Disclosures

• Medical consultant, TB Program
  Indiana Department of Health
• Owner of a 38 consecutive streak of negative TB screening tests!
• Genuine Iowa farm boy
• Grandfather of Avery Lynn
Objectives

• Review TB impact on world health

• Overview of LTBI treatments
  o New regimens and supply challenges

• Overview of TB treatments
  o First new regimens in decades have arrived
Global/U.S. TB Burden, 2020

- An estimated 10 million new TB disease cases
- 1.5 million deaths due to TB disease (1.2, ’19)
  - With 0.21 million deaths from TB among people living with HIV (0.20 last year)
- TB incidence is falling at about 2% per year
- Estimated up to 13 million persons in U.S. TB infected
- Incidence rate of U.S. cases, 2.2/100,000, total of 7,174

CDC: https://www.cdc.gov/tb/statistics/default.htm
Most Immediately Obvious Impact of COVID-related Disruptions

Big global drop in number of newly diagnosed/reported TB cases

- 7.1 million in 2019
- 5.8 million in 2020

18% drop, 2019-2020
Global Number of TB Deaths Increased in 2020
first year-on-year increase since 2005, back to the level of 2017
TB second only to COVID-19 as cause of death from single infectious agent

- 1.5 million in 2020, up from 1.4 million in 2019
- 9% reduction vs. 2015, one-quarter of the way to the 2020 milestone
- 214,000, small increase from 209,000 in 2019
Global Decline in TB Incidence Slowed in 2020

1.9% overall drop in 2019-2020, down from 2.3% 2018-2019

11% since 2015, only about halfway to 2020 milestone of 20%
Estimated World TB Incidence Rates, 2020
TB Determinants

Estimates of TB cases attributable to 5 risk factors in 2020

- Diabetes
- Smoking
- Alcohol use disorders
- HIV infection
- Undernourishment
Much Worse Impacts Forecast in 2021 and 2022

a) TB deaths

Impact of COVID-related disruptions on TB deaths likely to peak in 2021, could persist for much longer
Much Worse Impacts Forecast in 2021 and 2022

b) TB incidence

Impact of COVID-related disruptions on TB incidence likely to peak in 2022, could persist for much longer
8 Countries, Two-thirds of Global Cases in 2020
86% in 30 high TB burden countries
Treatment Outcomes

- People newly diagnosed with TB (new and relapse cases): 86% (2012-2019)
- People diagnosed with rifampicin-resistant/MDR-TB: 50% (2012-2015) and 59% (2016-2019)
~ 30% of heavily exposed persons will become infected.

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X = treatment of LTBI
LTBI Treatment Regimens

• An optimal LTBI treatment is minimally toxic and as short as possible to enhance completion rates.

• Preferred regimens:
  o 3 months once weekly isoniazid plus rifapentine (3HP)
  o 4 months daily rifampin alone (4R)
  o 3 months daily isoniazid plus rifampin (3HR)

• Alternative regimen:
  o 6–9 months of isoniazid monotherapy


TB Disease Treatment Regimens

For a number of years, the main treatment regimen for drug-susceptible TB disease has been a 6- to 9-month RIPE regimen consisting of:

- Rifampin (RIF),
- Isoniazid (INH),
- Pyrazinamide (PZA), and
- Ethambutol (EMB)

RIPE regimens for treating TB disease traditionally feature:

- Intensive phase of 4 drugs for 2 months
- Followed by a continuation phase of 2 or more drugs for 4 or 7 months
- Total of 6 to 9 months for treatment depending on severity and response
## RIPE

### TB Disease Treatment Regimen Table

<table>
<thead>
<tr>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Duration</td>
</tr>
<tr>
<td>INH RIF PZA EMB</td>
<td>8 weeks</td>
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<tr>
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</table>

**Do Not Use!!!** - Increased failure rate with twice weekly therapy of TB disease

**Abbreviations:** INH = isoniazid; RIF = rifampin; PZA = pyrazinamide; EMB = ethambutol; HIV = human immunodeficiency virus

**Source:** [https://www.cdc.gov/tb/topic/treatment/tbdisease.htm](https://www.cdc.gov/tb/topic/treatment/tbdisease.htm)
The New Frontier! Study 31 Background

• Reducing the duration for treating TB has been a longstanding goal:
  o Shorter regimens cure patients faster and have the potential to reduce treatment costs, improve patient quality of life and increase completion of therapy.

• Key study question:
  o Does high-dose daily rifapentine, with or without moxifloxacin, allow treatment shortening from 6 to 4 months for drug-susceptible TB?

Adapted from TB Centers of Excellence and the CDC presentation: Considerations for the New Four-Month Rifapentine-Moxifloxacin Regimen for Drug-Susceptible TB in the U.S. September 21, 2021.
Adapted from TB Centers of Excellence and the CDC presentation: Considerations for the New Four-Month Rifapentine-Moxifloxacin Regimen for Drug-Susceptible TB in the U.S. September 21, 2021.
Study 31 Results

On **May 5, 2021**, CDC’s Tuberculosis Trials Consortium and the National Institutes of Health-sponsored AIDS Clinical Trials Group published results from the randomized controlled trial—Study 31—in the *New England Journal of Medicine*.

- The study results indicated that a 4-month regimen containing rifapentine (RPT), moxifloxacin (MOX), isoniazid (INH) and pyrazinamide (PZA) **was as effective** as the standard 6-month RIPE regimen for TB treatment.

**This is the first new treatment regimen for drug-susceptible TB disease in almost 40 years!**
CDC Interim Guidance

In February 2022, the CDC issued interim guidance on the use of the 4-month Rifapentine-Moxifloxacin regimen for the treatment of drug-susceptible pulmonary TB.
The 4-month TB treatment regimen consists of:

- High-dose daily rifapentine (RPT) with
- Moxifloxacin (MOX),
- Isoniazid (INH), and
- Pyrazinamide (PZA)

The 4-month rifapentine-moxifloxacin regimen has an intensive phase of 4 drugs for 2 months, followed by a continuation phase of 3 drugs for 2 months and 1 week (total 17 weeks for treatment).
## Four-month TB Treatment Regimen Table – Study 31

<table>
<thead>
<tr>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Total Doses</th>
<th>Comments</th>
<th>Regimen Effectiveness</th>
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</thead>
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<tr>
<td><strong>Drugs</strong></td>
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<td></td>
<td><strong>Comments</strong></td>
<td><strong>Regimen Effectiveness</strong></td>
</tr>
<tr>
<td>RPT  MOX INH PZA</td>
<td>RPT MOX INH</td>
<td>119</td>
<td></td>
<td>The 4-month rifapentine-moxifloxacin TB treatment regimen is as effective as (noninferior to) the standard daily 6-month regimen in curing drug-susceptible TB disease.</td>
</tr>
</tbody>
</table>

**Abbreviations:** RPT = rifapentine; MOX = Moxifloxacin; INH = isoniazid; PZA = pyrazinamide

Source: [https://www.cdc.gov/tb/topic/treatment/tbdisease.htm](https://www.cdc.gov/tb/topic/treatment/tbdisease.htm)
Considerations for Specific Groups of People with TB Disease

CDC recommends the 4-month rifapentine-moxifloxacin regimen as an option for treating pulmonary TB disease caused by organisms that are not known or suspected to be drug-resistant for:

- People who are 12 years and older
- People with a body weight at or above 40 kg
- People with HIV with CD4 counts at or above 100 cells/microliter (μL), who are receiving or planning to start efavirenz as part of their ART regimen in the absence of any other known drug-drug interactions between antit-TB and anti-HIV meds
- People who have no contraindications to this regimen
- People with a negative sputum culture who in the judgment of the clinician likely represent paucibacillary or low mycobacterial burden TB disease unless the person is included in one of the non-recommended groups
Current Challenges with Supply of Rifampin

• There are ongoing issues with the supply of Rifampin:
  o IDOH/Purdue Pharmacy have obtained some supply from the Emergency Stockpile and from a neighboring jurisdiction for patients who were on therapy with Rifampin as part of their TB treatment regimen (at the time the supply issue arose) to continue to remain on Rifampin.
  o **Rifabutin should be used in place of Rifampin in the 4-drug regimen (RIPE) for new patients with TB disease.**
  o Any patients needing therapy for **LTBI** should be prescribed the **3HP** regimen containing Isoniazid and Rifapentine or **mono therapy with Isoniazid**.
• Rifabutin is not recommended to be used to treat LTBI due to the Rifampin shortage at this time.
Thank You!

Questions?

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<td>Drugs</td>
<td>Duration*</td>
<td>Frequency</td>
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<td>RPT</td>
<td>8 weeks</td>
<td>7 days/week for 56 doses</td>
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<td>MOX</td>
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<tr>
<td>RPT</td>
<td>9 weeks</td>
<td>7 days/week for 63 doses</td>
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Abbreviations: RPT = rifapentine; MOX = Moxifloxacin; INH = isoniazid; PZA = pyrazinamide

*Must be administered completely within 70 days from treatment initiation. If this target is not met, the patient should be considered to have interrupted therapy and should be managed as described in [TB treatment guidelines](https://www.cdc.gov/tb/topic/treatment/tbdisease.htm).

*At least 5 of 7 weekly doses should be administered under direct observation. Directly observed therapy means that a healthcare worker watches the TB patient swallow each dose of the prescribed drugs. The healthcare worker should ask the patient how he or she is feeling, check the medications before they are taken, ask the patient if he or she is experiencing any side effects, and answer any questions the patient may have. Where local policies, allow, eDOT has been shown to be an acceptable alternative to traditional DOT. Contact your [state or local TB control office](https://www.cdc.gov/tb/topic/treatment/tbdisease.htm) for more information about eDOT policies and procedures.

*Must be administered within 84 days from intensive phase completion. If this target is not met, the patient should be considered to have interrupted therapy and should be managed as described in [TB treatment guidelines](https://www.cdc.gov/tb/topic/treatment/tbdisease.htm).

Pyridoxine (vitamin B6), 25–50 mg/day, should be given with isoniazid to all patients.

*Drugs are administered with food once a day, every day of the week.
CDC recommends that clinical consultation be obtained to determine if the 4-month rifapentine-moxifloxacin regimen is an acceptable treatment option for:

- People at increased risk of Mycobacterium tuberculosis (M. tuberculosis) resistance to any drug in the 4-month regimen
- People who received more than 5 doses of TB treatment in the prior 6 months
- People who received more than 5 doses of latent TB infection treatment in the prior 6 months
- People who received more than 5 doses of treatment with any one or more of the following drugs for any reason (e.g., urinary tract infection, pneumonia) in the prior 30 days:
  - Isoniazid (INH), rifampin (RIF), rifabutin, rifapentine (RPT), pyrazinamide (PZA), or any fluoroquinolone
- People who have serum or plasma alanine aminotransferase or aspartate aminotransferase more than 3 times the upper limit of normal or total bilirubin more than 2.5 times the upper limit of normal, or with preexisting advanced liver disease
- People who have renal insufficiency or end-stage renal disease, or
  - Serum or plasma creatinine level more than 2 times the upper limit of normal, or
  - Plasma potassium level less than 3.5 milliequivalents per liter (mEq/L)
- People who have types of extrapulmonary TB that are likely to be paucibacillary, not pose a substantial risk of death or disability, and not require prolonged treatment (i.e., pleural or lymph node TB)
- People with a sputum specimen that is unable to be submitted for any M. tuberculosis resistance testing prior to initiating the 4-month treatment regimen
Considerations for Specific Groups of People with TB Disease, continued

**CDC does not recommend** the 4-month rifapentine-moxifloxacin regimen for:
- People who are younger than 12 years old
- People with a body weight below 40 kilograms (kg)
- People who are pregnant or breastfeeding
- People who have most types of suspected or documented extrapulmonary TB
- People who have a history of prolonged QT syndrome or concurrent use of one or more QT-prolonging medications (in addition to moxifloxacin (MOX))
- People who are receiving medications with known clinically relevant drug-drug interactions with INH, RPT, PZA, or MOX
- People with a baseline *M. tuberculosis* isolate known or suspected to be resistant to RIF, INH, PZA, or any fluoroquinolone
References

• https://www.cdc.gov/tb/topic/treatment/tbdisease.htm Accessed March 2022
• https://www.cdc.gov/tb/topic/treatment/ltbi.htm Accessed March 2022
For more information

Mobile app – country-specific as well as regional and global data for all key indicators

https://www.who.int/publications/i/item/9789240037021