Drug Resistant Tuberculosis

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When Does Lab Report Resistance?

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

XDR-TB

Extensively Drug Resistant Tuberculosis

Isoniazid

Ethambutol

Rifampin

Streptomycin

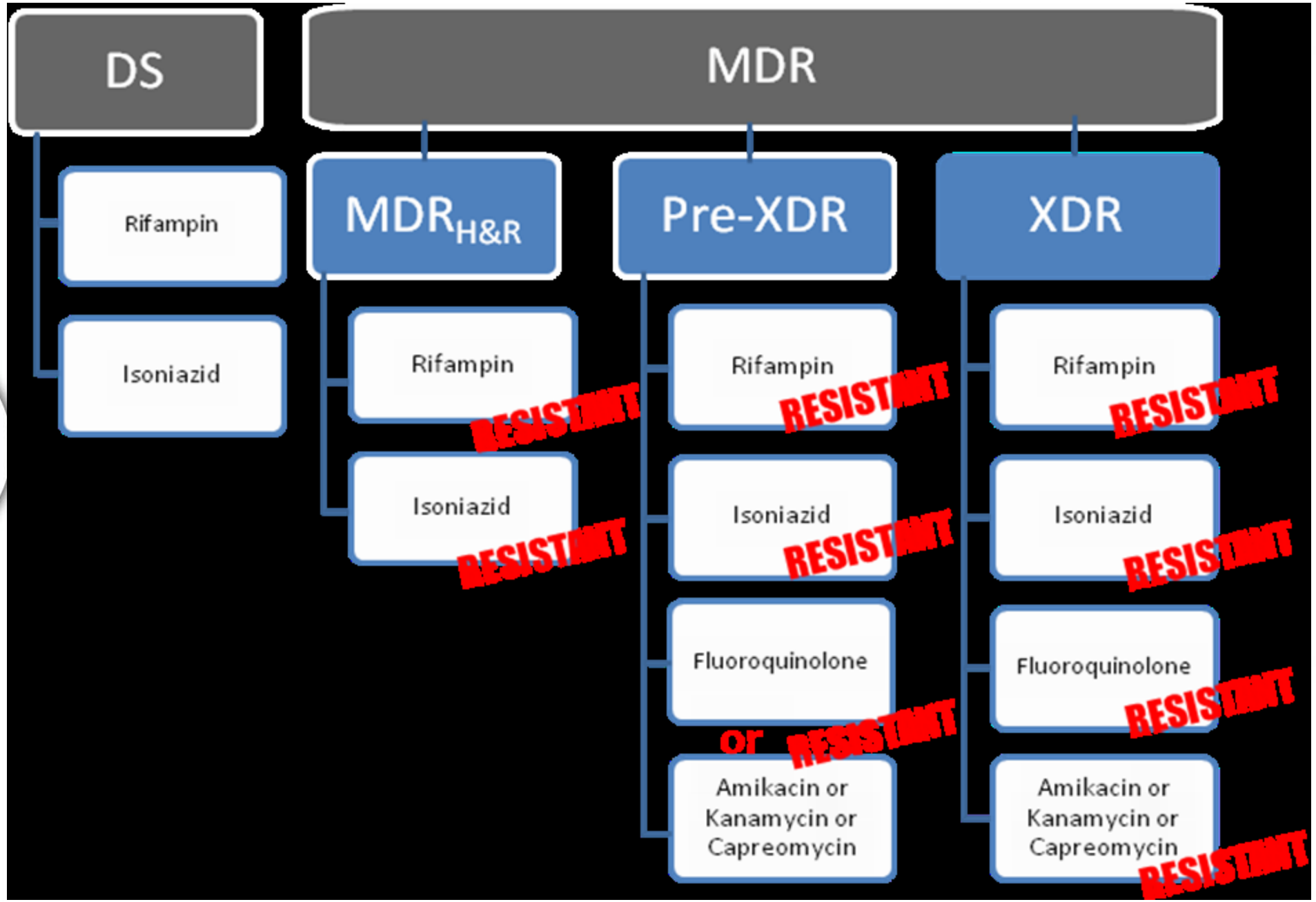
Ethionamide

Ofloxacin

Rifabutin

Kanamycin

Capreomycin


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:

Group A Drugs
Levofloxacin/Moxifloxacin
Bedaquiline
Linezolid

January 2021

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

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 **Fluoroquinolone 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 **Fluoroquinolone 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
  - Inadequate regimen
  - 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**
  - 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
- 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

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

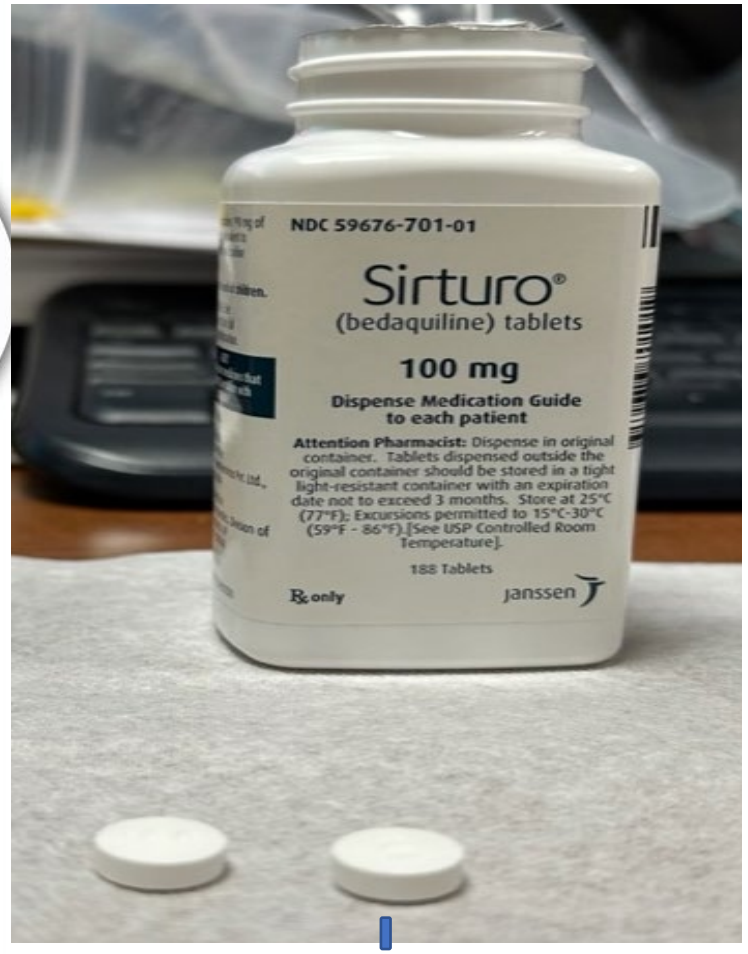
patient for one year. Patients need to undergo

treatment from 18–24 months

IDSA fact sheet 2013

- **Staggering Medication Burden**

2022: Bedaquiline - Core Drug for MDR/XDR TB



TAG PIPELINE REPORT 2012

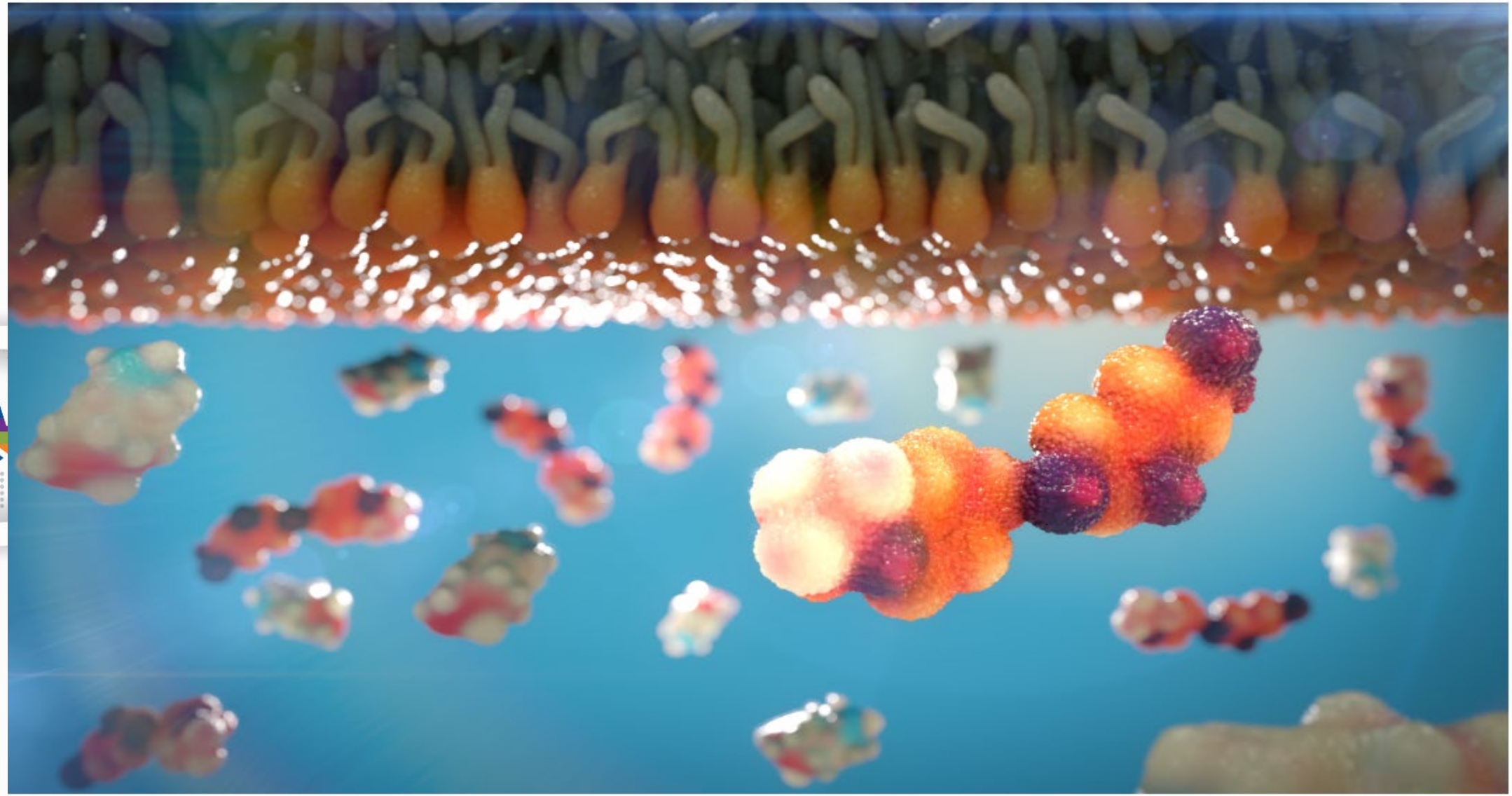
Novel Compounds to Treat Active TB Disease

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



Artist's rendering of the pretomanid compound.

TB Alliance

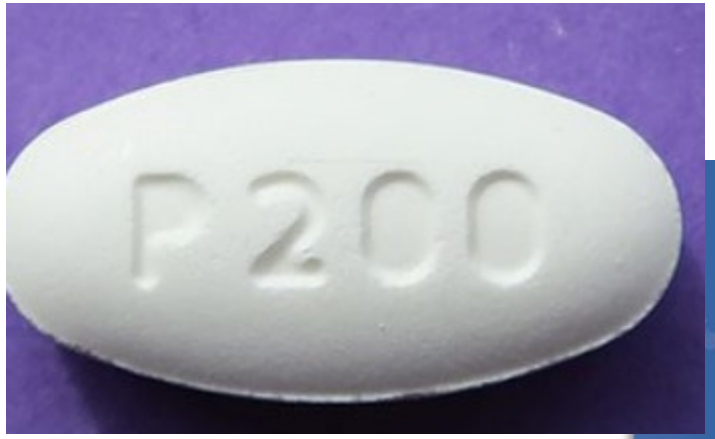
ABOUT WHY NEW TB DRUGS? R&D ACCESS NEWS DONATE

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
BPaLM
? Coming…BPaMZ



Treatment Options for RR/MDR TB – WHO

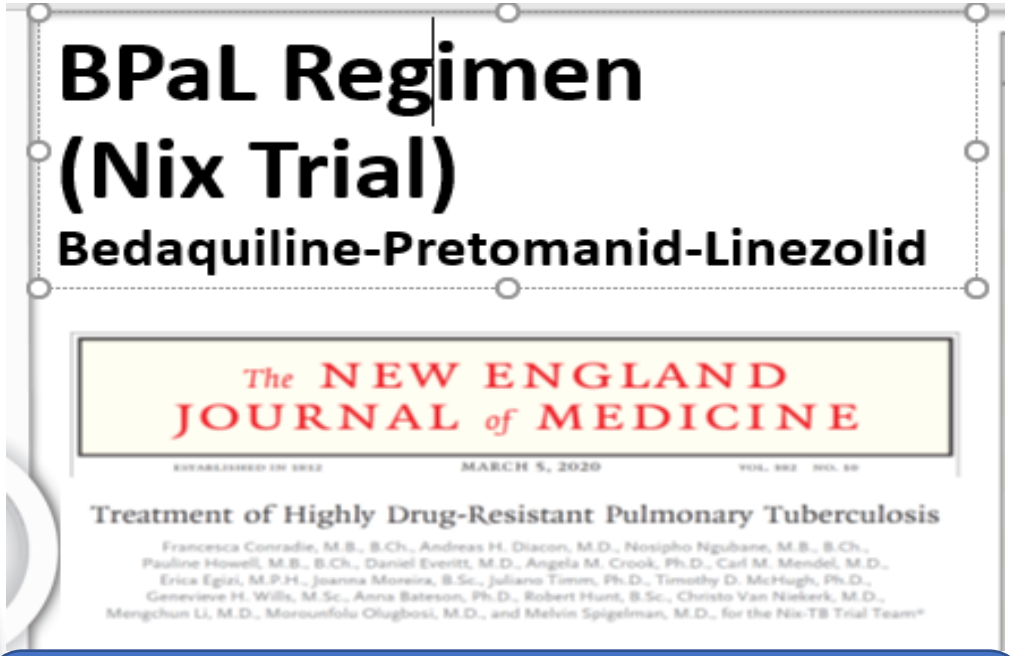
- **BPaLM:** BDQ/Pretomanid/Linezolid/Moxifloxacin 6-9mo
  - Linezolid dose 600 mg once daily
- **BPaL:** BDQ/Pretomanid/Linezolid 6-9 mo.
  - Linezolid dose 600 mg once daily as identified by ZeNix study
- **All oral 9-month regimen** (WHO)
  - 4-6 months of:
    - BDQ (4-6 mo.), Levofloxacin/Moxifloxacin (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 (BPaL plus Moxifloxacin - 5 tablets)

BDQ/Pretomanid/Linezolid/Moxifloxacin

BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid


The NEW ENGLAND JOURNAL of MEDICINE

MARCH 5, 2020

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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

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

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

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

Time to Culture Negative: MDR vs XDR TB

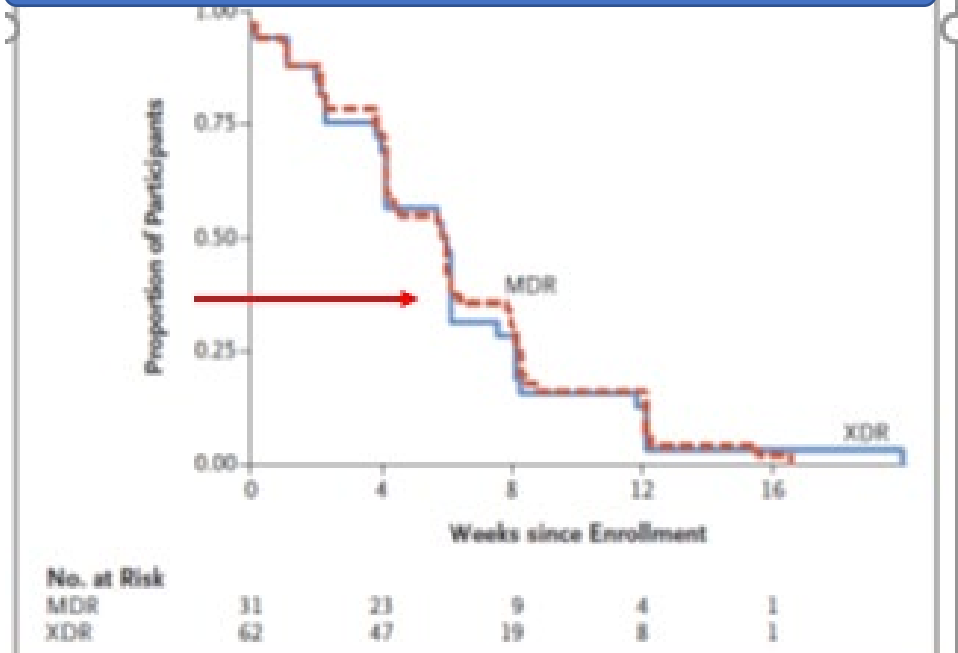


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

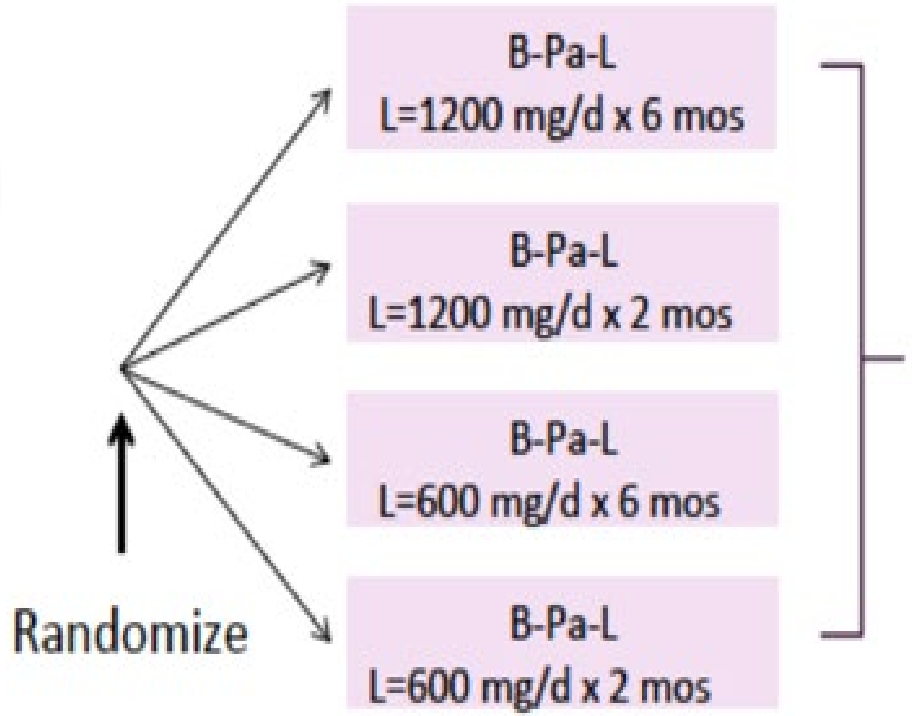
BUT …… BPaL Adverse Events

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

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

Myelosuppression 48%
Peripheral neuropathy 81%

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



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

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*

Bedaquiline dose
200 mg daily x 8 weeks
100 mg daily 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: Linezolid Optimization Trial

MDR or XDR TB Treatment Failure or Intolerant

Safety

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

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

Efficacy

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

TB PRACTECAL –

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

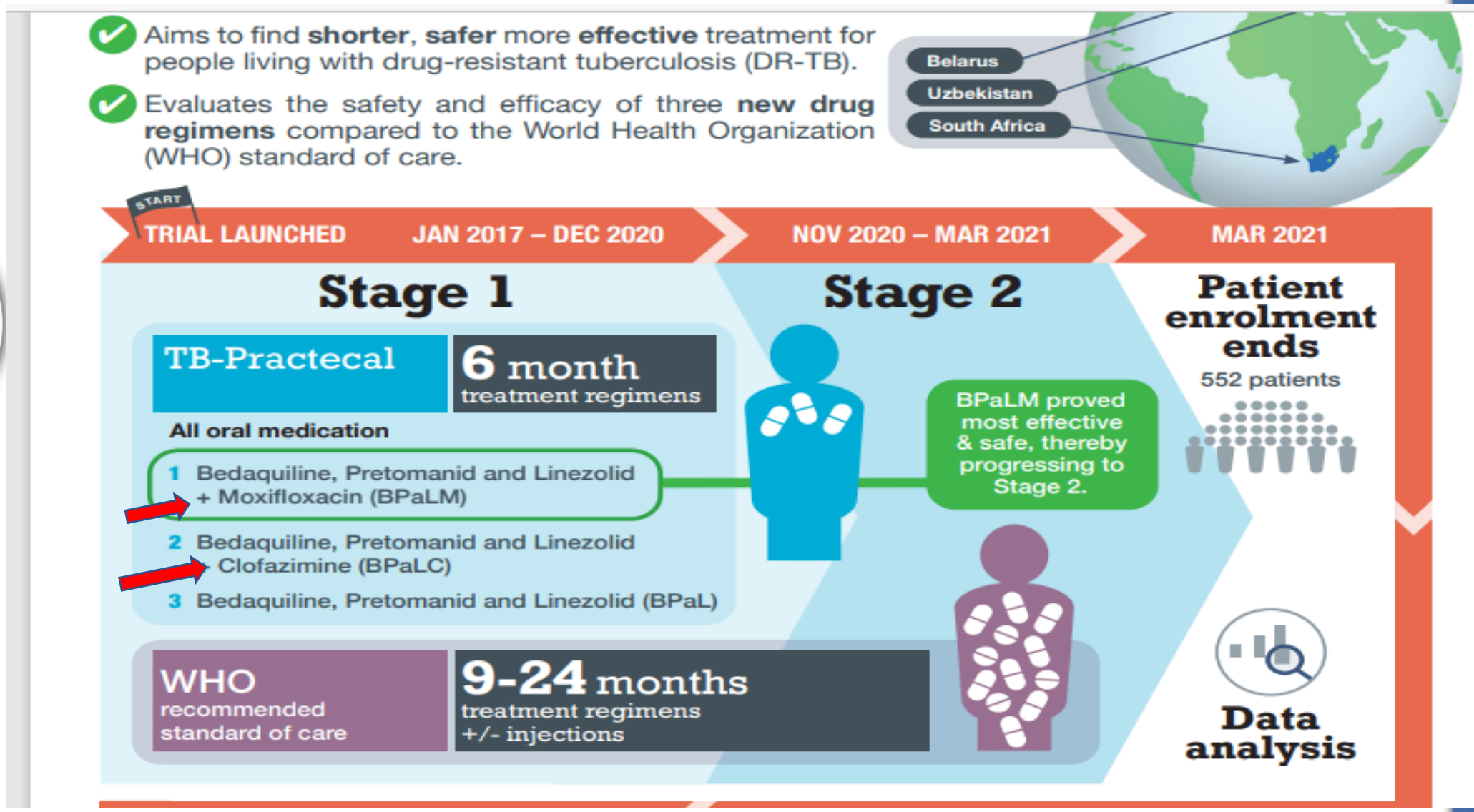
- Regimen 2:
- bedaquiline + pretomanid + linezolid + **clofazimine** for 26 weeks

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

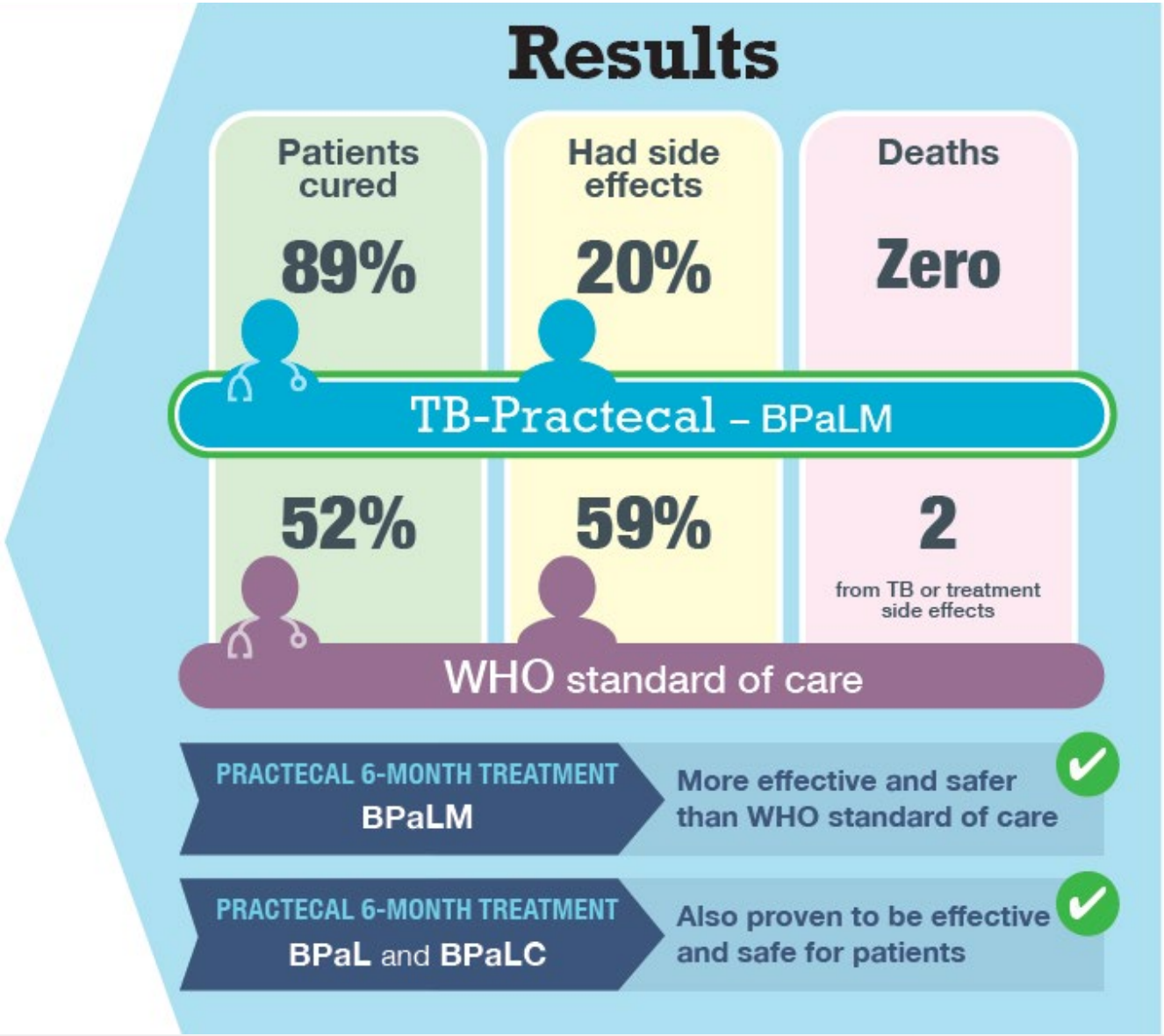
- Standard of Care in Country at the time

TB-Practecal Clinical Trial

randomized, controlled



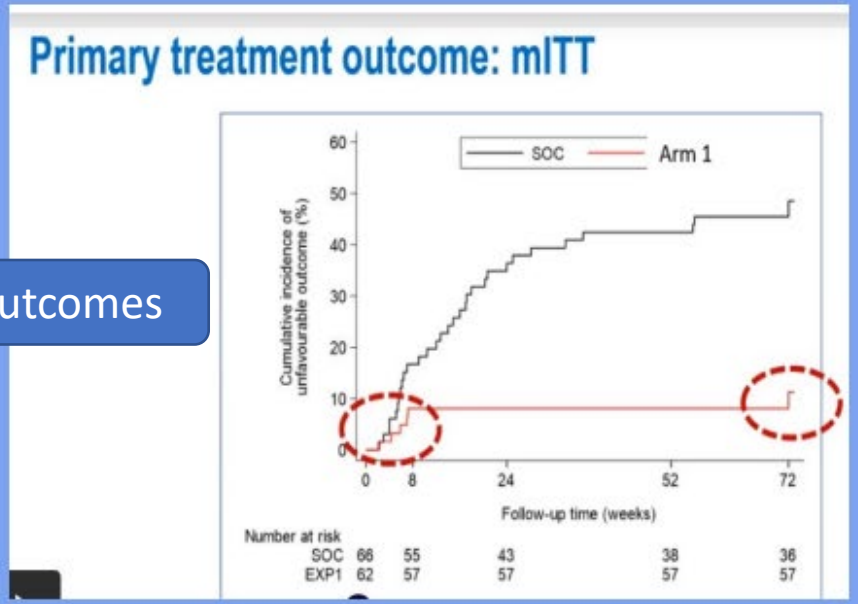
TB PRACTECAL



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-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

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

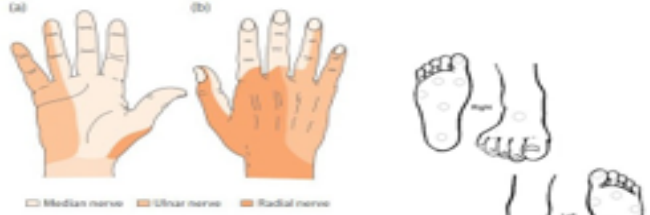
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

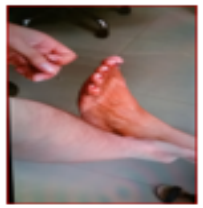
Additional information for selected nurse assessment (see complete toxicity assessment tool)

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.

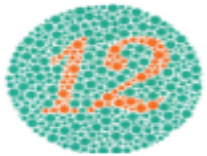
- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

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

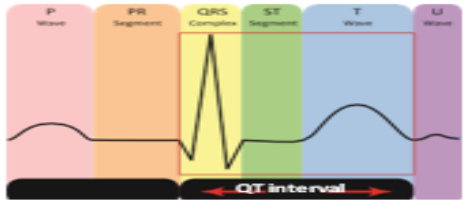
Monitoring for Adverse Effects

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

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

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

What substitutions are allowed?

- BPaLM

- BPaL

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

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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

Case study - new immigrant with abnormal CXR

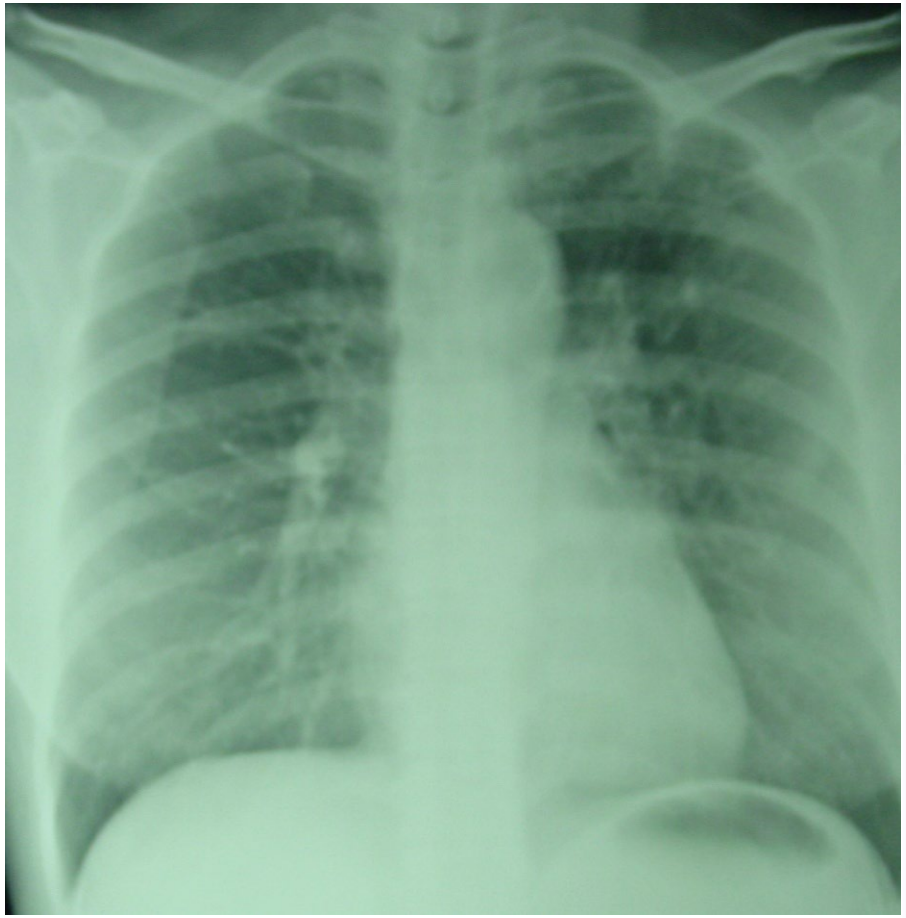
- 62-year-old Asian male enters U.S. Sept 2022
  - Rx TB in Viet Nam 2004-2005
  - Screened overseas prior to entry
  - Evaluation in U.S.
    - Smear negative, **Xpert positive, rifampin resistance detected**
  - What additional information do we need?
  - What is the diagnosis?

Case Study new immigrant with abnormal CXR

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

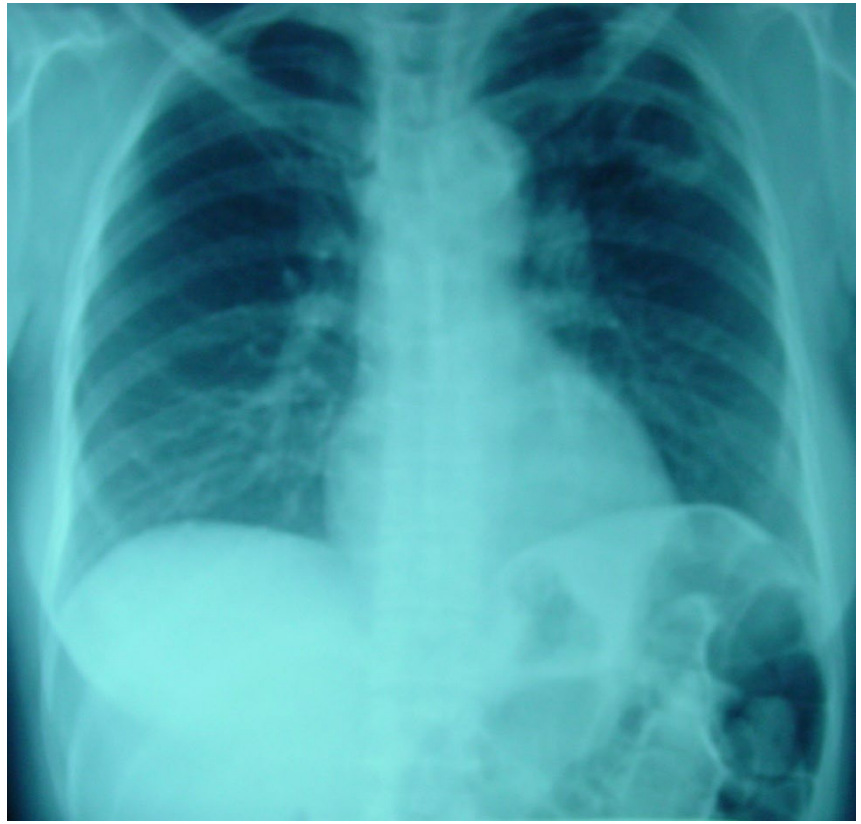
Case study new immigrant with abnormal CXR

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



Case study new immigrant with abnormal CXR

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



Case Study new immigrant with abnormal CXR

- 62-year-old Asian male enters U.S. Sept 2022
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      - **Moxifloxacin – probably not but possible**
      - **Linezolid - very likely isolate is susceptible**
      - **Bedaquiline - very likely isolate is susceptible**
      - **Pretomanid - very likely isolate is susceptible**
  - Evaluation in U.S.: **Smear negative, Xpert positive, rifampin resistance detected**
    - **New CXR with cavity**
  - **What is diagnosis?**

Case Study new immigrant with abnormal CXR

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