISTANT
Isoniazid
RESISTANT
Pre-XDR
Rifampin
RESISTANT
Isoniazid
RESISTANT
Fluoroquinolone
or
RESISTANT
Amikacin or Kanamycin or Capreomycin
XDR
Rifampin
RESISTANT
Isoniazid
RESISTANT
Fluoroquinolone
RESISTANT
Amikacin or Kanamycin or Capreomycin
RESISTANT

WHO Terminology to Classify Drug-Resistant TB

- XDR-TB:

January 2021

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

Note: No mention of the injectable agents by WHO

WHO Overarching Principals for New Definition of XDR-TB

- **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

CDC Terminology to Classify Drug-Resistant TB

OLD Terminology

- **Pre-XDR TB: no formal designation**

Updated Terminology - January 2022

- **Pre-XDR TB:** caused by an organism that is resistant to at least INH, rifampin, and a FQN **OR** by an organism that is resistant to INH, rifampin or a 2nd line injectable (amikacin, capreomycin and kanamycin)

CDC Terminology to Classify Drug Resistant TB

OLD Terminology

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

Combined changes to terminology CDC/WHO 2022

Multidrug-resistant or rifampin-resistant TB (MDR/RR-TB)	Caused by *M. Tb* with genotypic (molecular) or phenotypic (culture-based) resistance to rifampin (RIF): • MDR-TB resistant to both Isoniazid (INH) and RIF. • RIF mono-resistant TB is susceptible to INH. • TB resistant to RIF with unknown or unavailable INH susceptibility is classified as MDR/RR-TB. **All forms are treated with MDR-TB regimens.**
Pre-extensively drug-resistant TB (Pre-XDR-TB)	MDR/RR-TB that is *also* resistant to a fluoroquinolone or a second line injectable (amikacin).
Extensively drug-resistant (XDR-TB)	MDR/RR-TB that is *also* resistant to a fluoroquinolone *and* at least one additional Group A drug* (e.g., bedaquiline or linezolid) or a second line injectable (amikacin).

Fluoroquinolones: levofloxacin or moxifloxacin

* Group A drugs: levofloxacin, moxifloxacin, bedaquiline and linezolid.

Diagnosis of Drug-Resistant TB:
First step is to consider the possibility

WHEN Patient Notes:

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

WHO?

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

Diagnosis of Drug-Resistant TB

Initial specimen

- **Xpert**
  - Can do on sputum specimen
  - 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

- If rifampin resistance is confirmed
  - Molecular testing for other first line drugs and fluoroquinolones
  - Hopefully will soon also be able to do bedaquiline, linezolid, clofazimine and pretomanid
  - Culture based drug susceptibility studies for all first- and second-line drugs

When RR or MDR-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

What about Discrepancies in Rifampin Susceptibility?

Molecular tests and Culture Based DST

- **Rifampin?**
  - Molecular test done by whole genome sequencing pyrosequencing or Sanger sequencing is “Gold Standard”
    - 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
      - What has not been looked at is whether high dose (?how high) rifampin can overcome
      - What we have learned from INH is that it is hard to overcome even low-level resistance in most patients

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

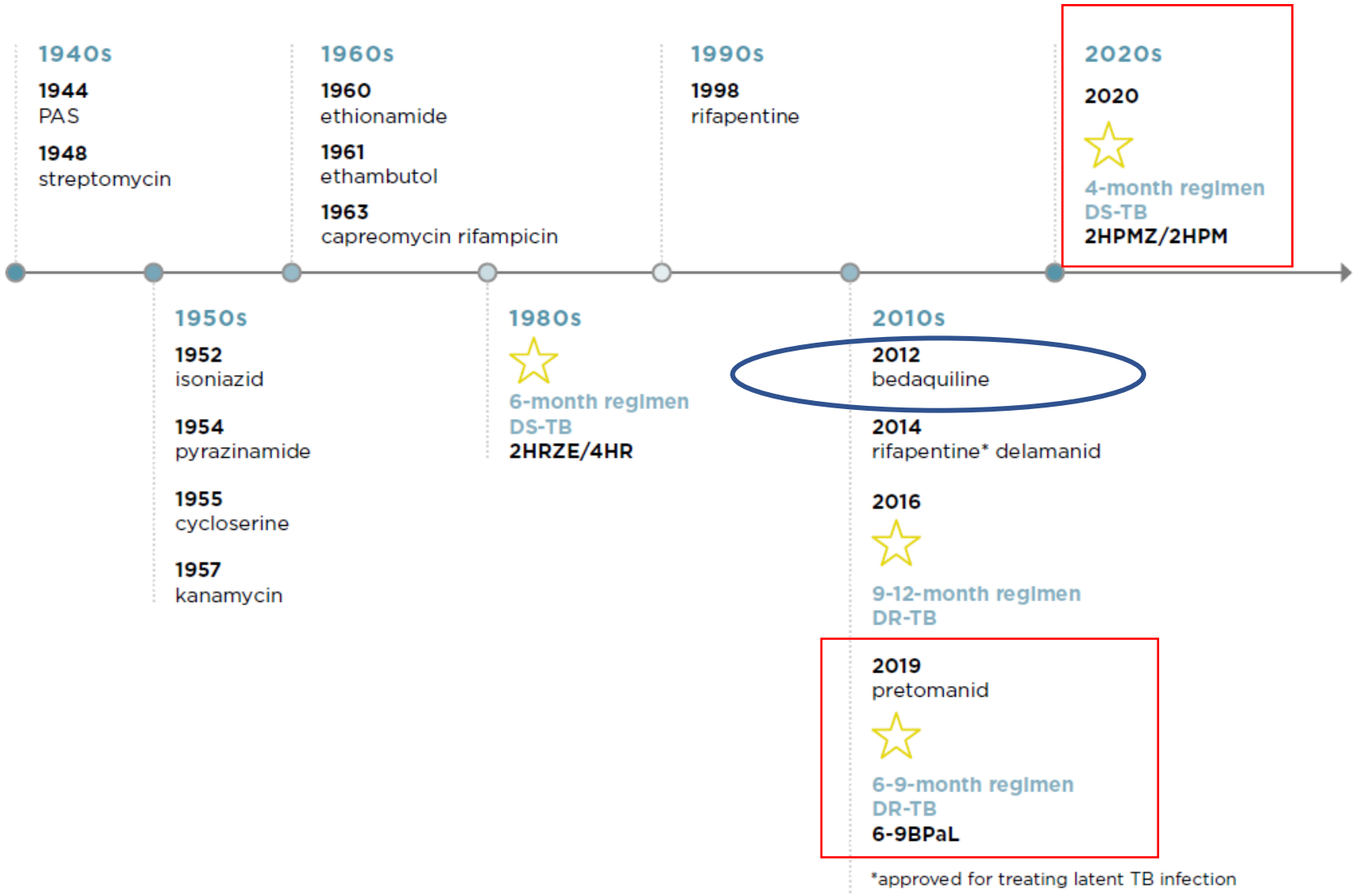
patient for one year. Patients need to undergo

treatment from 18–24 months

IDSA fact sheet 2013

- **Staggering Medication Burden**

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES

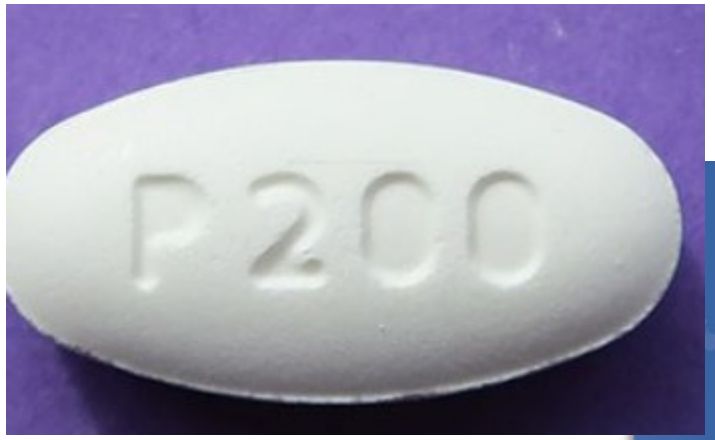


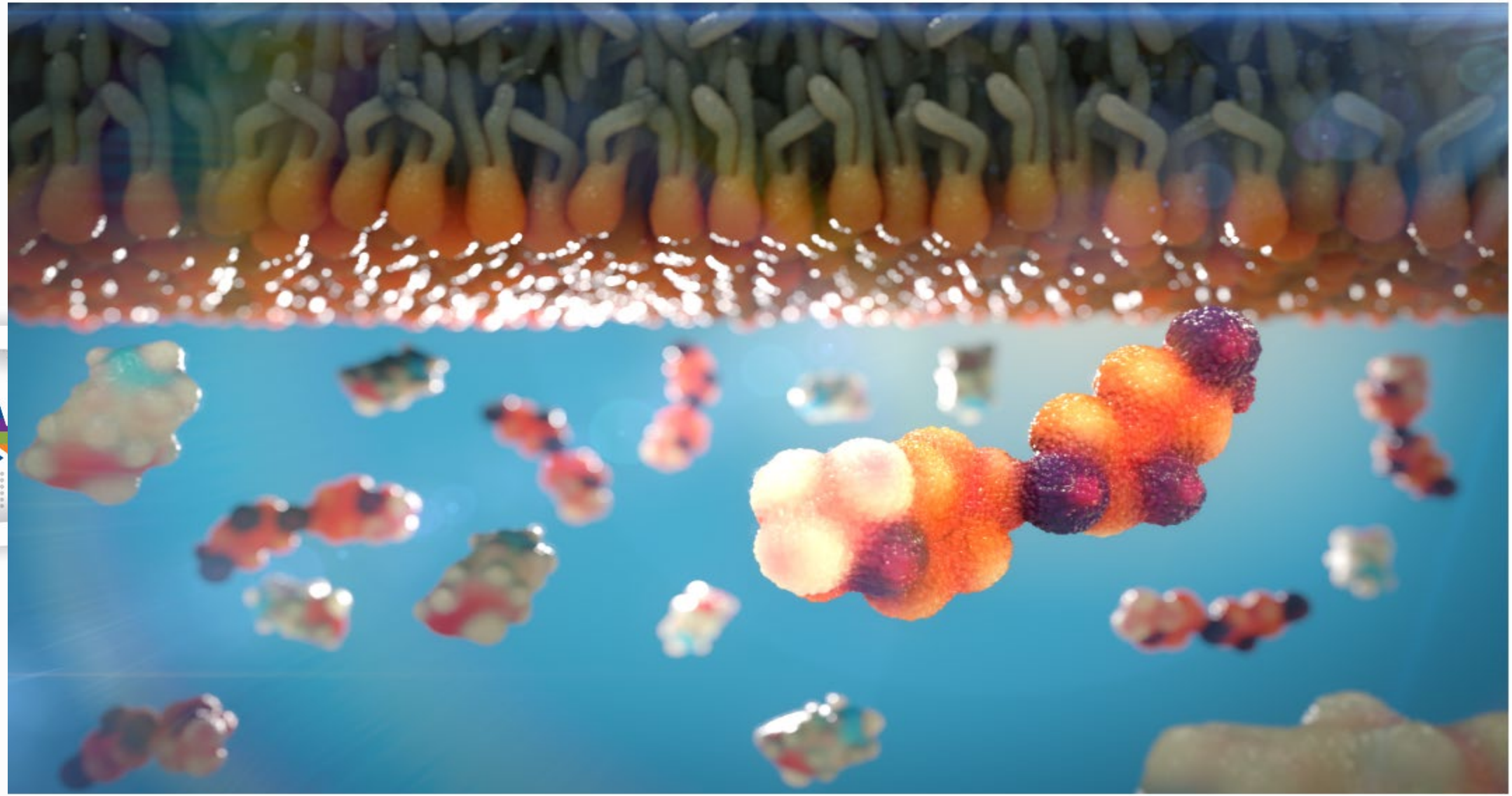
https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

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



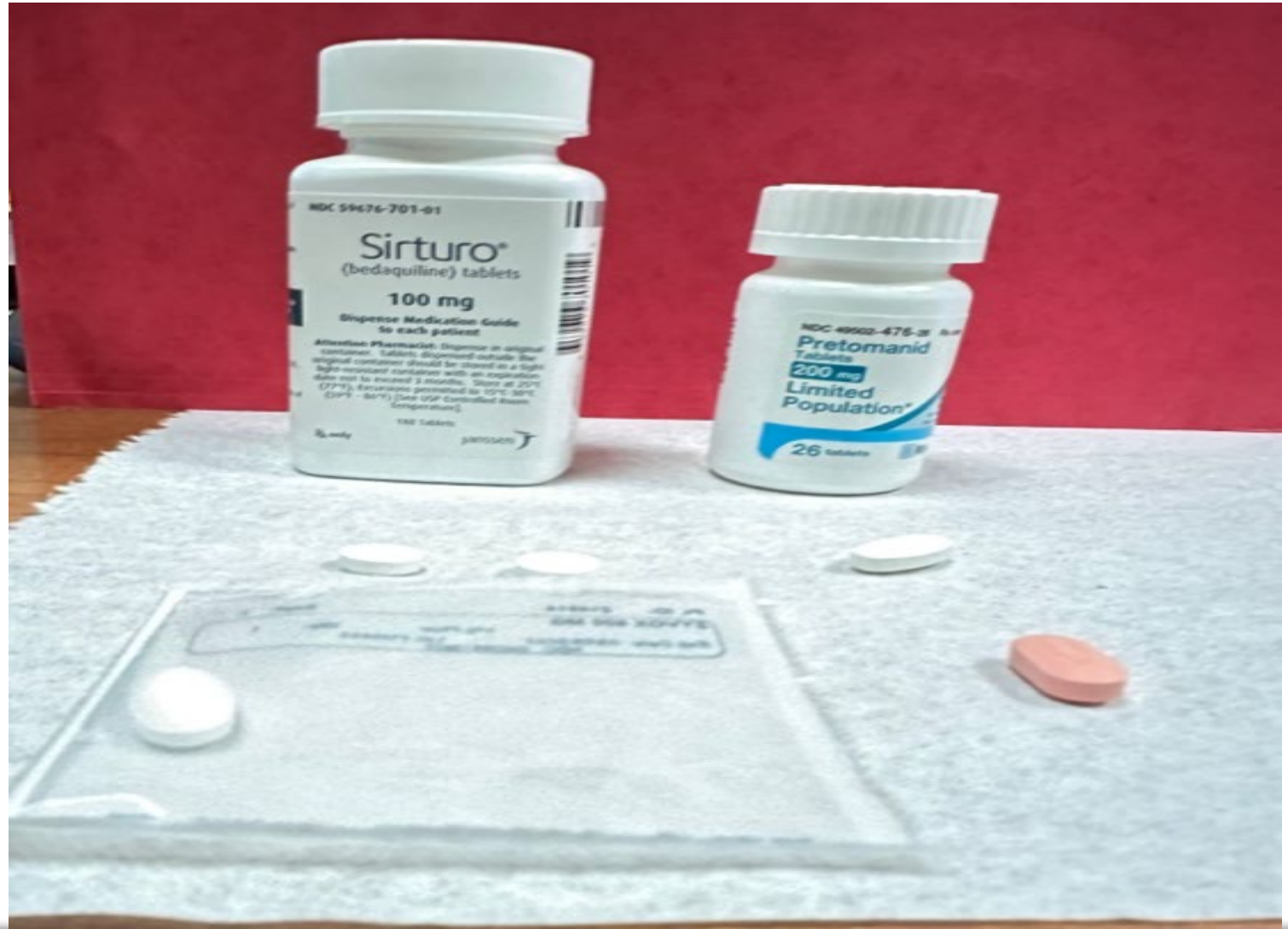


Artist's rendering of the pretomanid compound.

Treatment Options for RR/MDR-TB – WHO

- **BPaLM:** BDQ/Pretomanid/Linezolid/Moxifloxacin 6-9mo
  - Linezolid dose 600 mg once daily
- **BPaL:** BDQ/Pretomanid/Linezolid 6-9 mo.
  - Linezolid dose 600 mg once daily as identified by ZeNix study
- **All oral 9-month regimen** (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

BPaLM or BPaL plus Moxifloxacin (5 tablets)
BDQ/Pretomanid/Linezolid/Moxifloxacin



BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid

The NEW ENGLAND JOURNAL of MEDICINE

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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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- Open label, single group study
- All oral regimen
- 109 patients with MDR or XDR (65%) TB unresponsive to treatment or intolerant of other second line treatment
- Primary end point: unfavorable outcome

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Value (N=109)
Median age (range) — yr	35 (17–60)
Male sex — no. (%)	57 (52)
Race — no. (%)†	
Black	83 (76)
Mixed race	25 (23)
White	1 (1)
Median BMI (range)‡	19.7 (12.4–41.1)
HIV-positive — no. (%)	56 (51)
Median time since HIV diagnosis (range) — yr	4.0 (0.2–14.3)
Median CD4 cell count (range) — cells/mm^3§	343 (55–1023)
Cavities present on chest radiograph — no. (%)	
No	17 (16)
Unilateral	51 (47)
Bilateral	41 (38)
Karnofsky score — no. (%)¶	
100	9 (8)
90	50 (46)
80	29 (27)
70	19 (17)
60	2 (2)
<60	0
Median no. of tuberculosis drugs taken in month before enrollment (range)	7 (3–13)
Median time since original tuberculosis diagnosis (range) — mo	12 (<1–141)

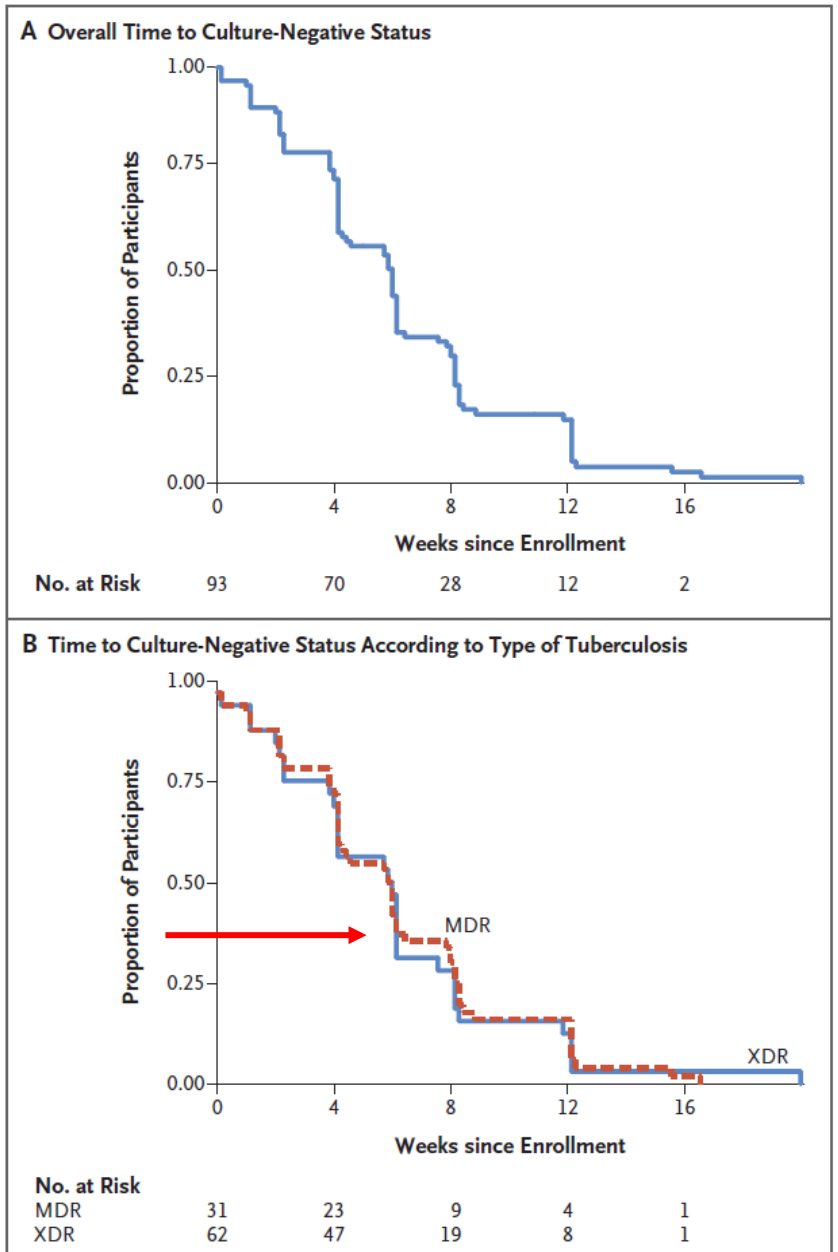


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

Table 2. Primary Efficacy Analysis.*

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡
Per-protocol population			
No. of patients	68	37	105
Favorable outcome			
No. of patients	62	35	97
Percent of patients (95% CI)	91 (82–97)	95 (82–99)	92 (86–97)
Unfavorable outcome — no. (%)	6 (9)	2 (5)	8 (8)
Deaths — no.	5	1	6
Relapse — no.	1	1	2‡

N Engl J Med 2020;382:893-902.

BPaL Adverse Events

Table 3. Adverse Events That Occurred or Worsened during Treatment.

Event*	HIV Status		Linezolid Regimen		Overall (N=109)
	Negative (N=53)	Positive (N=56)	600 mg Twice Daily (N=44)	1200 mg Daily (N=65)	
	number (percent)				
Adverse event	53 (100)	56 (100)	44 (100)	65 (100)	109 (100)
Adverse event leading to death	3 (6)	3 (5)	4 (9)	2 (3)	6 (6)
Serious adverse event	10 (19)	9 (16)	13 (30)	6 (9)	19 (17)
Grade 3 or 4 adverse event	27 (51)	35 (62)	27 (61)	35 (54)	62 (57)

* A patient could have had more than one type of event.

Myelosuppression 48%; Peripheral neuropathy 81%

ZeNix: Linezolid Optimization Trial

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

NEJM September 2022

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

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

Randomize

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

6 months of treatment

Additional 3 months if sputum culture positive at 4 months

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

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

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

ZeNix - Efficacy

Table 2. Primary End-Point Efficacy Analysis.*

Population and Outcome	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
Modified intention-to-treat population					
Not assessable					
Violent or accidental death during treatment period — no.	0	1	0	0	1
Lost to follow-up during follow-up period — no.	1	0	0	0	1
Withdrawn for other reason during follow-up period — no.	0	0	0	1	1
All participants — no. (%)	1 (2)	1 (2)	0	1 (2)	3 (2)
Assessable — no. (%)	44 (98)	45 (98)	45 (100)	44 (98)	178 (98)
Favorable outcome — no./total no. (%)	41/44 (93)	40/45 (89)	41/45 (91%)	37/44 (84)	159/178 (89)
95% CI for favorable outcome — %	81–99	76–96	79–98	70–93	84–93
97.5% CI for favorable outcome — %	—	74–97	77–98	—	—
Unfavorable outcome — no./total no. (%)	3/44 (7)	5/45 (11)	4/45 (9)	7/44 (16)	19/178 (11)
Confirmed relapse during follow-up period — no.†	0	2	1	1	4
Lost to follow-up during treatment period — no.	0	0	0	1	1
Retreatment during follow-up period — no.‡	2	0	1	1	4
Withdrawn during treatment period — no.					
Because of adverse event	1	1	0	2	4
Because of investigator or sponsor decision	0	0	1	0	1
Because of participant decision	0	2	1	1	4
Treatment failure during treatment period†	0	0	0	1	1
Intention-to-treat population					
Not assessable — no. (%)	0	0	0	0	0
Assessable — no. (%)	45 (100)	46 (100)	45 (100)	45 (100)	181 (100)
Favorable outcome — no./total no. (%)	41/45 (91)	40/46 (87)	41/45 (91)	37/45 (82)	159/181 (88)
95% CI for favorable outcome — %	79–98	74–95	79–98	68–92	82–92

ZeNix – Safety Analysis

Table 3. Safety Analysis.*

Variable	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
	number of participants (percent)				
≥1 Grade 3 or higher adverse event	14 (31)	11 (24)	9 (20)	11 (24)	45 (25)
≥1 Serious adverse event	3 (7)	4 (9)	1 (2)	3 (7)	11 (6)
Death from any cause	0	1 (2)	0	0	1 (1)
Tuberculosis-related death	0	0	0	0	0

Linezolid dose modified in 23/45 **(51%)** dose with LZD 1200 mg 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)

TB-PRACTECAL Trial

- Arm 1: BDQ+PTM+LZD*+MFX
- Arm 2: BDQ+PTM+LZD*+CF
- Arm 3: BDQ+PTM+LZD*
- Arm 4: SOC (variable)
- 301 adult patients, pulmonary MDR or XDR

*LZD 600 mg x 4mos then 300 mg x 2mos

Open label, randomized, controlled

2021 Union Conference Oral Presentation

TB-Practecal Clinical Trial

- 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

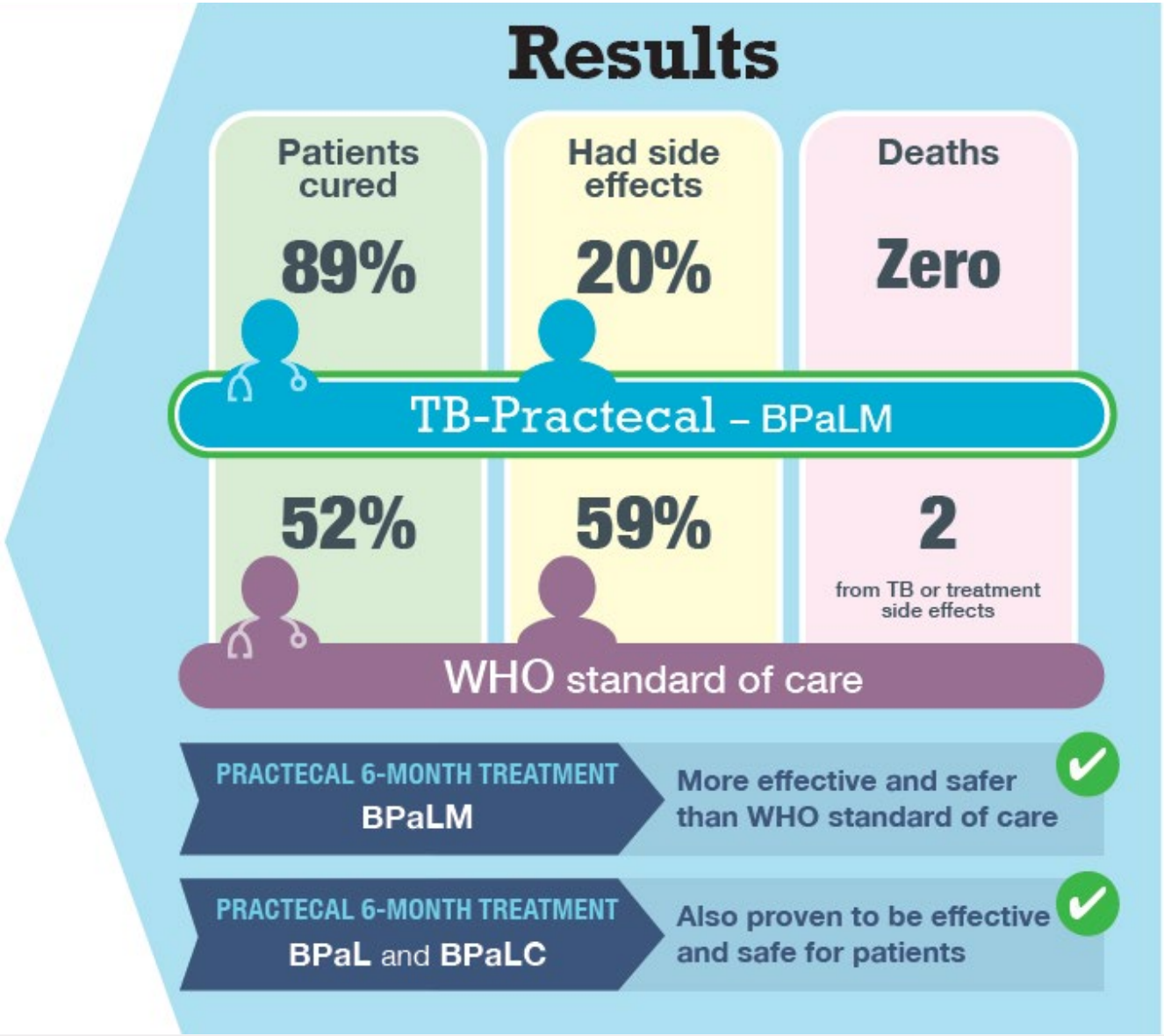
BPaLM proved most effective & safe, thereby progressing to Stage 2.

Patient enrolment ends

552 patients

Data analysis

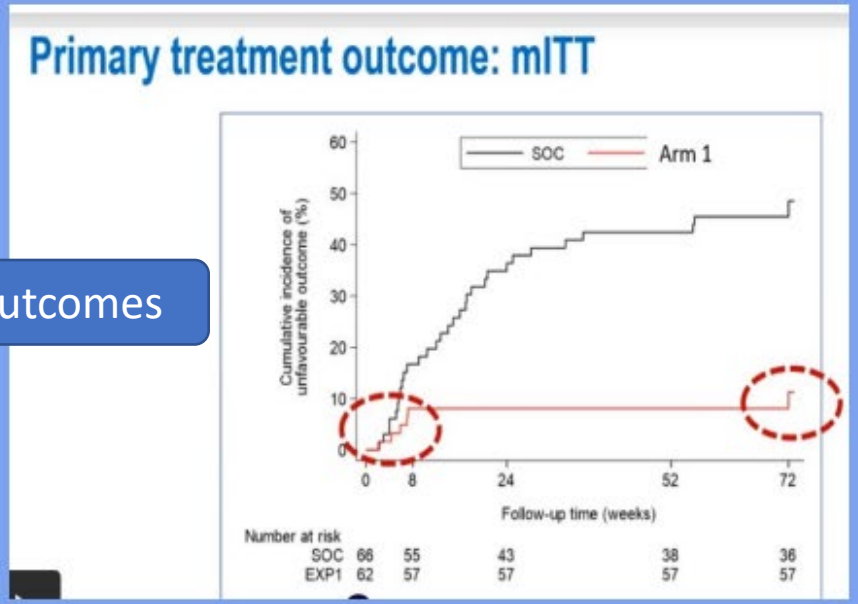
TB-PRACTECAL



TB-PRACTECAL - Efficacy

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

Cumulative incidence of unfavorable outcomes



Short course treatment options for drug-resistant TB

6 – 9 months

All oral

Core drugs:

Bedaquiline

Pretomanid

Linezolid

Moxifloxacin

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

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

Key Considerations for Selecting a Regimen

- 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 are contraindicated:
  - CNS disease
  - Pregnancy
  - Age < 15
  - Extensive disease or Extrapulmonary disease
    - may need RX extended or drugs added

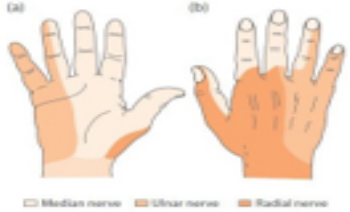
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

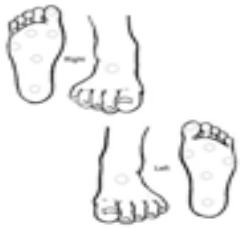
Additional information for selected nurse assessment (see complete toxicity assessment tool)

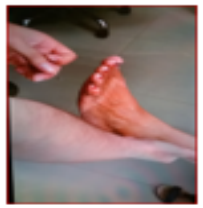
Peripheral Neuropathy

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







Early Identification of Toxicity
Monthly assessment
Patient Education to report if symptoms occur

Behavior and Mood

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

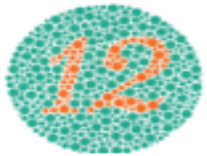
- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

Vision

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

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

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



Ishihara Vision Test

Snellen Eye Chart

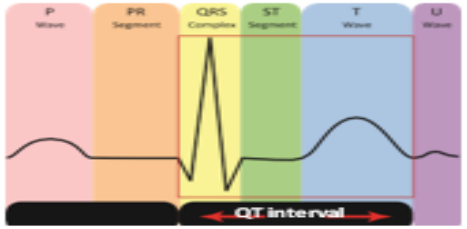
Monitoring for Adverse Effects

Cardiac Toxicity

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

What is the QT Interval?

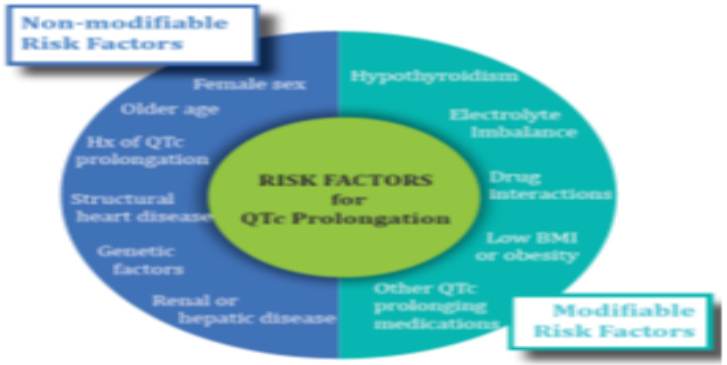
It is the portion of the EKG that begins at the start of the QRS complex and ends at the termination of the T wave. The QT is longer in women and those with lower heart rates. The QTc is a correction for extremes in heart rates.



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

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

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

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All Oral Regimen!

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

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

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

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

Management of Treatment Interruptions and substitutions

Treatment interruptions and substitutions

BPaLM

rash in 2nd week of treatment

Patient lost to F/U for one month while moving during BPaLM treatment

Peripheral neuropathy with either BPaLM or BPaL

Optic neuropathy with either BPaLM or BPaL

What substitutions are allowed?

- BPaLM

- BPaL

Treatment interruptions and substitutions

BPaLM

rash in 2nd week of treatment

Patient lost to F/U for one month while moving during BPaLM treatment

Peripheral neuropathy with either BPaLM or BPaL

Optic neuropathy with either BPaLM or BPaL

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

INT J TUBERC LUNG DIS 26(7):671–677

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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

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

When do we worry about bedaquiline resistance?

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

Lancet Infect Dis 2022;
22: 496–506

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

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

Conclusions

- Treatment regimens for TB are shortening
- Fluoroquinolones are playing a larger role in TB treatments
- 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