CDC U.S. TB Clinical Guidelines Update, 2022

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Drug Susceptible TB

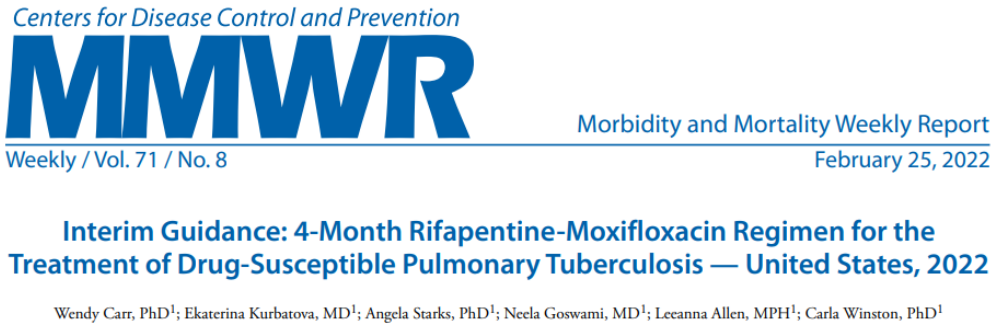
Background: CDC TB Trials Consortium (TBTC) Study 31 NIH AIDS Clinical Trials Group (ACTG) 5349

- Study 31/A5349 was an international, open label, phase 3 noninferiority clinical trial
- 2,516 AFB smear or Xpert MTB positive pulmonary TB participants were randomized at 34 clinical sites in 13 countries
- 4-month daily treatment regimen with high-dose rifapentine and moxifloxacin is as effective as (noninferior to) a standard daily 6-month regimen in treating drug-susceptible TB
- Safety data: no difference between arms in grade 3 or higher adverse events during study treatment

Dorman SE, et al. *N Engl J Med*. 2021 May 6;384(18):1705-1718

CDC Interim Guidance Recommendation

- Recommends the 4-month rifapentine-moxifloxacin regimen as an option for treating these patients:
  - 12 years and older
  - With body weight at or above 40 kg
  - With pulmonary TB caused by organisms not known or suspected to be drug-resistant
  - AND who have no contraindications to this regimen
- Intended to supplement 2016 ATS/CDC/IDSA TB Treatment Guidelines



https://www.cdc.gov/tb/publications/guidelines/treatment.htm

Nahid P, et al. *Clin Infect Dis*. 2016 Oct 1;63(7):e147-e195.

CDC Interim Guidance - Considerations

The 4-month regimen was not studied in and CDC does not recommend this regimen for the following patient groups:

- Body weight less than 40 kg
- Age less than 12 years old
- Pregnant or breastfeeding
- Most types of suspected or documented extrapulmonary TB
- History of prolonged QT syndrome or concurrent use of one or more QT-prolonging medications (in addition to moxifloxacin)
- Receiving medications with known clinically relevant drug-drug interactions with RPT, MOX, INH or PZA
- Baseline *M. tuberculosis* isolate known or suspected to be resistant to INH, PZA, RIF, or fluoroquinolones

https://www.cdc.gov/tb/publications/guidelines/treatment.htm

CDC Interim Guidance Recommendation

- Treatment consists of
  - Intensive phase composed of 8 weeks of daily treatment with rifapentine (RPT), isoniazid (INH), pyrazinamide (PZA), and moxifloxacin (MOX)
  - Continuation phase of 9 weeks of daily treatment with RPT and INH and MOX
- Anti-TB drugs should be administered once daily **with food**, 7 days per week for a total of 119 treatment doses
  - At least 5 of 7 weekly doses should be administered under direct observation
  - Intensive phase doses (56) should be administered within 70 days from treatment initiation
  - Continuation phase doses (63) should be administered within 84 days from intensive phase completion

https://www.cdc.gov/tb/publications/guidelines/treatment.htm

Evaluations - Microbiology

- A respiratory specimen for acid-fast bacilli smear microscopy and culture should be obtained
- Sputum should be collected for bacteriology at least monthly during treatment until two consecutive specimens are negative on culture
- Baseline molecular drug susceptibility testing for rapid identification of mutations associated with resistance to at least RIF, INH, PZA, and fluoroquinolones (FQ) is advisable
- Phenotypic DST should follow with a panel to include at least RIF (as surrogate for RPT), INH, PZA, and MOX as the preferred fluoroquinolone

https://www.cdc.gov/tb/publications/guidelines/treatment.htm

Drug Resistant TB

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 to 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)
- The 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)

BPaL Clinical Trial (Nix-TB)

- 109 patients enrolled, treated for 26 weeks
  - 71 (65%) XDR TB, 92 (84% cavitary)
  - 56 (51%) HIV infected
  - 90% had favorable outcomes
  - All had adverse events; 57% grade 3 or higher

- Study Regimen
  - Pretomanid 200mg daily
  - Bedaquiline 400mg daily 2 wks, then 200mg 3x/wk
  - Linezolid 1200mg daily
    - Only 15% completed 26 weeks at 1200mg w/o interruptions or dose reductions

Conradie F, et al. *N Engl J Med* 2020;382(10):893–902

CDC Guidance for Novel Agents

FDA = Food and Drug Administration

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Linezolid Dose in the BPaL Regimen

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Supplement_1
November 2021

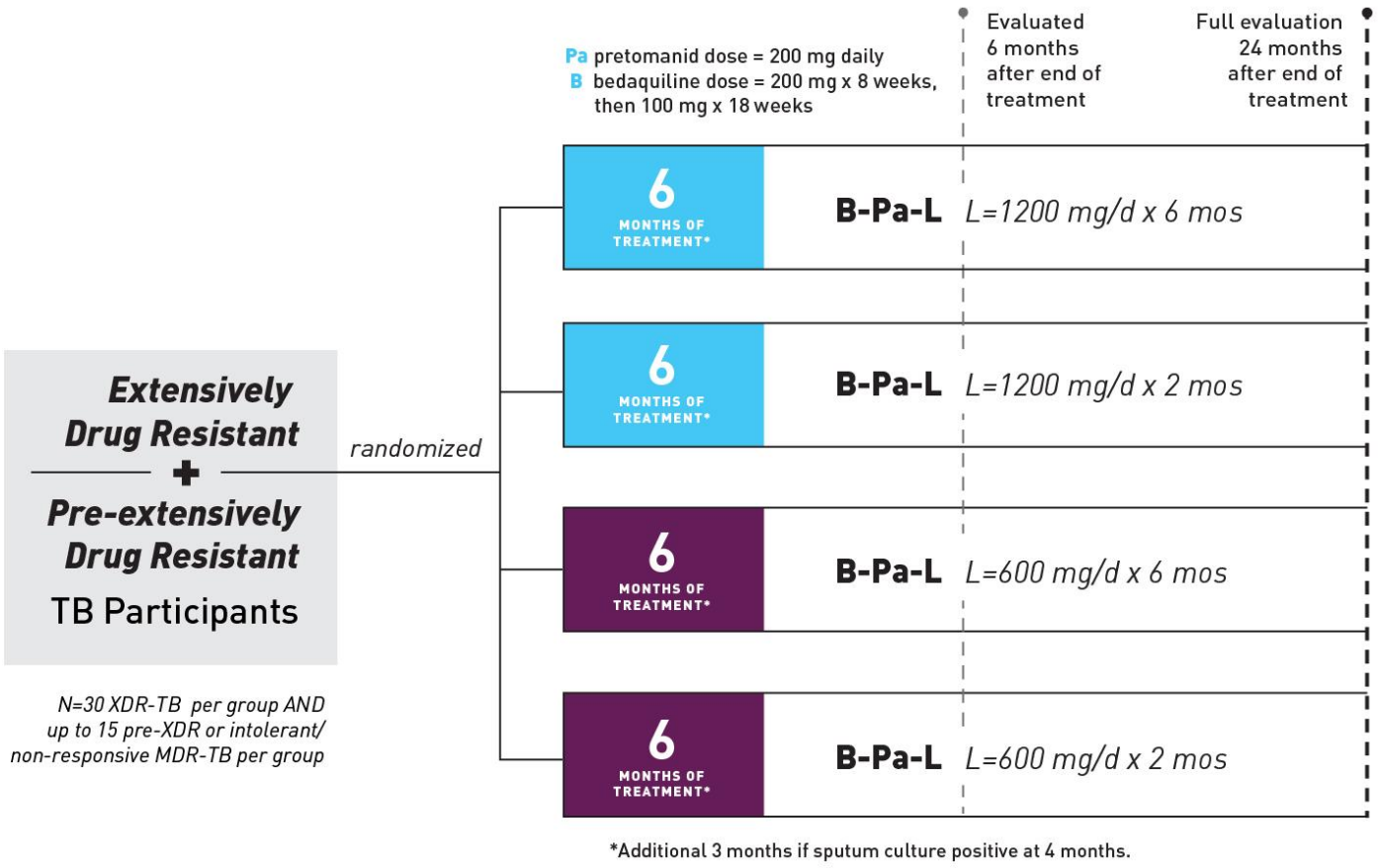
1400. Pretomanid in the Treatment of Patients with Tuberculosis in the United States: the Bedaquiline, Pretomanid and Linezolid (BPaL) Accelerated Monitoring (BAM) Project

Neela Goswami, MD, MPH, Lakshmi Praveena Peddareddy, MD, John Jereb, MD, Angel Colon Semidey, MD, Elaine Darnall, RN, Patricia Macias, MD, Supriya Jasuja, MD, MPH, Karen Landers, MD, Shom Dasgupta, MD, Margaret Oxtoby, MD, Christopher Spitters, MD, MPH, Lana Dov, RN, Masa Narita, MD, Malini DaSilva, MD, MPH, Tracina Cropper, PHA, Cricket Gullickson, BS, David Ashkin, MD, Connie Haley, MD, MPH

- 94% (16/17) patients received less than initial 1200 mg linezolid daily (most 600 mg daily)
- 88% (15/17) patients had linezolid drug levels with intention of minimizing adverse events
- At 12 months after BPaL initiation, all patients had completed treatment, without TB recurrences or deaths

ZeNix: Linezolid Optimization Trial, presented July 2021

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



- 181 participants, 20% HIV+
- A high success rate at the primary endpoint similar to Nix-TB, was observed:
  93% in 1200L6M
  89% in 1200L2M
  91% in 600L6M
  84% in 600L2M
- Fewer adverse events, treatment interruptions, discontinuations in the 600L6M and 600L2M

https://www.tballiance.org/portfolio/trial/11883

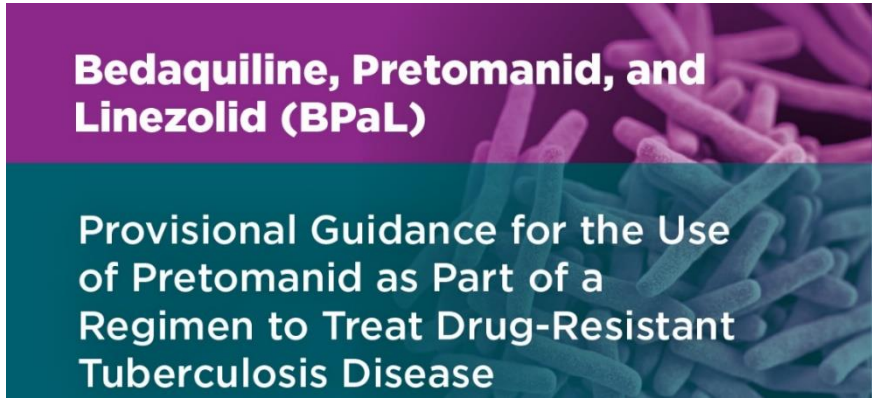
TB PRACTECAL Trial Results, presented October 2021

- Multi-arm, multistage, open label, randomized controlled trial, enrolled patients with any multidrug-resistant TB
- BPaL + moxifloxacin vs. standard of care
- Linezolid dose = 600mg daily for 16 weeks then 300mg daily (or 600mg 3 times per week) for remaining 8 weeks
- A data and safety monitoring board recommended stopping the trial at interim analysis
- Standard-of-care control arm had higher percentage of study participants with an unfavorable outcome than BPaL + moxifloxacin arm
- Difference in the proportion of unfavorable outcomes driven by a higher rate of treatment discontinuations in the control arm

52nd IUATLD Abstract Book TB PRACTECAL: trial results and next steps. S31 SP-34. https://clinicaltrials.gov/ct2/show/NCT02589782

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



https://www.cdc.gov/tb/topic/drtb/bpal/

Patient Eligibility for the BPaL Regimen

- Patients with pulmonary XDR TB, pre-XDR TB or MDR TB who are treatment intolerant or nonresponsive
- Rapid molecular testing for resistance in patients being evaluated for drug-resistant TB should be obtained **with confirmatory sequencing;** phenotypic results should also be obtained
- Management decisions in the care of patients … may be modified based on what is clinically indicated by unique patient circumstances

https://www.cdc.gov/tb/topic/drtb/bpal/

Additional Sections in CDC Provisional Guidance

- Candidates for the BPaL Regimen
- Dosing and Administration
  - FDA approved linezolid starting at 1200mg orally per day, but given toxicities in Nix TB trial and preliminary results from the ZeNix trial, initiating BPaL with **a reduced dose of linezolid of 600 mg daily may be considered**
  - Pretomanid is not recommended for use as a single drug or in ad hoc combinations
- Laboratory Considerations
- Precautions and Adverse Event Monitoring during BPaL Treatment
- Follow-up after BPaL Treatment Completion
- Reporting Patients Treated with BPaL

https://www.cdc.gov/tb/topic/drtb/bpal/

Summary

- The 4-month rifapentine-moxifloxacin regimen is a treatment option for patients 12 years and older with drug-susceptible pulmonary TB
- The 6-month bedaquiline-pretomanid-linezolid regimen is a treatment option for some patients with multi-drug resistant TB
- Additional studies are needed to understand the pharmacokinetics and efficacy of these regimens in patients for whom the regimen is not currently recommended
- Clinicians should carefully review a patient's clinical history, social determinants of health, risk factors for adverse drug reactions, current evidence, and be in close contact with local and state TB public health authorities in making decisions on best regimens for their patients

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QUESTIONS?

For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.