MDR-TB

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7/14/23

Disclosures

- No financial disclosures
- I will be discussing DR-TB drug regimens for populations that currently do not have FDA approval (but many TB medications used for DR TB do not have FDA approval)
- Drug Resistant TB treatment is rapidly evolving. This lecture may be outdated soon

Outline

- Definitions
- Epidemiology and history of MDR-TB treatment
- Testing for drug resistance (briefly)
- Treatment regimens for MDR-TB
  - “Old” regimen based on 2019 guidelines
  - New, shorter, all oral regimens with predetermined durations
  - Monitoring (briefly)
- MDR-TB post-treatment surveillance
- MDR-TB contacts

Drug Abbreviations

- BDQ: Bedaquiline
- LZD: Linezolid
- Pa: Pretomanid
- MFX: Moxifloxacin
- LFX: Levofloxacin
- CS: Cycloserine
- CFZ: Clofazimine

Definitions

- RR-TB: Resistant to RIF (INH resistance unknown or INH sensitive)
- MDR-TB: Resistant to RIF and INH
- Pre-XDR TB: MDR-TB, plus resistant to…
  - WHO 2021: FQs
  - CDC 2022: FQs OR 2nd line injectable
- XDR-TB: MDR-TB, plus resistant to….
  - WHO 2021: FQs plus (BDQ or LZD)
  - CDC 2022: FQs plus (BDQ or LZD or 2nd line injectable)

Epidemiology

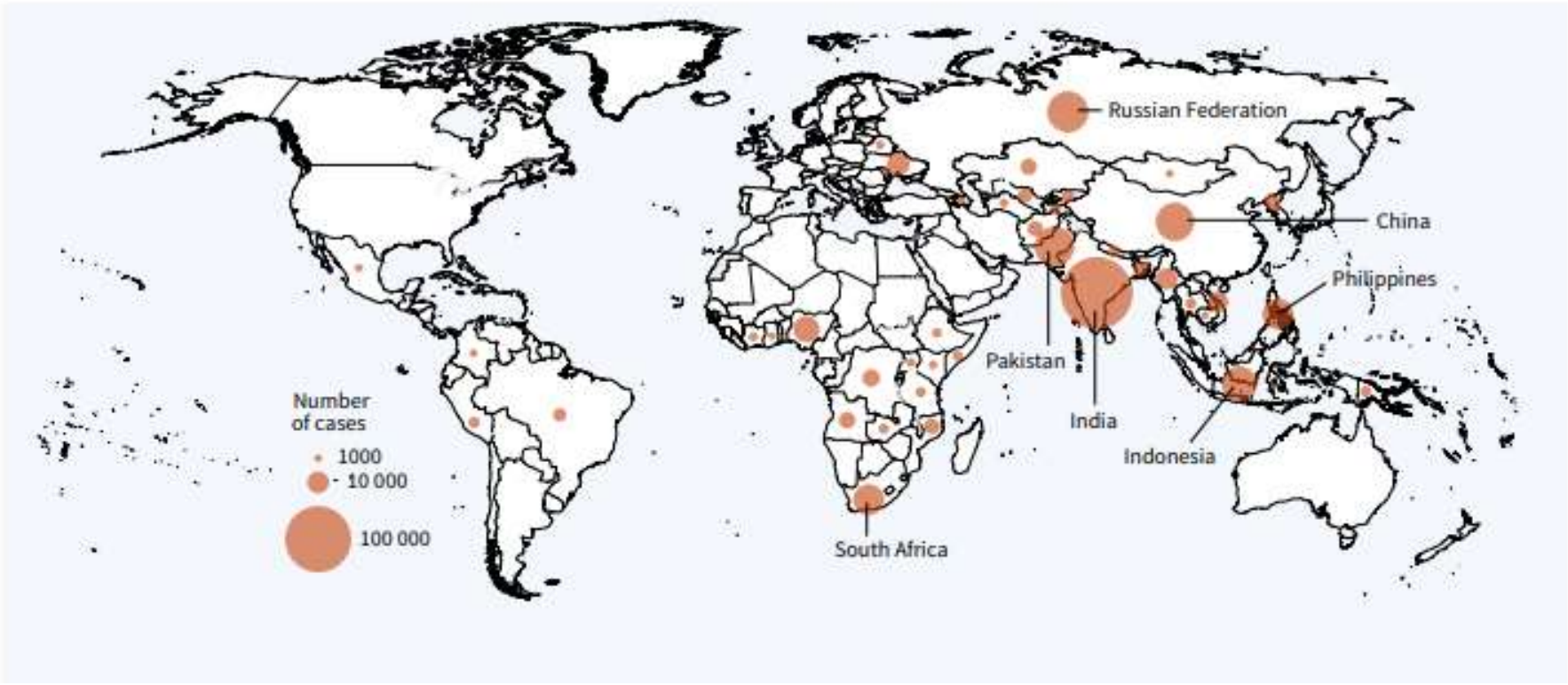
- 2021 Worldwide data (WHO 2022 TB Report):
  - Estimated 450,000 incident cases of RR/MDR-TB
  - 3.6% of new TB cases with no prior treatment had RR/MDR-TB
  - 18% of TB cases with prior treatment had RR/MDR-TB

- Note: WHO treats RR and MDR-TB as essentially the same entity
  - INH resistance usually (but not always) coexists with RIF resistance
  - Many international settings rely on Xpert only for DST

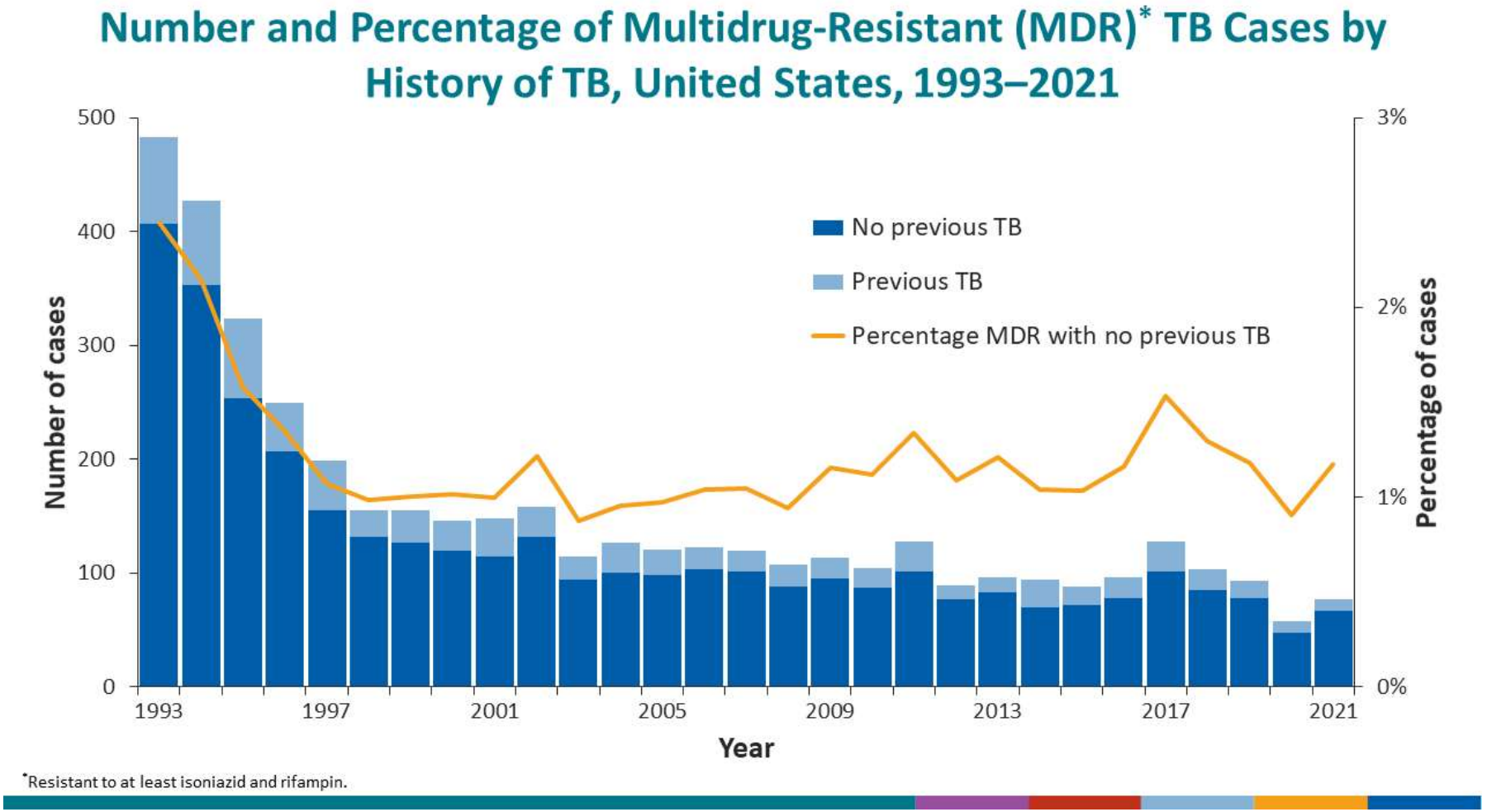
FIG. 17

Estimated incidence of MDR/RR-TB in 2021, for countries with at least 1000 incident cases

The seven countries with the highest burden in terms of numbers of MDR/RR-TB cases, and that accounted for two thirds of global MDR/RR-TB cases in 2021, are labelled.



WHO Global TB Report 2022



CDC Surveillance Report

Historical MDR-TB Treatment

- MDR-TB has historically been:
  - long (i.e., 18-24+ months)
  - Toxic (including ototoxicity and nephrotoxicity from injectables)
  - multiple drugs (i.e. 4-7+)
  - Associated with suboptimal success

- CDC US data 2014-2018*
  - 443 MDR-TB cases, 72 pre-XDR cases, 9 XDR cases
  - Only 63% completed treatment within 24 months
  - 8% died before treatment completion

*CDC provisional BPaL recommendations 2023 update

Recent Advances in DR-TB Treatment

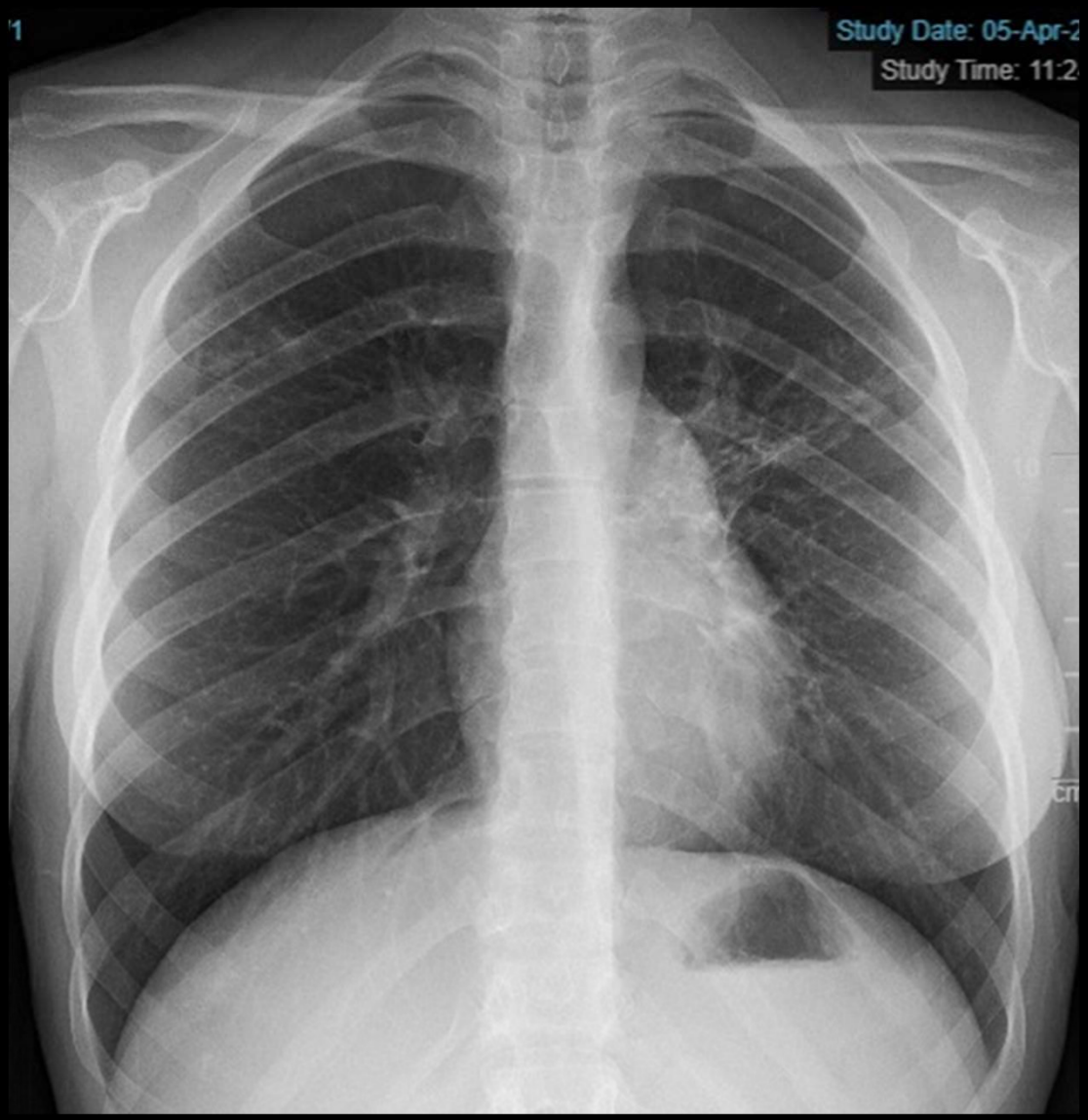
- Early 2000s: LZD repurposed for TB treatment
- 2012: BDQ approved
- 2019: All oral regimens recommended by WHO and CDC
- 2019: Pretomanid approved by FDA as part of BPaL for XDR-TB or treatment intolerant/nonresponsive MDR-TB; pulmonary only
- 2022: CDC provisional guidance on BPaL
- 2022: WHO recommends BPaLM
- 2023 (expected): New CDC guidelines

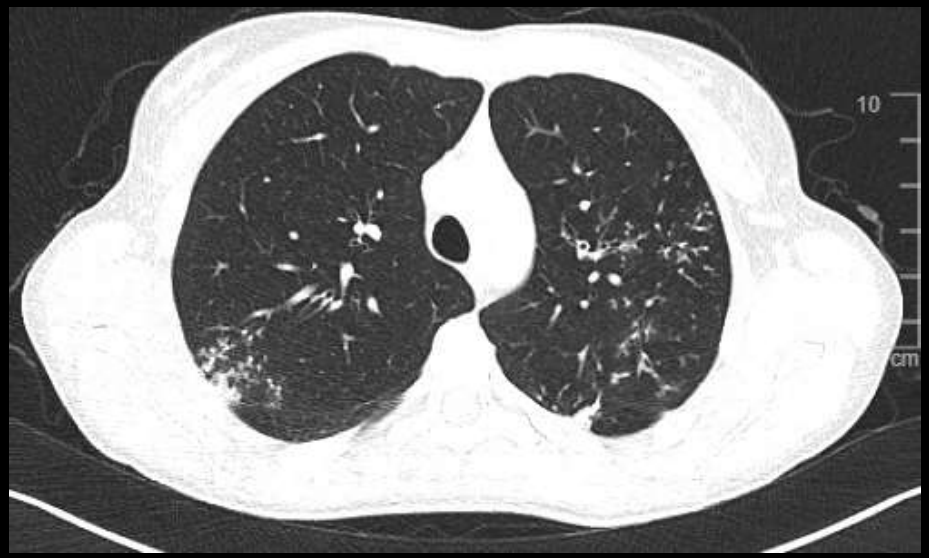
Key Resources For An Evolving Field

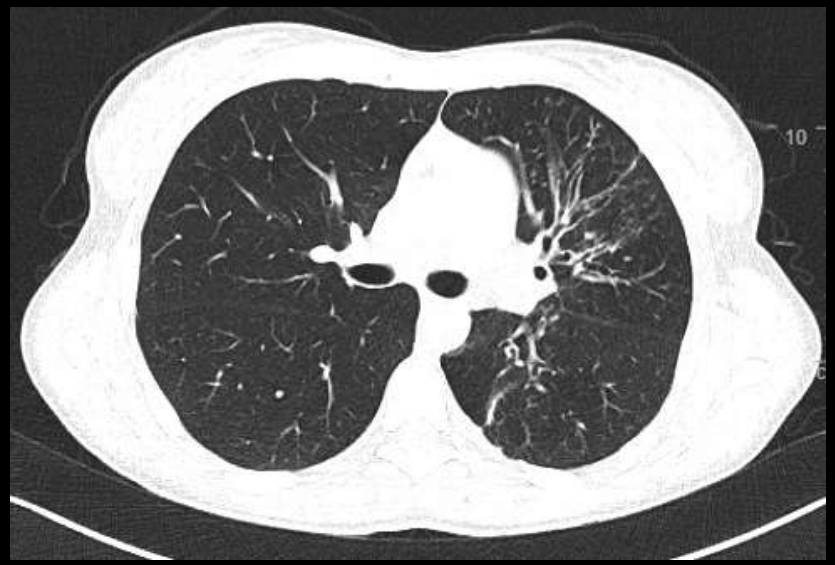
- Curry Center MDR-TB Survival Guide, recently updated
  - https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
- WHO Drug Resistant TB Treatment 2022 Update
  - https://www.who.int/publications/i/item/9789240063129
- CDC 2022 (updated 2023) provisional guidelines on BPaL
  - https://www.cdc.gov/tb/topic/drtb/bpal/default.htm
- 2019 ATS/CDC/ERS/IDSA DR-TB Treatment Guidelines, prior to BPaLM
  - https://www.cdc.gov/tb/publications/guidelines/treatment.htm

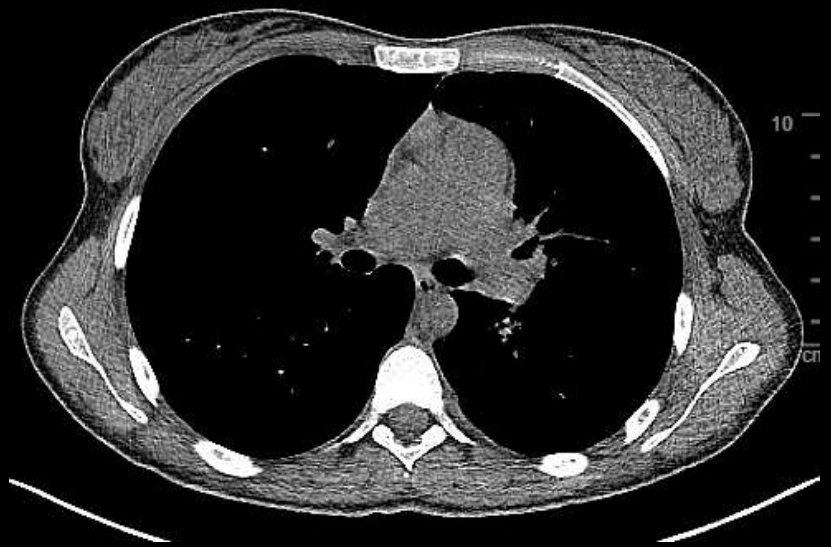
20 yo F with chronic cough

- HPI: 1.5 years of intermittently productive cough
- No past medical history or meds
- Social: Immigrated from Ukraine about 5 years ago
- Family History: Her father had TB when she was age 10, further details unknown. She was not tested or treated at that time
- Exam is unremarkable


Study Date: 05-Apr-2
Study Time: 11:2







You suspect pulmonary TB and order AFB smear/culture. Anything else?

WHO Country Profiles Can Help Estimate MDR Risk

Tuberculosis profile: Ukraine

Population 2021: 44 million

Estimates of TB burden*, 2021

	Number	(Rate per 100 000 population)
Total TB incidence	31 000 (20 000-44 000)	71 (47-100)
HIV-positive TB incidence	6 300 (4 100-8 900)	14 (9.4-20)
MDR/RR-TB incidence**	11 000 (6 800-15 000)	25 (16-35)
HIV-negative TB mortality	3 600 (3 500-3 700)	8.3 (8-8.5)
HIV-positive TB mortality	2 000 (1 300-2 900)	4.7 (3.1-6.6)

Estimated proportion of TB cases with MDR/RR-TB*, 2021

New cases	31% (31-32)
Previously treated cases	45% (44-46)

https://worldhealthorg.shinyapps.io/tb_profiles

When To Suspect DR-TB?

- Prior non-DOT treatment
- Failing standard treatment (cx positive at 3 mo)
- Known MDR-TB Contact
- From/travel to an area with high MDR-TB burden

- Practically, most if not all patients should have up front rapid molecular testing for RIF resistance (Xpert MTB/RIF)

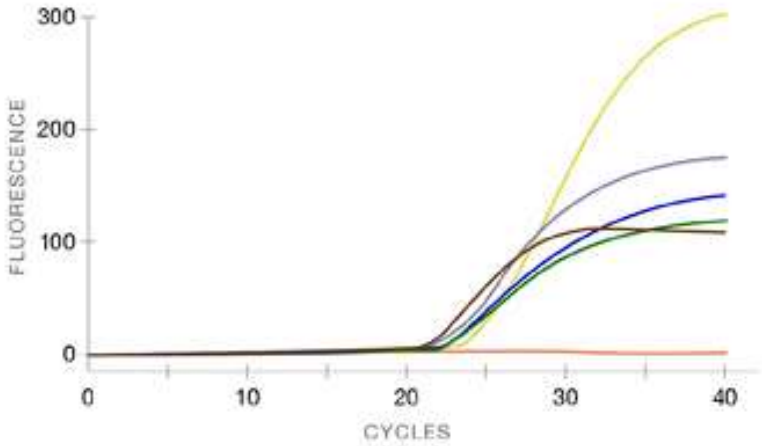
Our Patient's Sputum Results

- Sputum AFB smear neg, neg, 1+
- Sputum Xpert MTB/RIF positive, rpoB mutation identified

MTBC detected, RIF-R detected

FIGURE 7.

	Ct	EndPt	Analyte Result
Probe D	24.8	144.0	POS
Probe C	23.6	177.0	POS
Probe E	0	2.0	NEG
Probe B	24.3	118.0	POS
SPC	25.4	301.0	NA
Probe A	23.2	109.0	POS



Result explanation (Fig 7):

- Four probes yield signals so MTBC is detected in the specimen
- Ct range is 23-25 indicating a moderate amount of MTBC DNA
- Probe E has no signal (Ct=0)
- A mutation is detected because ΔCt max > 4 (24.8 – 0 = 24.8)

Reason for result:

- A mutation is present in the segment of *rpoB* covered by probe E. Probe E detects the most common mutation conferring RIF resistance, S450L.

Possible clinical responses or conclusions:

- RIF-R result should be **confirmed by a sequencing method.**
- It is advisable to **obtain reports issued from Xpert computer** such as shown in the figures. The detailed information in the report may help decipher results.

Xpert MTB/RIF

- Test characteristics for rifampin resistance:
  - Sensitivity: 96%
    - False negatives with low DNA load, inhibitors, mixed NTM/TB samples
  - Specificity: 98%
    - False positives with silent mutation, most commonly in region of probe B
- Positive test for RIF resistance should be confirmed with both
  - sequence based molecular testing: MDDR, Pyrosequencing, WGS
  - growth based DST

- In this case, with high pretest probability for RIF resistance the PPV of a positive Xpert test for RR is > 95%

Suspected MDR-TB: Next Steps

- Reinforce isolation
- Consult an expert
- Request both:
  - Sequence-based molecular DST (in WA state, this means send to CDC for MDDR)
  - 2nd line DST (WA state DOH and CDC)
- Pick an MDR-TB regimen and prepare for close monitoring

Consult an Expert

- Curry Center Warmline:
  - https://www.currytbcenter.ucsf.edu/consultation
- WA State TB ECHO:
  - https://doh.wa.gov/you-and-your-family/illness-and-disease-z/tuberculosis-tb/training-and-education/tb-echo
- WA TB Collaborative Network (WTCN):
  - 206-744-4579 then select option 1
  - WTCN@kingcounty.gov
  - https://redcap.iths.org/surveys/?s=HWPNJX897RFLC7FN

Timing of DST Results

- Probe-based molecular testing (Xpert MTB/RIF): Hours, but batched testing may mean result is available in days
- Sequence-based molecular testing (i.e. MDDR): CDC aims for 5-7 day turnaround time, but our experience in King Co is time from request to results is about 25 days
- Growth-based DST: Variable time to growth of MTB based on disease burden (days to many weeks), then additional 1-4 weeks for DST

Molecular Detection of Drug Resistance (MDDR)

- CDC program that provides sequence-based DST
  - Also do and report growth-based 2nd line DST
- Criteria for submission:
  - Samples: MTB isolate or NAAT positive sediment; also except fixed tissue samples with positive MTB NAAT
  - Risk for RIF resistance; positive test for RIF resistance (Xpert or growth-based DST); high public health import; intolerance of 1st line drugs (i.e. severe reaction to RIF); growth-based DST not possible (mixed or non-viable culture)
- Send requisition through state public health lab

MDDR sensitivity/specificity for resistance*

Sequencing 2012–2021

Drug	Locus or loci examined	Sensitivity (%)	Specificity (%)
Rifampin	*rpoB* RRDR[1], codons 170 and 491	99.8	91.8[2]
Isoniazid	*fabG1-inhA*_upstream, *katG* codon 315, *fabG1* codon 203	93.6	99.2
Ethambutol	*embB* (partial)	80.6	94.2
Pyrazinamide	*pncA*	69.8[3]	95.7
Fluoroquinolones	*gyrA* QRDR[4]	86.4	99.3
Kanamycin	*rrs* (partial) *eis*_upstream	93.9	99.3
Amakacin	*rrs* (partial)	95.8	99.9
Capreomycin	*rrs* (partial) *tlyA*	98.3	95.3

*Compared to growth-based DST

*Does not currently include test characteristic data for:

- BDQ
- LZD
- CFZ

https://www.cdc.gov/tb/topic/laboratory/mddr-user-guide.htm

Rifampin (RIF)	Result	Interpretation
RIF interpretation		RIF resistant
rpoB*	Ser450Leu	

Comments and Disclaimers

* DTBE Reference Laboratory has transitioned from the E. coli to the M. tuberculosis numbering system for reporting rpoB gene mutations.

Isoniazid (INH)	Result	Interpretation
INH interpretation		INH resistant
inhA	No mutation	
fabG1	No mutation	
katG	Ser315Thr	

Ethambutol (EMB)	Result	Interpretation
EMB interpretation		Cannot rule out EMB resistance.
embB	No mutation	

Pyrazinamide (PZA)	Result	Interpretation
PZA interpretation		Cannot rule out PZA resistance.
pncA	No mutation	

Fluoroquinolones (FQ)	Result	Interpretation
FQ interpretation		Cannot rule out FQ resistance.
gyrA	No mutation	
gyrB	No mutation	

- Our patient's actual (deidentified) MDDR report
- Ser450Leu means
  - At codon 450
  - Wild type amino acid SER mutated to Leu

Amikacin, Capreomycin, and Kanamycin (AMK, CAP, and KAN)	**Result**	**Interpretation**
AMK CAP and KAN interpretation		Cannot rule out resistance to AMK, CAP, and KAN.
rrs	No mutation	
eis	No mutation	
Bedaquiline (BDQ)	**Result**	**Interpretation**
BDQ interpretation		Cannot rule out BDQ resistance.
atpE	No mutation	
rv0678	No mutation	
pepQ	No mutation	
Clofazimine (CFZ)	**Result**	**Interpretation**
CFZ interpretation		Cannot rule out CFZ resistance.
pepQ	No mutation	
rv0678	No mutation	
Linezolid (LZD)	**Result**	**Interpretation**
LZD interpretation		Cannot rule out LZD resistance.
rplC	No mutation	
rrl	No mutation	

- Our patient's actual (deidentified) MDDR report
- What's missing? CDC MDDR does not currently include:
  - Pa
  - CS

Our Patient's 1st Line Growth-Based DST (WA DOH)

Receive Comments:			Date
WB16- Missing collection date.			5/1/2023

Microscopy Report

	Result	Performed by	Date
AFB Smear	**Not provided**	Harborview	5/1/2023

Culture Report

		Performed by	Date
	Mycobacterium tuberculosis complex	Harborview	5/1/2023
118) SIRE and PZA sensitivities pending by: WAPHL			5/1/2023

Susceptibility Report - 1st Line of Drugs

Drug (mcg/mL)	Result	Performed by	Date
MGIT Pyrazinamide (PZA) 100	**Sensitive**	KMH	5/25/2023
MGIT Streptomycin (SM) 1.0	**RESISTANT**	KMH	5/25/2023
MGIT Isoniazid (INH) 0.1	**RESISTANT**	KMH	5/25/2023
MGIT Rifampin (RIF) 1.0	**RESISTANT**	KMH	5/25/2023
MGIT Ethambutol (EMB) 5.0	**Sensitive**	KMH	5/25/2023
119) Drug resistance to be confirmed by 7H-10 Plate Method.			5/25/2023

Our Patient's 2nd Line Growth-Based DST (WA DOH)

Susceptibility Report - 2nd Line of Drugs

Drug (mcg/mL)	Result	Percent Resistance	Colonies at 10-3	Colonies at 10-5	Performed by	Date
Growth Control	Satisfactory	0	500	250	CKD	6/16/2023
Isoniazid 0.2	Resistant	100	500	250	CKD	6/16/2023
Isoniazid 1.0	Resistant	100	500	250	CKD	6/16/2023
Rifampin 1.0	Resistant	100	500	250	CKD	6/16/2023
Streptomycin 2.0	Resistant	100	500	250	CKD	6/16/2023
Streptomycin 10.0	Resistant	100	500	250	CKD	6/16/2023
Ethionamide 5.0	Resistant	50.00	250	75	CKD	6/16/2023
Ethambutol 5.0	Sensitive	0	0	0	CKD	6/16/2023
Ethambutol 10.0	Sensitive	0	0	0	CKD	6/16/2023
p-Aminosalicylic Acid 2.0	Sensitive	0	0	0	CKD	6/16/2023
Amikacin 6.0	Sensitive	0	0	0	CKD	6/16/2023
Ofloxacin 1.0	Sensitive	0	0	0	CKD	6/16/2023

Lab Comments Report

999) No DOC on req. "3/30/23" on tube. 5/1/2023

Additional drugs on WA state DOH 2nd Line DST:

- Different concentrations of INH, SM, EMB
- Ethionamide
- PAS
- Amikacin
- Ofloxacin

Our Patient's 2nd Line Growth-Based DST (CDC)

MTBC Agar Proportion Susceptibility*	% Resistant	Interpretation
Isoniazid 0.2 µg/mL	100 %	Resistant
Isoniazid 1.0 µg/mL	100 %	Resistant
Isoniazid 5.0 µg/mL	67 %	Resistant
Rifampin 1.0 µg/mL	100 %	Resistant
Ethambutol 5.0 µg/mL	0 %	Susceptible
Streptomycin 2.0 µg/mL	100 %	Resistant
Streptomycin 10.0 µg/mL	100 %	Resistant
Rifabutin 2.0 µg/mL	33 %	Resistant
Ciprofloxacin 2.0 µg/mL	0 %	Susceptible
Kanamycin 5.0 µg/mL	0 %	Susceptible
Ethionamide 10.0 µg/mL	33 %	Resistant
Capreomycin 10.0 µg/mL	0 %	Susceptible
PAS 2.0 µg/mL	0 %	Susceptible
Ofloxacin 2.0 µg/mL	0 %	Susceptible
Amikacin 4.0 µg/mL	0 %	Susceptible

Comments and Disclaimers
* Susceptibility testing method: Indirect agar proportion, 7H10 medium. Resistance is defined as >1% (growth on drug-containing medium compared to drug-free medium).
This test has not been cleared or approved by the FDA. The performance characteristics have been established by the DTBE Reference Laboratory.

MTBC Pyrazinamide Susceptibility*	Result
Pyrazinamide 100 µg/mL	Susceptible

Comments and Disclaimers
* Susceptibility testing method: Mycobacteria Growth Indicator Tube (MGIT)

Compared to WA state DOH 2nd line testing, additional drugs on CDC 2nd line growth-based DST:

- Rifabutin
- Ciprofloxacin
- Kanamycin
- Capreomycin

CDC 2nd line DST does not currently include:

- LZD
- BDQ
- CFZ
- Pa
- CS

Picking an MDR-TB Regimen: BPaL/M vs 2019 regimens

- BPaL/M
  - Drugs: (MFX), BDQ, LZD, Pa
    - Essentially subbing Pa for CS and CFZ
  - Duration: 6 mo (extended to 9 for delayed response)
  - CDC approved for XDR-TB, pre-XDR-TB, or MDR-TB that is treatment nonresponsive/intolerant
- 2019 regimen
  - Drugs: MFX/LFX, BDQ, LZD, CFZ, CS
    - Sub lower ranked drugs as needed
  - Duration: 15-21 months past cx conversion
  - Approved for all MDR-TB per 2019 CDC recommendations

2019 ATS/CDC/ERS/IDSA DR-TB TREATMENT GUIDELINES

- Recommendations based on IPDMA evaluating over 12,000 pts from 50 studies
- Based recommendations on rates of…
  - Death
  - Treatment success
  - Serious adverse effects
- Looked at
  - # of drugs
  - Duration of treatment (intensive and continuation phase)
  - Specific individual drugs
- Developed before BPaL or BPaLM trials

Reclassified DR-TB Medications

		ATS/CDC/ERS/IDSA		WHO
Choose 5 INTENSIVE	1. Choose one FQ	Levofloxacin OR Moxifloxacin	Lfx Mfx	WHO Group A: Include all three
	2. Use BDQ and LZD	Bedaquiline	Bdq	
		Linezolid	Lzd	
	3. Use CFZ and CS	Clofazimine	Cfz	WHO Group B: Add one or both
		Cycloserine	Cs	
then drop to 4 CONTINUATION	4. Add inj. as needed	Amikacin (OR Streptomycin[1])	Am (S)	WHO Group C: Add to complete the regimen *[WHO rank order: E, Dlm, Z, Ipm-Cln/Mpm, Am(S), Eto/Pto, PAS]*
	5. Add as needed	Delamanid	Dlm	
		Ethambutol	E	
		Pyrazinamide	Z	
	6. Add as needed	Ethionamide	Eto	
		Imipenem-cilastatin OR Meropenem (PLUS clavulanate)	Ipm-Cln Mpm	
		p-aminosalicylic acid	PAS	
		High-dose Isoniazid	H^{HD}	

Order molecular & SL-DST if RIF-R

BDQ and LZD for all cases (BDQ for age 6y+)

Need to address access!

No injectable for most!! (No capreomycin for any)

First line drugs demoted

NO LONGER RECOMMENDED:
- Kanamycin
- Capreomycin
- Amoxicillin/clavulanic acid

- Comparison 2019 ATS/CDC/ERS/IDSA guidelines and 2016 & 2020 WHO

Intensive phase: 5-7 months post cx conversion
Continuation phase: complete 15-21 total months of treatment post cx conversion

Slide C/o Lisa Chen

When building the regimen, consider

- Prioritize all oral regimen as able
- Patient characteristics and side effect risk
- Susceptible or low likelihood of resistance
  - Avoid drugs used previously unless documented sensitive
- Tissue penetration
  - See Curry Guide medication fact sheets for data on CNS penetration
- Cross-resistance
  - INH and ETA
  - MFX and LFX
  - BDQ and CFZ
  - Amikacin and Kanamycin

Exciting Recent MDR-TB Trials

- 3 recent small studies of BPaL/M have informed
  - WHO guidelines
  - CDC provisional guidelines (and likely full guidelines released later this year)
  - Current US based MDR-TB practice
- 1 additional study outlining early adopter experience with BPaL in the US
- BPaL
  - 3 drugs with limited pre-existing resistance and 3 different mechanism of action

ORIGINAL ARTICLE

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., et al., for the Nix-TB Trial Team*

- "Nix-TB"
- March 2020
- Open label, single arm trial at 3 sites in South Africa
- N=109 (71 XDR-TB, 38 treatment unresponsive/intolerant MDR-TB)
  - Age 17-60, pulmonary TB, 51% HIV+, 84% cavitary
- BPaL regimen:
  - BDQ 400 mg daily X 2 wks, then 200 mg TIW X 24 wks
  - Pretomanid 200 mg X 26 weeks
  - LZD 1200 mg X minimum 4 weeks, goal 26 weeks
    - most required interruption, dose adjustment, or cessation (30%)
  - Regimen taken with food
  - Extended to 39 weeks if culture positive at 16 weeks (n=2)

Nix-TB Trial

- Results: Effectiveness
  - Followed for 24* months after treatment
  - Only 13 pts (12%) with “unfavorable outcome”
    - 7 deaths: 6 during treatment, 2 due to TB, none clearly from study med
    - 1 withdrew, 2 lost to follow up
    - 3 relapsed, one with apparent acquired BDQ resistance
- Results: Adverse Events, attributed mostly to LZD
  - 81% peripheral neuropathy, most but not all improved with LZD cessation
  - 48% myelosuppression
  - 2 pts optic neuritis, resolved with LZD cessation

*24 mo f/u reported at CROI but not yet published

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

Francesca Conradie, M.B., B.Ch., Tatevik R. Bagdasaryan, M.D., Sergey Borisov, M.D., Pauline Howell, M.D., Lali Mikiashvili, M.D., Nosipho Ngubane, M.D., Anastasia Samoilova, M.D., Sergey Skornykova, M.D., Elena Tudor, M.D., Ebrahim Variava, M.D., Petr Yablonskiy, Ph.D., Daniel Everitt, M.D., et al., for the ZeNix Trial Team*

- "ZeNix"
- Sept 2022
- Randomized, dose-blind trial of LZD 1200 or 600 mg for 9 or 26 weeks; no standard of care comparator
- N=181 pts divided over 4 arms (75 XDR, 85 pre-XDR, 21 treatment nonresponsive/intolerant MDR)
  - Age>14 (IQR 30-44), pulmonary TB, 62% cavitary, 20% HIV+, excluded if "risk of arrythmia"
  - Excluded extrapulmonary TB requiring extended treatment
- BPaL regimen
  - BDQ 200 mg for 8 wks, then 100 mg for 18 wks
  - Pretomanid 200 mg for 26 weeks
  - LZD at dose of either 1200 mg or 600 mg for either 9 or 26 weeks

ZeNix Trial

- Results:
  - Followed for 78 weeks after treatment completion
  - More bacteriologic failure in LZD for 9 week groups
  - More toxicity in higher dose or longer duration LZD groups
  - LZD 600 mg daily for 26 weeks was
    - Similar to 1200 mg daily for 26 weeks in terms of favorable outcomes (91% vs 93%)
    - Better compared to 1200 mg daily for 26 weeks in terms of toxicity (24% neuropathy vs 38%, 2% myelosuppression vs 22%)

ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., et al., for the TB-PRACTECAL Study Collaborators*

- "TB-PRACTECAL"
- Dec 2022
- Open label, randomized, non-inferiority trial
- Stage 1: compared culture conversion at 8 wks for WHO standard regimen, BPaL, BPaLM, BPaL+CFZ
  - All experimental arms performed well, but BPaLM did best
  - Used this data to select BPaLM for stage 2

TB-PRACTECAL

- Stage 2: WHO standard regimen vs BPaLM
- N=128 pts with RR/MDR-TB in modified intention to treat
  - Age 19-71, pulmonary TB, 23% HIV+, cavitation differed between groups (71% standard regimen, 53% BPaLM)
  - Included patients with FQ resistance (28% of the BPaLM group)
  - Excluded CNS and bone/joint TB
- Regimens
  - 9-20 month standard WHO regimen (changed over time)
  - BPaLM X 24 wks
    - BDQ 400 mg X 2 weeks, then 200 mg TIW X 22 wks
    - Pretomanid 200 mg X 24 wks
    - MFX 400 mg X 24 wks
    - LZD 600 mg daily X 16 wks, then 300 mg daily for 8 wks

TB-PRACTECAL

- Results
  - Trial terminated early due to interim analysis showing BPaLM superiority
  - 89% of BPaLM pts cured compared to 52% of standard regimen pts
  - No TB recurrence or relapse in either group
  - 4 deaths attributed to treatment, all in standard regimen
  - Probably similar efficacy between the regimens, but more side effects causing treatment discontinuation in standard regimen arm

BPaL and BPaLM study limitations

- Small
  - May miss rare but serious adverse events
- Limited long term follow up
  - May miss late relapse, including with acquired resistance
- Did not include EPTB or some special populations (no pregnant or young pediatric patients; did include PLHIV)

CDC Provisional Guidance for BPaL

- Published Feb 2022, updated May 2023
- BPaL for XDR, pre-XDR, and treatment unresponsive/intolerant MDR
- LZD 600 mg daily dosing, TDM may be helpful
- Extend to 9 mo for delayed treatment response within the first 8 weeks
- Not for EPTB
- PLHIV: OK if CD4>50 and not on efavarinz or cobicistat
- Pregnancy and children: Not included in studies (except older teenagers), weigh risks/benefits of BPaL on case by case basis
- Liver disease: OK if mild/moderate, not if severe
- ESRD on HD: Caution, no data
- No guidance on BPaLM

WHO MDR-TB Treatment Guidelines 2022

- Suggests BPaLM X 6 months for RR/MDR-TB, drop M if FQ resistant
  - OK to use for:
    - All EPTB except CNS, osteoarticular, disseminated
    - Age 14+
    - < 1 mo exposure to BDQ, Pa, LZD, or delaminid; of if they have DST showing still susceptible
  - Not enough data to support use in: pregnant, breastfeeding
  - LZD dose: 600 mg daily
- Also recommendations for all oral BDQ containing 9 mo regimen
- Reserve longer individual regimen (similar to 2019 CDC guidelines) for those unable to take the shorter all oral regimens

JOURNAL ARTICLE ACCEPTED MANUSCRIPT EDITOR'S CHOICE

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 FREE

Connie A Haley, MD, MPH ✉, Marcos C Schechter, MD, David Ashkin, MD,

- May 2023 CID
- Retrospective observational study of early adoption of off label BPaL use in US for RR or RIF intolerant TB, including some EPTB
- N=70 (68 completed BPaL, 2 switched to RIF based regimens)
  - Age 14-83, 46% cavitary
  - 10% EPTB only, 14% EPTB and pulmonary; none CNS
  - 15% had treatment extended to 39 weeks
- Effectiveness: variable follow up, 81% at least 6 months
  - No deaths or treatment failures
  - 2/68 relapsed
- LZD toxicity
  - Most patients had TDM targeting trough < 2 mcg/mL
  - 3 patients stopped LZD early due to side effects
  - 4 with baseline anemia required blood transfusion

Reasons to use BPaL/M

- Compared to previous regimens, small trials have shown that BPaL/M is
  - More effective
  - Less toxic
  - Shorter
- Components are similar to 2019 recommended regimens, with exception of Pa. Subbing Pa for CFZ/CS allows shorter, less toxic regimen
  - BPaLM: MFX, BDQ, LZD, Pa
  - 2019 regimen: MFX, BDQ, LZD, CFZ, CS

Reasons Not To Use BPaL/M

- Provider decision (awaiting further CDC guidance)
- Patient decision (declines after informed consent)
- Age <14, pregnant, breastfeeding
- EPTB, especially CNS (limited data for BDQ and Pa CNS penetration)
- Resistance (as of now, only would be shown on sequence-based molecular DST)

Bedaquiline (BDQ)

- Novel mechanism of action: ATP synthase inhibitor
- Activity: Bactericidal and probably sterilizing
- Taken with food
- LONG half life (5.5 months)
- Main adverse events:
  - Hepatotoxicity
  - QTc prolongation requiring EKG monitoring. In IPDMA used for 2019 guidelines, 0.9% of pts discontinued due to long QTc
- Cross resistance with CFZ
- Metabolized by CYP3A4 (RIF interaction)
- Possible synergy with LZD or CFZ (2019 IPDMA)
- Expensive: Almost $23,000 for 24 weeks
  - Wholesale pricing covers only 24 weeks of therapy. See NTCA document regarding procurement: https://www.tbcontrollers.org/resources/bdq-access/

Pretomanid (Pa)

- Novel mechanism: kills replicating bacteria by inhibiting mycolic acid biosynthesis and non-replicating bacteria by nitric oxide release
- Activity: Bactericidal and sterilizing
- Main adverse events: Difficult to assess based on small trials thus far with concurrent meds given; see BPaL(M) discussions
- Cross resistance with delaminid (same class)
- Metabolized by CYP3A4 (RIF interaction)
- Typically supplied in bottles of 26 pills

Linezolid (LZD)

- Inhibits protein synthesis
- Activity: Bactericidal
- Adverse effects: peripheral neuropathy, optic neuritis, myelosuppression, c. dif, serotonin syndrome (i.e. with SSRIs)
- Many US experts advocate for TDM to minimize toxicity, targeting a trough < 2 mcg/mL
  - Reference laboratories: University of FL, National Jewish (Denver)

Other DR-TB Drug Notes

- CFZ
  - Only available under investigational new drug (IND) protocol through FDA
  - Adverse events: skin discoloration/thickening, QTc prolongation

- CS
  - Significant rate of neuropsychiatric side effects (20-30% of pts)
  - Experts recommend ramp-up dosing and TDM
  - Experts recommend B6 to prevent neurotoxicity
  - No available DST (molecular or phenotypic)

Choose a regimen for our patient:

- Raise your hand and vote for:
  - 2019 regimen: MFX, BDQ, LZD, CS, CFZ
  - BPaL
  - BPaLM

Symptoms	Medications
G.I. symptoms	Ethionamide, PAS, Quinolones, Clofazimine, Rifabutin, Linezolid
Hearing loss, vestibular toxicity	Aminoglycosides
Renal insufficiency/Electrolyte	Aminoglycosides
Hepatotoxicity	PZA, PAS, Rifabutin, Ethionamide, Quinolones (MFX)
Peripheral neuropathy	Linezolid, INH, Quinolones, Ethionamide, Cycloserine
Neuropsychiatric: depression, agitation, psychosis, difficulty concentrating, insomnia	Cycloserine, Quinolones, Ethionamide
QTc prolongation	Bedaquiline, Clofazimine, Quinolones
Rash	All
Visual changes	EMB, Rifabutin, Linezolid
Hypothyroidism	Ethionamide, PAS
Headache	Quinolones, Cycloserine, Ethionamide, EMB

Common Side Effects & Resources

Survival Guide Chapter 9

Slide c/o Lisa Chen

TOOL: 7 **BPaL/BPaLM TB Care Plan**

Activity	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7-9
Request and review medical records	Medical/social history, physical exam	Physician assessment every 1-2 weeks	Physician assessment minimum monthly	→	→	→	→	→
Drug susceptibility testing (DST)	Review DST results; request 2nd-line DST/MDDR	N/A	N/A	Repeat DST **if culture remains (+)** after 2M	Repeat as indicated	Repeat as indicated	Repeat as indicated	
Imaging	**PA chest** [other view(s) if indicated]	N/A	N/A	Consider repeat imaging	N/A	N/A	End of treatment imaging	
Height and weight	**Calculate BMI**/LBW. Obtain weight monthly	→	→	→	→	→	→	→
Vision screening	Assess **visual acuity and color vision** monthly	Monthly while taking Linezolid	→	→	→	→	→	→
Peripheral neuropathy screening	Assess at baseline and monthly	→	→	→	→	→	→	→
CBC with differential	Obtain at baseline	Obtain every 1-2 weeks	Obtain every 1-2 weeks	Monthly (or more frequently as indicated while on Linezolid)	→	→	→	→
Metabolic panel (CMP)	**CMP to include:** K, Ca, Mg, creatinine, bicarbonate, (amylase and lipase)*	Listed components of CMP monthly	→	→	→	→	→	→
Liver function (LFTs)	**LFTs to include:** ALT, AST, total bilirubin, and alkaline phosphatase	**LFTs** (at week 2)*, **monthly** (if symptomatic, consider more frequent monitoring)	→	→	→	→	→	→
Other lab testing	**Obtain HIV test;** consider hep serology, A1C when risk factor(s) present; TSH* when indicated	Repeat only if indicated	→	→	→	→	→	
Electrocardiogram (ECG)	Obtain baseline ECG **(check QTcF)**	**Week 2 following treatment start** (check QTcF)	Repeat as indicated	**Week 12 ECG** (check QTcF)	Repeat as indicated	Repeat as indicated	**Week 24 ECG** (check QTcF)	
Sputum monitoring (pulmonary TB)	Sputum x 3 (one early morning) for AFB smear & TB culture	Consider at least 1 sputum 1x/wk until Sm(-) then one every 2 wk until culture conversion	Monthly sputum for TB culture following culture conversion	→	→	→	Extend 3 months **if sputum remains culture (+) after M2**	→
Airborne isolation precautions	Continue until deemed non-infectious per local/state guidelines	→	→	→				
Therapeutic drug monitoring	Not performed at baseline	Obtain **Linezolid peak** (2hr & 6hr) **and trough 1-2wks following treatment start**	Repeat peak/trough drug levels if needed until targets achieved	→				
Treatment monitoring	Directly observed therapy (DOT)/patient education	→	→	→	→	→	→	→
Nutritional assessment	→	→	→	→	→	→	→	→
Assess overall health, mental, emotional needs	→	→	→	→	→	→	→	→

* These are laboratory examinations recommended in the *Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease* (2021) but may not be necessary for all patients. Consider performing amylase/lipase when there are underlying concerns for pancreatitis, TSH if prolonged QT interval on baseline ECG or concern for hypothyroidism, and LFTs at week 2 if elevated risk for hepatotoxicity.

Curry Survival Guide Ch. 8: Monitoring and Case Management has some very useful checklists and figures, like this one for BPaL/M

MDR-TB Post-Treatment Monitoring

- Most experts recommend monitoring for 2 years after treatment
- One protocol in use
  - Symptom screen, sputum, and CXR at 3, 6, 12, 18, 24 months after completion

MDR-TB Contacts

- Step 1: Rule out TB disease
- Step 2: Is this a new infection? Evaluate level of exposure and any prior TB infection testing
  - If have a prior positive TST/QFT, impossible to tell if recently infected with drug resistant TB and risks of treatment may outweigh benefits
- Treatment regimens (2019 guidelines)
  - 6-12 months FQ
  - Consider adding 2nd agent based on DST, i.e. EMB (preferably not PZA due to toxicity)
- If don't treat, monitor for 2 years

Summary

- Know when to suspect drug resistant TB
- Important to obtain molecular and 2nd line phenotypic DST up front when MDR-TB is suspected
- Treatment of MDR-TB is rapidly evolving: Consult an expert