Ukrainian Humanitarian Parolees: Tuberculosis

December 1, 2022

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Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

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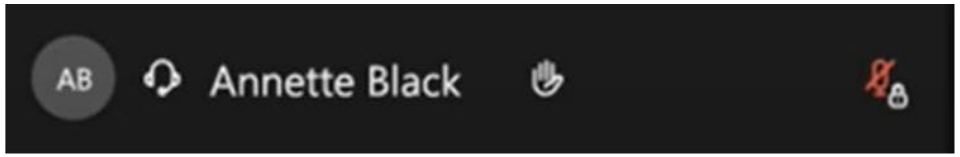

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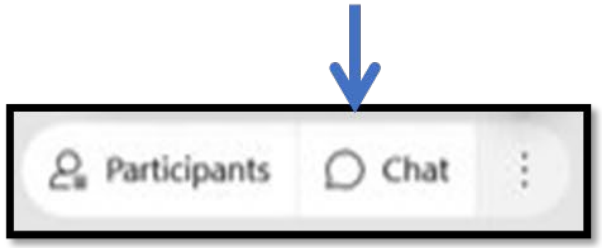

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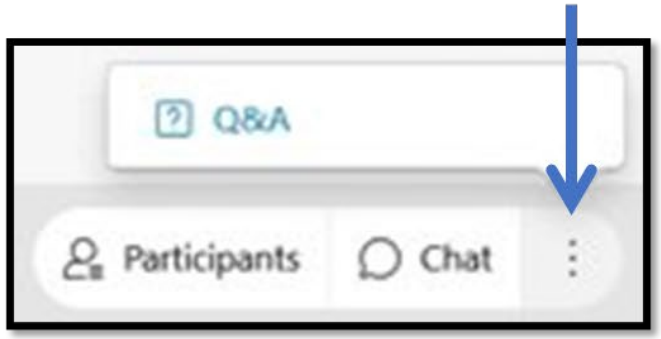

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Learning Objectives

- Describe the epidemiology of tuberculosis in Ukraine.
- Review LTBI and TB disease workup and management.
- Identify two to three tuberculosis-related technical assistance resources.

Poll #1

Question: **What is your role in newcomer health?**

a. Clinician
b. Nurse / Local public health nurse
c. Public health professional
d. Other

Uniting for Ukraine

Neela Goswami MD

Medical Officer, Field Services Branch, Division of TB Elimination
Centers for Disease Control and Prevention

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Uniting for Ukraine Program

- On May 21, 2022, President Biden signed into law emergency supplemental appropriations (Public Law 117-128 [https://www.congress.gov/117/plaws/publ128/PLAW-117publ128.pdf]) that included funds for medical support, screening, and other public health activities related to populations displaced from Ukraine.

- This provides a pathway for Ukrainian citizens to be paroled into the United States and stay temporarily for a two-year period.

- Ukrainians participating in the program must meet specific health requirements (USCIS: Uniting for Ukraine Vaccine Attestation [https://www.uscis.gov/humanitarian/uniting-for-ukraine/uniting-for-ukraine-vaccine-attestation]), including vaccinations and tuberculosis (TB) testing.

Uniting for Ukraine Program and Tuberculosis

- In the Uniting for Ukraine program, Ukrainian parolees are required to undergo testing with a TB-specific interferon-gamma release assay (IGRA) and subsequent TB diagnostic studies as needed.

- Parolees are also required to be vaccinated for several other infections.

- On July 14, the U.S. Department of Homeland Security extended the time period for completing the TB requirement from 14 days to 90 days (USCIS: Uniting for Ukraine Vaccine Attestation [https://www.uscis.gov/humanitarian/uniting-for-ukraine/uniting-for-ukraine-vaccine-attestation]).

Uniting for Ukraine Program and CDC DTBE

- To support this effort, in August 2022, CDC's Division of Tuberculosis Elimination (DTBE) awarded nearly $8 million in supplemental funding under CDC-RFA-PS20-2001 [CDC TB: Notice of Funding Opportunity (NOFO) – FY2022 (https://www.cdc.gov/tb/education/funding-opportunity-notice.htm)] to currently funded states, cities, and territories for screening, evaluation, and treatment of latent TB infection and TB disease among Ukrainians paroled into the United States.
- CDC anticipates awarding a second supplement to support U.S. Department of Homeland Security: Uniting for Ukraine (https://www.dhs.gov/ukraine) in Fiscal Year 2023.

Ukraine and Tuberculosis

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)

[World Health Organization (WHO) 2021 TB Profile for Ukraine](https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22UA%22)
(https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22UA%22)

Uniting for Ukraine Program and CDC DTBE Cont'd

Is the TB epidemiology of the Uniting for Ukraine parolees similar to that of Ukrainians living in Ukraine, Ukraine-born persons already in the United States or to applicants at immigration panel sites in Ukraine?

- **In the World Health Organization (WHO) 2020 TB profile for Ukraine**, 17,533 new and relapse cases were reported.
  - Of those, 4,257 cases were MDR TB or at least rifampin resistant and 1,172 were extensively drug resistant (XDR) or pre-XDR TB.
  - WHO projected that TB was approximately 50% underreported in Ukraine, and testing and reporting for drug resistance in Ukraine are not systematic
  - Of culture-confirmed cases, 32.6% were MDR TB, including XDR and pre-XDR TB.
- **For 2014–2020 in CDC's National TB Surveillance System**, 122 cases of TB were reported in non–U.S.-born persons with Ukraine as the place of birth.
  - Of these cases, 104 (85%) were culture confirmed, and 102 had susceptibility results for at least isoniazid and rifampin.
  - Any isoniazid resistance was reported for 24 (24%), any rifampin resistance for 13 (13%), and MDR TB for 13 (13%), which included XDR or pre-XDR TB for 3 (3%). The pre-2021 definitions for XDR and pre-XDR TB were used.
- **From U.S. immigration panel sites in Ukraine during 2016–2021**, the results of medical examinations for 54,493 Ukrainians who were applying for immigrant or refugee admission to the United States were reported to CDC's Division of Global Migration and Quarantine (CDC: Tuberculosis Technical Instructions for Panel Physicians [https://www.cdc.gov/immigrantrefugeehealth/panel-physicians/tuberculosis.html]).
  - 36 applicants had Class A Active TB, for a prevalence rate of 66/100,000 persons examined.
  - Of the 36 cases, 31 (86%) were culture confirmed: 6 (19%) were drug resistant besides MDR or XDR TB, and 7 (23%) were MDR TB, which included 2 (6%) XDR TB.

Ukraine and Multidrug-Resistant Tuberculosis

- Data from CDC and the World Health Organization (WHO) indicate a prevalence rate of multidrug-resistant (MDR) TB among Ukrainians who had culture-confirmed TB in the United States or in Ukraine of 13% to 33%.
- When Ukrainian parolees are being examined for possible TB disease, microbiological testing should include rapid molecular methods for detecting drug resistance.
- TB disease must be excluded before any regimen for treating LTBI is started.
- If drug-resistant TB or LTBI is suspected, clinical consultation should be obtained for assistance in selecting drugs for treatment.

Poll #2

Question: **How many Ukrainian newcomers have you seen in your practice in the past month?**

a. 0 - 5
b. 6 - 10
c. 11 - 20
d. > 20

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Ukrainian Parolee with Complicated MDR-TB

Alfred Lardizabal, MD
Rutgers Global Tuberculosis Institute

Case History

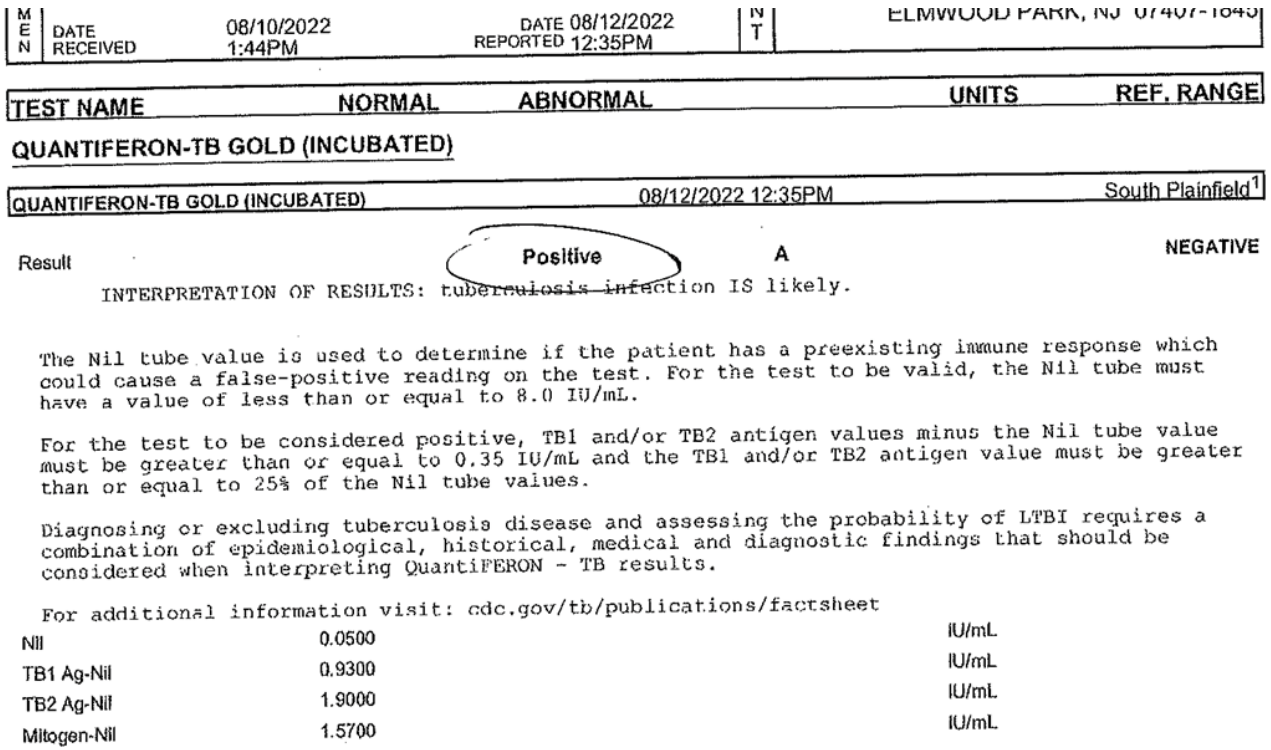
38-year-old single male Ukrainian parolee arrived in the US to be with his brother on August 5, 2022

He worked in construction as a mason. Over the years, he temporarily migrated to Poland and Russia for work

(+) 30 pack-year smoking history
(-) alcohol abuse, incarceration

As required upon arrival in the US, he seeks a local physician to undergo TB evaluation and testing

QuantiFERON-TB Gold Plus



M E N | DATE RECEIVED 08/10/2022 1:44PM | DATE REPORTED 08/12/2022 12:35PM | IN T | ELMWOOD PARK, NJ 07407-1645

TEST NAME	NORMAL	ABNORMAL	UNITS	REF. RANGE
QUANTIFERON-TB GOLD (INCUBATED)				
QUANTIFERON-TB GOLD (INCUBATED)	08/12/2022 12:35PM		South Plainfield[1]	
Result		Positive A		NEGATIVE

INTERPRETATION OF RESULTS: tuberculosis infection IS likely.

The Nil tube value is used to determine if the patient has a preexisting immune response which could cause a false-positive reading on the test. For the test to be valid, the Nil tube must have a value of less than or equal to 8.0 IU/mL.

For the test to be considered positive, TB1 and/or TB2 antigen values minus the Nil tube value must be greater than or equal to 0.35 IU/mL and the TB1 and/or TB2 antigen value must be greater than or equal to 25% of the Nil tube values.

Diagnosing or excluding tuberculosis disease and assessing the probability of LTBI requires a combination of epidemiological, historical, medical and diagnostic findings that should be considered when interpreting QuantiFERON - TB results.

For additional information visit: cdc.gov/tb/publications/factsheet

Nil	0.0500	IU/mL
TB1 Ag-Nil	0.9300	IU/mL
TB2 Ag-Nil	1.9000	IU/mL
Mitogen-Nil	1.5700	IU/mL

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Poll #3

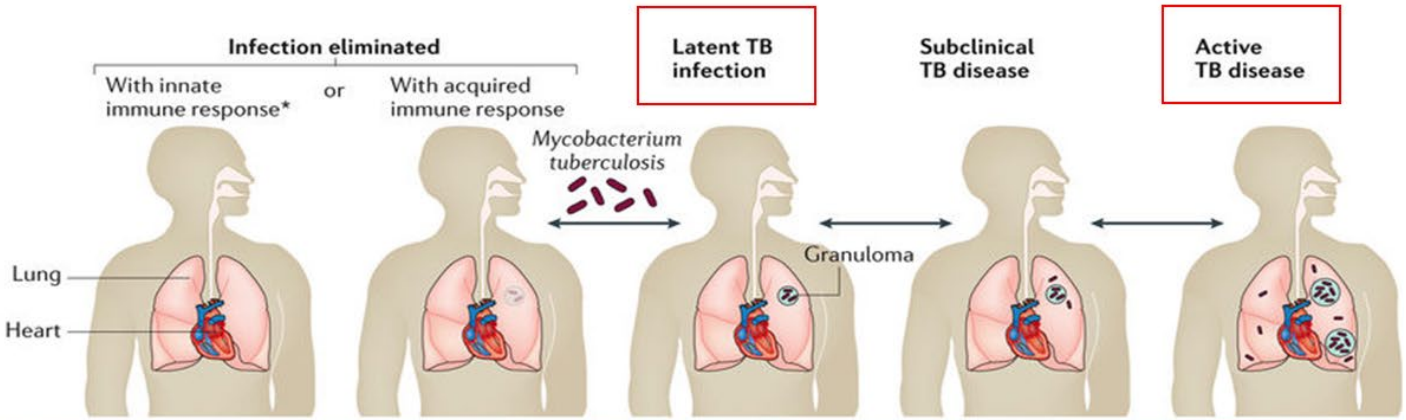
Question: **The person's IGRA test is positive. What would you do next?**

a. Get a chest x-ray
b. Treat for LTBI
c. Assess for symptoms
d. Treat for active TB disease
e. Educate the patient
f. a, c, & e
g. c, d, & e
h. Nothing, positive IGRA is not reportable

TB Pathogenesis

Figure 1 : The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease.

From: Tuberculosis



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Nature Reviews | Disease Primers

Pai, M., Behr, M., Dowdy, D. *et al.*
Nature Reviews Disease Primers 2016: Tuberculosis
(https://doi.org/10.1038/nrdp.2016.76)

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Chest X-ray

Poll #4

Question: **The person's chest x-ray is abnormal. What would you do next?**

a. Don't panic
b. Contact your local or state TB program
c. Continue with work-up for active TB disease
d. Educate the patient
e. All of the above

Case History Cont'd

Local doctor is told that he is currently on treatment for TB

Referred to the local health department

Poll #5

What do you think will happen to this patient after you connected them to TB care?

1. Patient will be cured
2. Worried the patient might die
3. Patient will be admitted to TB sanitorium

Information Sharing

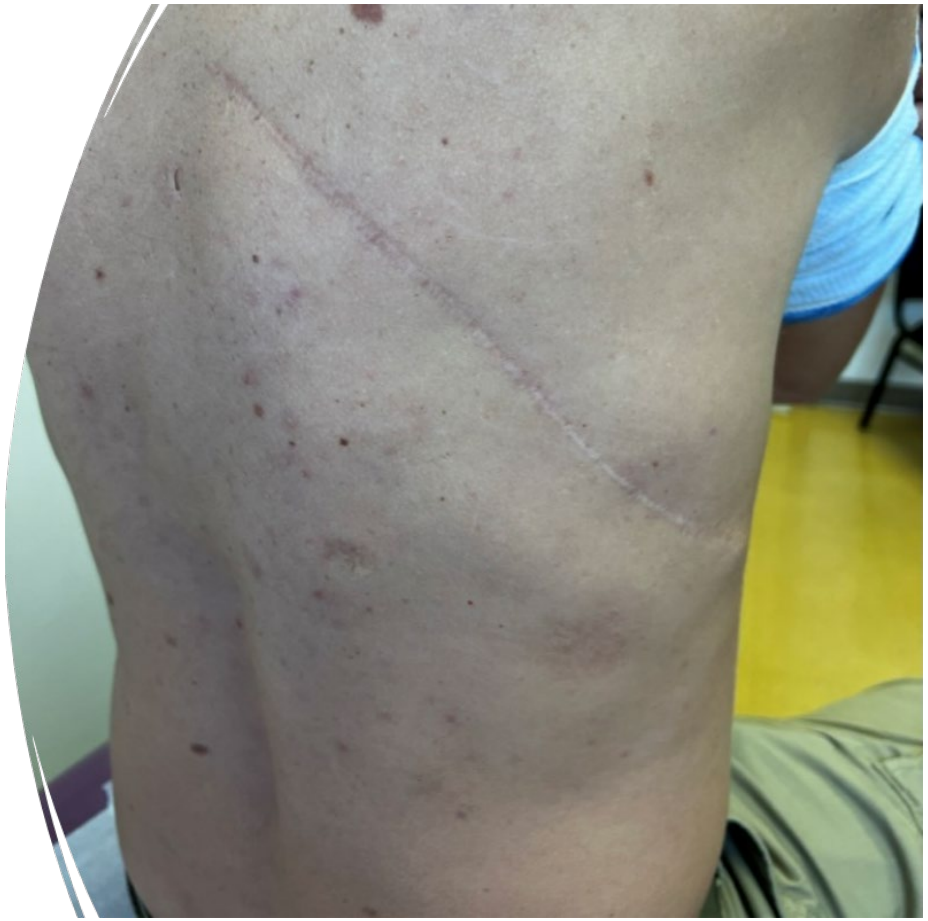
CureTB

CureTB accomplishes its community-centered goal of reducing the spread of TB by:

- Linking patients to care outside the United States.
- Collecting and providing high-quality clinical information to healthcare providers.
- Educating patients and motivating them for continued adherence.
- Promoting integrated care by coordinating with US and global partners.
- Determining treatment outcomes.

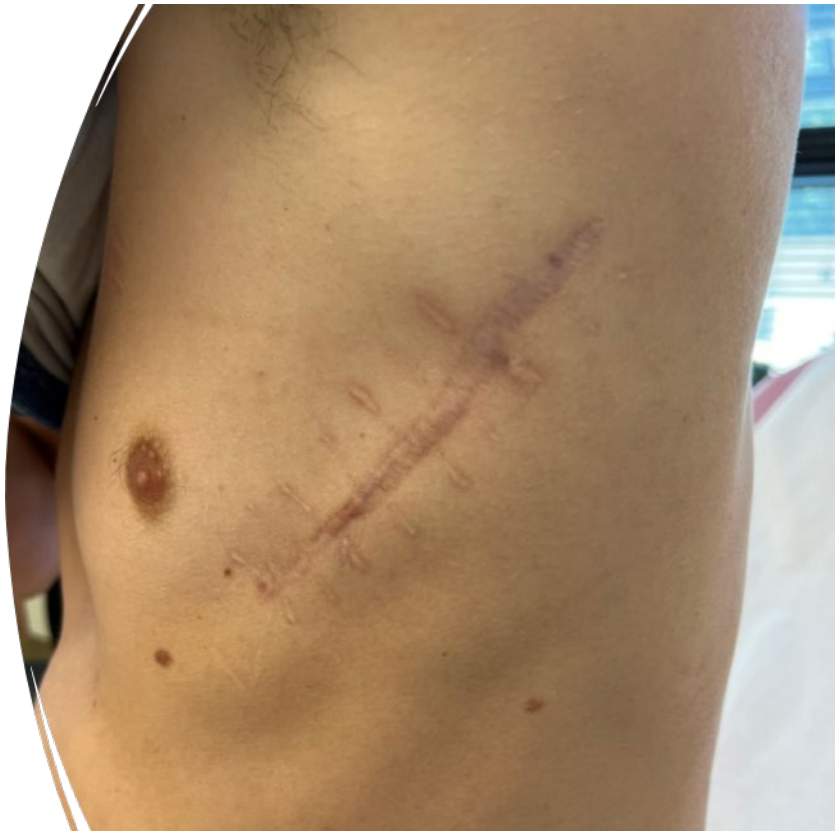
Past Medical History

- 2012: Diagnosed with MDR-TB after returning from Russia
- Placed on a MDR regimen containing Kanamycin x 2 years
- Treatment included a lobectomy, right upper lobe in 2013



History of Present Illness

- July 2021: Patient's tuberculosis relapses
- **9/28/21: Bedaquiline, Levofloxacin, Linezolid, Delamanid, Cycloserine**
- September 2021: Surgery of the left upper lobe
- 12/28/21: MTB resistant to: Isoniazid, Rifampin, Pyrazinamide
- **01/05/22: Bedaquiline, Levofloxacin, Linezolid, Clofazimine, Cycloserine**
- **01/21/22: Bedaquiline, Clofazimine, Cycloserine, Delamanid**
- **02/01/22: Bedaquiline, Moxifloxacin, Linezolid, Clofazimine**



Bacteriology

Date	Smear	NAAT	Culture
12-29-21	Negative	Not done	MTB
01-05-22	Positive	Not done	Not done
02-01-22	Negative	Not done	MTB
06-28-22	Negative	Not done	MTB
08-02-22	Negative		Not done
09-07-22	Negative	Negative	Negative
09-08-22	Negative		MTB
10-11-22	Negative		MTB
10-24-22	Negative		Pending
11-14-22	Negative		Pending

Current regimen: Bedaquiline 200 mg TIW, Moxifloxacin 400 mg QD, Linezolid 600 mg QD, Clofazimine 100 mg QD

Laboratory Findings

CDC MDDR: [Resistant]

- Rifampin: (rpoB His526Asn, Ile572Met)
- Isoniazid: (katG Ser315Thr)
- Pyrazinamide: (pncA Gly108Glu)

JHU (Parrish Lab)

- Bedaquiline: 0.5
- Linezolid: 1.0 •
- Pretomanid: 0.25 •
- Moxifloxacin: 0.12
- Isoniazid: 1.6
- Rifampin: >4
- Ethionamide: 0.5
- Clofazimine: 0.5

FL MDDR [Resistant]

- Rifampin: (rpoB His 526Asn, Ile491Mat)
- Isoniazid: (katG Ser 315Thr)
- Pyrazinamide: (pncA Gln497Arg)
- No mutations for:
  - gyrA
  - atpE
- MIC:
  - Bedaquiline: 1.0
  - Clofazimine: 2

Wadsworth (pending)

Principles of Drug-resistant TB (DR-TB) Treatment Cont'd

- Consultation should be requested with a TB expert when there is suspicion of or confirmation of DR-TB
- Molecular DSTs should be obtained for rapid detection of mutations associated with resistance
- When rifampin resistance is detected (such as by Gene Xpert), additional DST should be performed
- Regimens should include only drugs to which the patient's M. tuberculosis isolate has documented or high likelihood of susceptibility
- Drugs known to be ineffective based on in vitro growth-based or molecular resistance should NOT be used.

Principles of Drug-resistant TB (DR-TB) Treatment Cont'd (2)

- Treatment response should be monitored clinically, radiographically, and bacteriologically, with cultures obtained at least monthly for pulmonary TB
- When cultures remain positive after 3 months of treatment, susceptibility tests for drugs should be repeated
- Weight and other measures of clinical response should be recorded monthly
- Patients should be educated and asked about adverse effects at each visit. Adverse effects should be investigated and ameliorated
- Patient-centered strategies and interventions should be used to minimize barriers to treatment.

Progress on the Multidrug-resistant (MDR) TB Frontier

- Availability of novel drugs allows potent and better-tolerated MDR-TB treatment regimens to minimize injectable use
- In 2013, CDC issued guidance on the use of bedaquiline
- In 2014, delamanid received its first global approval, accessible in the U.S. via a compassionate use program
- During this time, duration for MDR TB treatment remained 18-24 months
- In 2019, STREAM trial results published, supporting a 9-month regimen*
- In 2019, CDC/ATS/ERS/IDSA issued first stand-alone U.S. MDR-TB treatment guidelines.

* 4 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol

Mase S, et al. *MMWR* 2013; 62(9): 1-12; Lardizabal AA, et al. *MMWR* 2018; 67(35):996-7; A.J. Nunn, et al. *N Engl J Med* 2019;380:1201-13
P. Nahid et al. *Am J Respir Crit Care Med* Vol 200, Iss 10, pp e93–e142, Nov 15, 2019

U.S. FDA Approves Novel Regimen for Highly Drug-Resistant Forms of TB, 2019

- Pretomanid developed by the non-profit TB Alliance
- Approved under the LPAD pathway for the treatment of XDR TB or treatment-intolerant/ non-responsive MDR TB
- Approved as part of a regimen known as BPaL (bedaquiline + pretomanid + linezolid)
- 3-drug, all-oral, 6-month regimen
- Studied in the Nix-TB clinical trial.

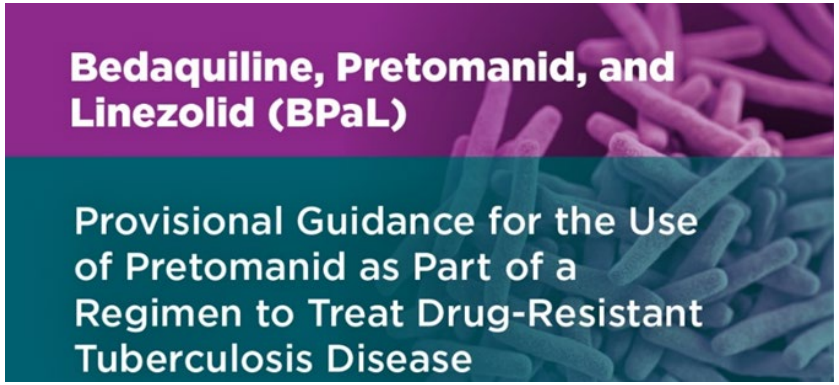
Courtesy of Dr. Francesca Conradie

LPAD = Limited Population Pathway for Antibacterial and Antifungal Drugs
XDR TB = resistant to INH, RIF, at least one fluoroquinolone, and at least one of amikacin, capreomycin, or kanamycin
MDR TB = resistant to at least isoniazid (INH) and rifampin (RIF)

CDC Provisional Guidance, February 2022

- Any consideration of initiation of the BPaL regimen for a TB patient should be reported promptly to the local and state TB public health authorities
- A physician with expertise in drug-resistant TB treatment should be involved in the patient's treatment plan.
- Providers should ensure the ability to monitor for safety and adherence prior to initiation of the BPaL regimen.

[CDC: Bedaquiline, Pretomanid, and Linezolid (BPaL) (https://www.cdc.gov/tb/topic/drtb/bpal/)](https://www.cdc.gov/tb/topic/drtb/bpal/)



Resources

- **Ukraine Clinical Guidance** (https://www.health.state.mn.us/communities/rih/about/ukrainian.html)
- **National TB Controllers Association (NTCA)** (find your local TB program) (https://www.tbcontrollers.org/community/statecityterritory/)
- **Ukrainian and Russian TB-related translated materials, videos:**
  - **Ukranian** (https://findtbresources.cdc.gov/search?topic=&format=&audience=&language=13271&max_rows=20)
  - **Russian** (https://findtbresources.cdc.gov/search?topic=&format=&audience=&language=1798&max_rows=20)
- **CDC TB Centers of Excellence consultations** (https://www.cdc.gov/tb/education/tb_coe/default.htm)
- **CDC TB Guidelines** (https://www.cdc.gov/tb/publications/guidelines/)
- **CDC Core Curriculum on Tuberculosis: What the Clinician Should Know** (https://www.cdc.gov/tb/education/corecurr/index.htm)

Questions?

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- Upcoming trainings (ECHO trainings, Ukrainian Health) at [Center of Excellence in Newcomer Health: Webinars (www.health.state.mn.us/communities/rih/about/coe.html#webinar)](www.health.state.mn.us/communities/rih/about/coe.html#webinar)

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