

RESISTANCE IS FUTILE:

Treatment Of Drug Resistant TB

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TB Intensive, Rochester MN October 2026

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- 18.25 *AMA PRA Category 1 Credit™*
- 18.25 ANCC
- 18.25 Attendance
- 18.25 IPCE

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LEARNING OBJECTIVES

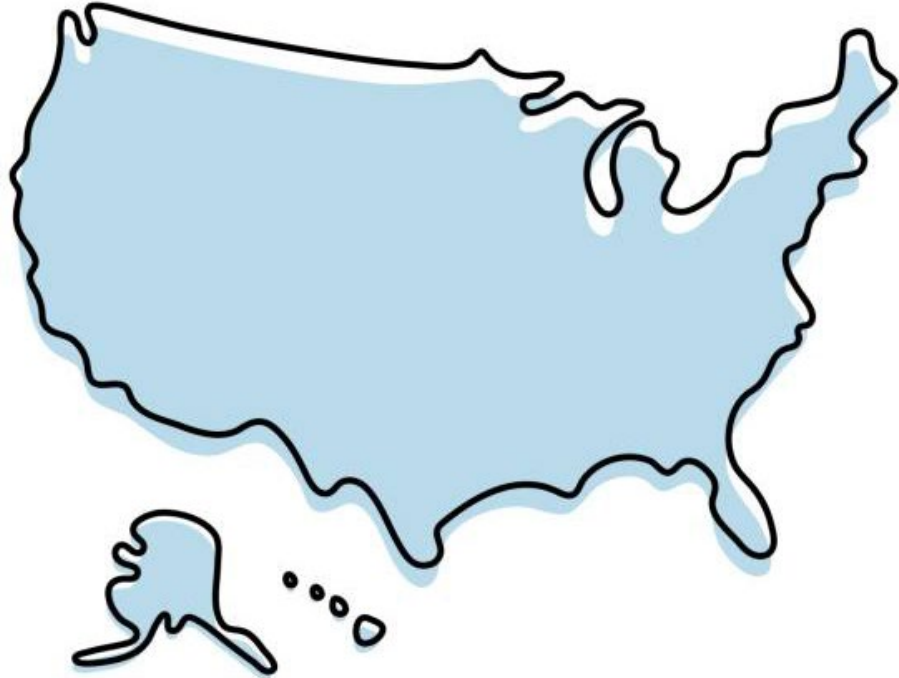
- Define drug resistant TB
- Describe approach to diagnosing drug resistant TB
- Recognize common adverse effects of drug resistant TB treatment

DEFINITIONS OF DRUG-RESISTANT TUBERCULOSIS

MDR TB	INH and RIF resistance
Pre-XDR TB	MDR-TB + fluoroquinolone resistance
XDR TB	Rifampin resistance + fluoroquinolone resistance + resistance to at least one additional group A drug (bedaquiline or linezolid)

RIFAMPIN RESISTANCE

- Rifampin – key drug in TB treatment
- Rifampin resistance without isoniazid resistance is rare
- Rifampin resistance = MDR TB



Drug-resistant TB in the US 2020-2024

- Total = 456 cases (1%)
- CA 17%, TX 9%, NY 7%, FL 5%
- Non-US born = 412 cases (95%)
- Around 40% had been in the US for 4 years or less
- Pre-XDR = 46 cases
- XDR = 9 cases

CASE

- 22-year-old man with 4 months of productive cough, unintentional 35 lb. weight loss
- Immigrated to the US from India one year prior to presentation
- Received 9 months of antitubercular therapy in India (unknown regimen)
- Sputum: AFB 4+ positive, MTB PCR positive with rifampin resistance detected
- CT chest: Bilateral miliary opacities, tuberculosis spondylitis



What is the next best step in management in this case of rifampin resistant disseminated tuberculosis?

- A.** Start RIPE
- B.** Start treatment for rifampin monoresistant TB
- C.** Obtain genotypic resistance testing
- D.** Await resistance testing before starting TB treatment

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CONCERN FOR DRUG-RESISTANT TB

Prior TB treatment

- Unknown regimen, dosing
- Unknown susceptibility
- Unknown culture conversion
- Unknown adherence, treatment completion
- Unknown DOT

High risk area for MDR-TB

- India has around a quarter of global disease burden of MDR-TB

RISK OF DRUG RESISTANT TB

- Culture positive ≥ 2 months on 4 drug RIPE therapy
- Prior TB treatment
 - Recent treatment
 - Unknown regimen, dosing
 - Unknown susceptibility
 - Unknown culture conversion
 - Unknown adherence, treatment completion, DOT
- HIV: Rifampin mono-resistance, MDR-TB
- Exposure to drug resistant TB

RISK OF DRUG RESISTANT TB

- Birth, residence or recent extended travel to countries with high rates of drug resistant TB (greater than 2%)
- Locally identified groups at risk

Proportion of RR or MDR TB cases	
Angola	4%
Azerbaijan	12%
Belarus	40%
China	3%
India	2.5%
Indonesia	2.2%
Kazakhstan	34%
Mongolia	7.2%
Myanmar	4.1%
Nepal	4%
Nigeria	2.1%
Pakistan	2.3%
Peru	4.9%
Philippines	2.5%
Russia	37%
Somalia	4.6%
South Africa	2.9%
Tajikistan	28%
Ukraine	29%
Uzbekistan	16%
Vietnam	4.5%

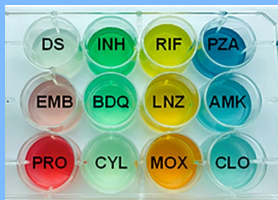
DRUG RESISTANCE TESTING



Rapid TB diagnosis with combined molecular resistance



Molecular (genotypic) resistance assays



Growth-based (phenotypic) drug susceptibility testing

DRUG RESISTANCE TESTING

Molecular (genotypic) resistance assays

- Detects gene mutations most frequently associated with drug resistance to first and second line drugs
- Absence of mutations cannot always completely rule out resistance

Growth-based (phenotypic) drug susceptibility testing

- Reference standard for drug resistance determination
- Based on in vitro minimum inhibitory concentration (MIC) values of each tested antimicrobial to the MTB isolate in solid or liquid growth media
- Slow (14-21 days), requires specialized infrastructure and skills

MOLECULAR RESISTANCE TESTS

- Cepheid Xpert MTB/RIF
 - RT-PCR
rpoB mutation → Rifampin resistance
- Molecular Detection of Drug Resistance Markers (MDDR)
 - Targeted next generation sequencing
 - Molecular detection of well-characterized drug-resistance variants for first and second line TB drugs
- Line-probe assay for FQ, rifampin and isoniazid resistance (NJH)
- Whole genome sequencing

DRUG RESISTANT TB TREATMENT

PRIOR TO 2019

- Intensive phase: At least 4-5 effective drugs, including a second line injectable drug (amikacin, kanamycin, capreomycin)
- Injectable drug ≥ 6 months and ≥ 4 months after smear or culture negativity
- Overall treatment durations 9-20 months

2019

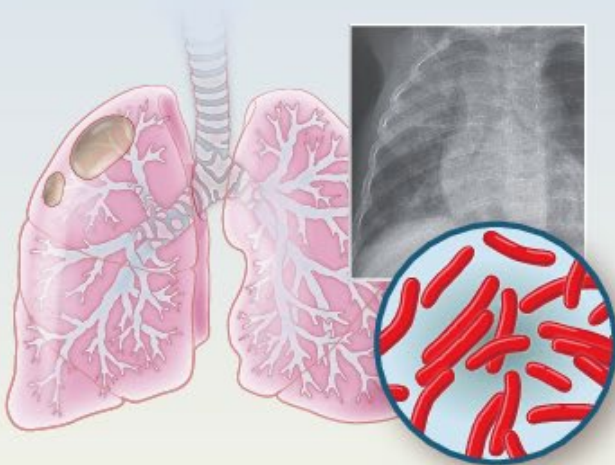


Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients

with confirmed tuberculosis



Three-drug regimen (26 wk)

Bedaquiline



Pretomanid
(recently approved)



Linezolid



**XDR
tuberculosis**

N=71
(65%)

Nonresponsive or
treatment-intolerant
MDR tuberculosis

N=38
(34%)

**Clinical resolution at
6 mo after therapy**

90% of all patients had favorable outcomes
89%

95% CI, 79–95

95% CI, 83–95

92%

95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

DRUG RESISTANT TB TREATMENT

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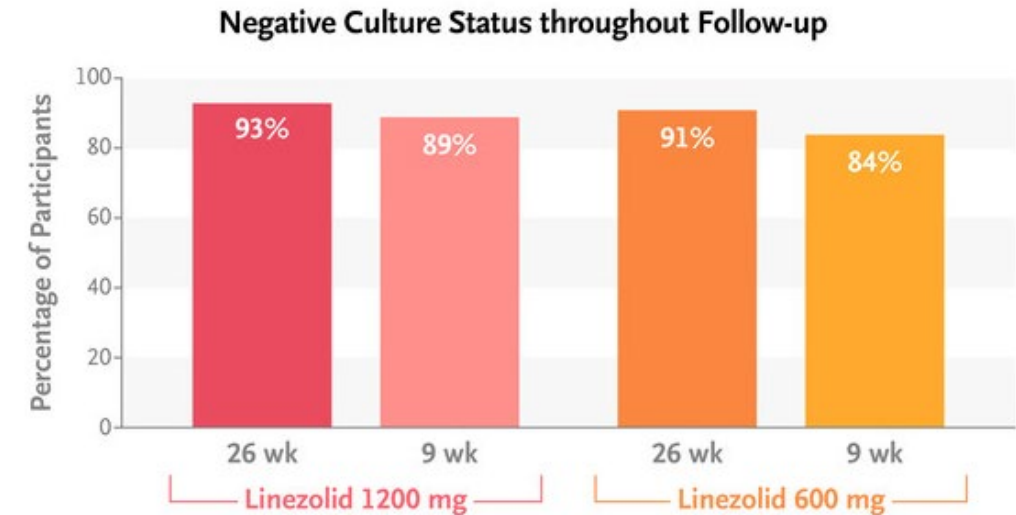
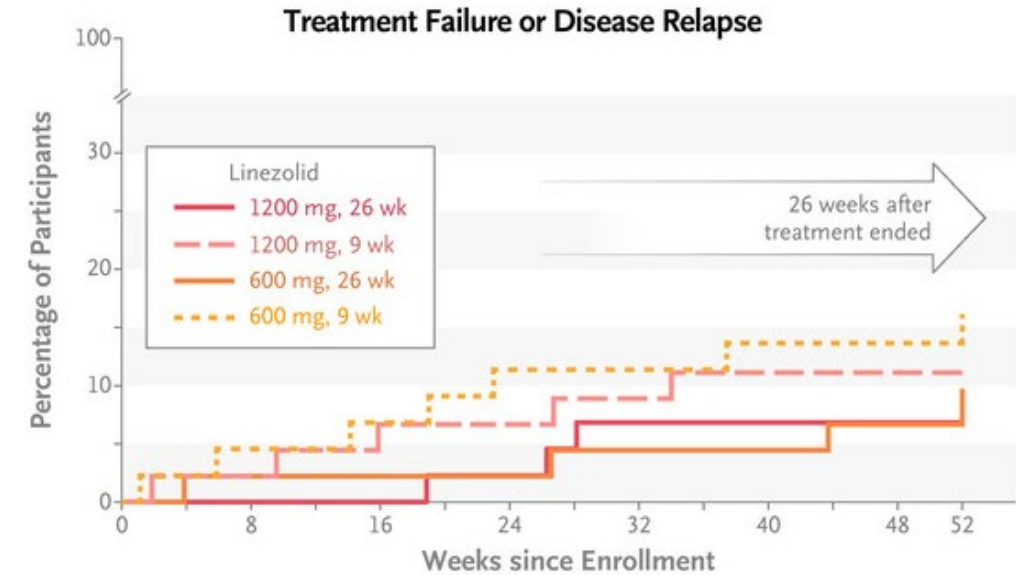
2019

- BPaL approved for pulmonary XDR, treatment intolerant, non-responsive MDR-TB

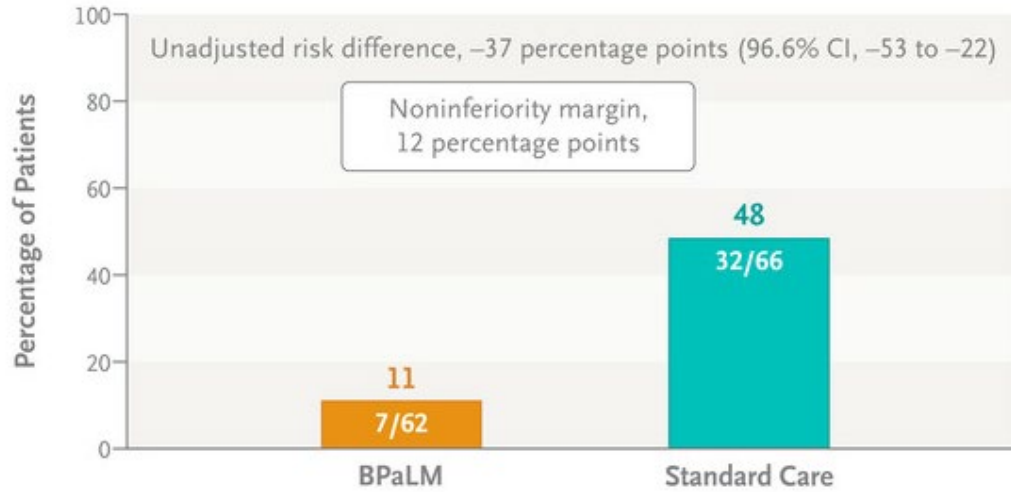
2019

ZENIX TB TRIAL

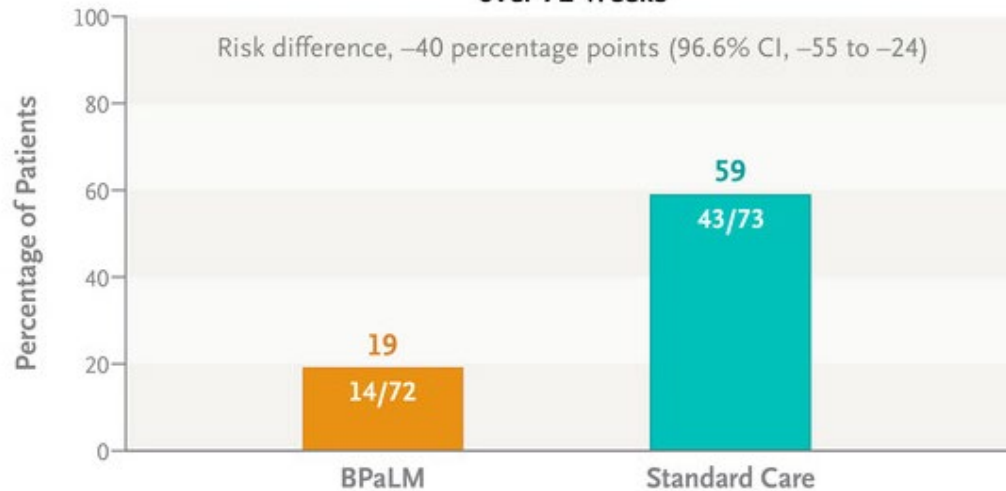
- 181 participants with pre-XDR or XDR-TB
- Compared LZD 1200 mg for 26 or 9 weeks, or 600 mg for 16 or 9 weeks
- Conclusion: LZD 600 mg for 26 weeks had the most favorable outcomes/side effect profile



Unfavorable Outcome in Modified Intention-to-Treat Analysis



≥1 Serious Adverse Event or Adverse Event of Grade ≥3 over 72 Weeks



TB-PRACTECAL TRIAL

- Open label multicenter randomized controlled non-inferiority trial
- 24-week all-oral regimen for treatment of rifampin resistant TB
- Enrollment terminated early for benefit
- All-oral 24-week treatment was non-inferior and better tolerated than standard care treatment for RR-TB

DRUG RESISTANT TB TREATMENT

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2019

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2022

- BPaL/BPaL-M all oral 6-month regimen recommended for MDR/RR-TB, pre-XDR-TB

2019

2022

BPaL

- Bedaquiline 400 mg orally once daily x 2 weeks (load), then 200 mg orally 3x/week x 24 weeks
- Pretomanid 200 mg orally once daily x 26 weeks
- Linezolid 600 mg orally once daily x 26 weeks

DURATION OF BP_aL TREATMENT

- 6-month duration recommended in most cases
- Consider extending to 9 months (39 weeks) in select cases
 - Delayed clinical response to treatment
 - Delayed microbiologic response to treatment (culture positivity > 8 weeks after starting effective therapy)
 - Consider for certain extra-pulmonary TB disease (vertebral, CNS) or high disease burdens

Which of the following is correct about BPaLM adverse effects and monitoring?

- A. Pretomanid commonly causes hearing loss
- B. Regular CBC monitoring is recommended on linezolid
- C. Bedaquiline's main adverse effect is optic neuritis
- D. Regular ECG monitoring is needed as moxifloxacin can cause QTC prolongation

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PATIENT ASSESSMENT

- History & physical exam
- Nutrition assessment, BMI
- Psychosocial assessment (mental health, social support)
- Labs: CBC, CMP, UA, TSH, HIV, pregnancy test, ECG
- Radiology: Chest xray or CT (if not already done)
- Medication review – focus on possible drug-drug interactions or overlapping toxicities with BP aL-M

MONITORING ON TREATMENT

- Regular clinical assessment (nausea, headache, hemoptysis, chest pain, arthralgia, rash, liver toxicity, signs of optic and peripheral neuropathy)
- DOT daily (or Mon-Fri)
- Labs: CBC, ALT, ALP, creatinine at 2 weeks, then every 4 weeks
- Sputum every 1-2 weeks until smear negative, then 2 samples monthly until culture conversion then 1 sample monthly until treatment completion

ECG MONITORING

- Monitor ECG at 2, 12 and 24 weeks after starting BPaL
- Monitor ECG weekly if
 - Other QTC prolonging medications
 - History of torsades de pointes, congenital long QT syndrome, hypothyroidism and bradyarrhythmias, decompensated heart failure
 - Low serum K, Ca, Mg
- Discontinue BDQ and any other QTC prolonging medications
 - Clinically significant ventricular arrhythmia
 - QTC > 500 msec
- Obtain K, Ca, Mg, TSH at baseline and monthly

MONITORING ON TREATMENT

- Consider therapeutic drug level monitoring
 - LZD trough $< 2 \mu\text{g/mL}$ associated with lower risk of toxicities
 - LZD peak 12–26 $\mu\text{g/mL}$ (or $> 4\text{--}16 \times \text{MIC}$)
- LZD could be reduced to 300 mg daily or held for toxicity
- Monitor visual acuity and color vision

MANAGEMENT PRINCIPLES

- Drug-resistant TB is a joint management responsibility between medical providers and local/state Public Health
- Public Health should be contacted immediately to support local providers with medication provisions, engagement in longitudinal TB case management (DOT, contact investigations, etc.)
- Medical consultation with CDC funded TB Centers of Excellence

GI ADVERSE EFFECTS

- Hepatotoxicity
 - Managed with treatment interruption and successful resumption
 - May be more likely in those with HIV
 - Around 26% in ZeNix trial
- GI symptoms (nausea, vomiting, dyspepsia, diarrhea)
 - Around 36% in Nix-TB trial
- Acute pancreatitis
 - Around 3% in Nix-TB, animal BDQ studies

GI ADVERSE EFFECTS

- LFTs at baseline, then 2 weeks and every 4 weeks
- More frequent LFT monitoring
 - Underlying liver disease
 - Other hepatotoxic medications
 - Signs/symptoms of liver dysfunction (fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly)
- Discontinue BP aL
 - ALT > 8 x ULN
 - ALT < 5 x ULN for > 2 weeks
 - Abnormal ALT and total bilirubin > 2 x ULN

OTHER ADVERSE EFFECTS

- Lactic acidosis in 2.8% in Nix-TB trial
- Mild QT prolongation in 5.5% in Nix-TB trial, 0 in ZeNix
- Optic neuritis in 4% in Nix-TB, 1% in ZeNix
- Peripheral neuropathy in 80% in Nix-TB
- Anemia in 8%, neutropenia in 9% in ZeNix

MONITORING ON TREATMENT

- Repeat drug susceptibility testing if culture positive ≥ 3 months or culture reversion (negative to positive)
- Chest xray at baseline, then every 3-6 months during treatment and at end of treatment

POST-TREATMENT MONITORING

- Clinical assessment, sputum and CXR at 6, 12, 18 and 24 months after treatment completion

ACCESSING BEDAQUILINE: Metro Medical Solutions/Cardinal health

MMS SOLUTIONS[®]
METRO
PHARMACY

239 Mason Rd

La Vergne, TN 37086

www.mmspharmacy.com


Sirturo[™]
bedaquiline
100mg tablets

Prescription Order

FAX TO: 615-312-9903

MMS Phone: 855-691-0963 (toll free); 615-312-9888 (local)

Date:	_____	Facility Name:	_____
PO#:	_____	Metro Account #:	_____
Patient Last Name:	_____	Facility Phone:	_____
Patient First Name:	_____	Facility Fax:	_____
Patient Date of Birth:	_____	Facility Address:	_____
Patient Phone:	_____	Facility City, ST, Zip:	_____
Patient Address:	_____		
Patient City, ST, Zip:	_____		

***Orders cannot be shipped directly to Patient

**All orders must be shipped to the Prescriber address or Facility/Site of Care Address

Drug Allergies: _____

ITEM #	MEDICATION	QTY	DIRECTIONS FOR USE
	Sirturo 100mg tabs (NDC:59676-0701-01)	68	Take 400mg daily for 2 weeks
Other	_____	_____	then 200mg 3 x a week for 2 weeks
Other	_____	24 w/4 refills	Take 200mg 3 x a week
Other	_____	_____	_____
Other	_____	_____	_____
Other	_____	_____	_____
Other	_____	_____	_____
Other	_____	_____	_____
Other	_____	_____	_____

Prescriber Name:	_____	Prescriber Phone:	_____
Prescriber NPI:	_____	Prescriber Signature:	_____

SHIPPING METHOD

☐ 2nd Day Air
☐ (Standard Method)

☐ Overnight



CardinalHealth

MMS Solutions
 239 Mason Drive
 LaVergne, TN 37086

Fax: 615-312-9903
MMS Phone: 855-691-0963

Patient Intake Form

Demographics

Name (First): _____ Name (Last): _____ Date of Birth: __________

Address: _____

Gender: _____ Phone Number: _____ Language Spoken: _____

Weight (if pediatric): _____ Hearing/visually impaired: _____

Emergency Contact: _____ Phone Number: _____

Medical History

Allergies:

Current Medications:

Medical Conditions:

Patient Therapy

Prescribed Therapy: _____ Duration of Therapy: _____

Date of Diagnosis: _____ Diagnosis: _____ ICD-9 or ICD-10: _____

CASE OVERVIEW

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Centers for Disease Control and Prevention
National Tuberculosis Reference Laboratory

Rifampin (RIF)	<u>Result</u>	<u>Interpretation</u>
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)	<u>Result</u>	<u>Interpretation</u>
INH interpretation		INH resistant
inhA	No mutation	
fabG1	No mutation	
katG	Ser315Thr	
Ethambutol (EMB)	<u>Result</u>	<u>Interpretation</u>
EMB interpretation		EMB resistant
embB	Met306Val	
Pyrazinamide (PZA)	<u>Result</u>	<u>Interpretation</u>
PZA interpretation		Effect of mutation unknown. Cannot rule out PZA resistance.
pncA	Asp56frameshift	
Fluoroquinolones (FQ)	<u>Result</u>	<u>Interpretation</u>
FQ interpretation		FQ resistant
gyrA	Ala90Val	
gyrB	No mutation	



Centers for Disease Control and Prevention
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**Amikacin, Capreomycin, and Kanamycin
(AMK, CAP, and KAN)**

AMK CAP and KAN interpretation

rrs

Result

No mutation

eis

No mutation

Interpretation

Cannot rule out resistance
to AMK, CAP, and KAN.

Bedaquiline (BDQ)

BDQ interpretation

atpE

Result

No mutation

rv0678

No mutation

pepQ

No mutation

Interpretation

Cannot rule out BDQ
resistance.

Clofazimine (CFZ)

CFZ interpretation

pepQ

Result

No mutation

rv0678

No mutation

Interpretation

Cannot rule out CFZ
resistance.

Linezolid (LZD)

LZD interpretation

rplC

Result

No mutation

rrl

No mutation

Interpretation

Cannot rule out LZD
resistance.

CASE OVERVIEW

- 22-year-old man from India with disseminated tuberculosis (miliary pulmonary disease, spondylitis, paraspinal abscess)
- Sputum acid fast smear and MTB PCR positive
- CDC MDDR: Resistance to RIF, INH, EMB, FQ
- **Diagnosis: Pre-XDR-TB**
- **Treatment: BPaL for at least 6 months**

What do you recommend for latent TB infection treatment of an immune compromised household contacts of this case?

- A. PZA + EMB
- B. Linezolid
- C. Bedaquiline
- D. Close clinical observation for 2 years

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PRESUMED MDR LATENT INFECTION

- Based on source case susceptibility data
- Levofloxacin or moxifloxacin for 6-12 months
- Linezolid for 6 months
 - Prolonged use: Myelosuppression, peripheral and optic neuropathy
 - Consider lower dose, therapeutic drug monitoring
- Pyrazinamide/ethambutol
 - High rates of toxicity and discontinuation
 - Less effective
- Consider close clinical monitoring with extended followup for 2 years

Implementing a Program of Comprehensive Tuberculosis Preventive Treatment: Safety, Effectiveness, and Acceptability of Moxifloxacin or Bedaquiline Use for Contacts Exposed to Drug-Resistant Strains

Alexandra V. Solovyeva,^{1,✉} Grigory V. Volchenkov,^{2,✉} Oksana I. Ponomarenko,¹ Tatiana A. Kuznezova,² Tatiana R. Somova,² Evgenia V. Belova,² Sven Gudmund Hinderaker,^{3,✉} Einar Haldal,^{4,✉} and Salmaan Keshavjee^{5,6,7,✉}

¹Independent Nonprofit Organization Center of Partnership Assistance in Healthcare “Zdorovye.ru”, Moscow, Russia; ²Vladimir Regional TB Control Center, Vladimir, Russia; ³Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; ⁴LHL International, Oslo, Norway; ⁵Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA; ⁶Division of Global Health Equity, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, USA; and ⁷Partners In Health, Boston, Massachusetts, USA

Results. Over 24 months, 403 people started TPT. No life-threatening ADRs or deaths occurred. The lowest ADR rate and highest completion were seen with 3Bdq (95.2%) compared to 3HP (75.9%, *Mid-P exact* = .03). Tuberculosis incidence per 1000 person-years was 4 times higher among eligible individuals who declined TPT versus those initiating it.

QUESTIONS & ANSWERS





THANK YOU