LATENT TB INFECTION (LTBI) TREATMENT GUIDELINES

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Disclosures

• Medical Consultant, TB Control Program
  Indiana Department of Health

• Have personally endured over 40 Tuberculin skin tests
  (either negative or misinterpreted...)

Major thanks to the Indiana Department of Health TB Program for updated statistics and amazing support throughout the year!
Objectives

- Review TB impact on world health
- Contrast TB impact on U.S. and Indiana
- Compare TB disease to latent TB infection (LTBI)
- Overview of LTBI treatments
Global/U.S. TB Burden, 2019

- An estimated 10.0 million new TB disease cases
- 1.2 million deaths due to TB disease (1.2, ‘18)
  - With 0.20 million deaths from TB among people living with HIV (0.25 last year, 69% drop since 2000)
- The rate of decline remains low at 2.3% per year (2.0%, ‘18)
  - Not fast enough decline to reach first milestone of End TB Strategy
- Estimated up to 13 million persons in U.S. TB infected
- Incidence rate of U.S. cases, 2.7/100,000, total of 8,916

TB Epidemiology, Worldwide by regions

- Africa and South-East Asia have the highest TB incidence rates
- Rates shown are cases per 100,000 population

<table>
<thead>
<tr>
<th>Region</th>
<th>2019 Total TB Incidence</th>
<th>2018 Total TB Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High TB burden countries</strong></td>
<td>177 (156–198)</td>
<td>180 (159–202)</td>
</tr>
<tr>
<td>Africa</td>
<td>226 (201–252)</td>
<td>231 (206–257)</td>
</tr>
<tr>
<td>The Americas</td>
<td>29 (27–31)</td>
<td>29 (27–31)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>114 (90–141)</td>
<td>115 (91–142)</td>
</tr>
<tr>
<td>Europe</td>
<td>26 (23–30)</td>
<td>28 (24–32)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>217 (173–266)</td>
<td>220 (175–271)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>93 (77–111)</td>
<td>96 (79–114)</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>130 (116–143)</td>
<td>132 (118–146)</td>
</tr>
</tbody>
</table>

Source: WHO Global Tuberculosis Reports 2020 and 2019
TB Epidemiology, drug-resistant strains

- During 2019, close to half a million people developed rifampicin-resistant TB of which 78% had multi-drug resistant TB
  - Recall that MDR are by definition resistant to INH and rifampin
- Three countries (China, India, and Russian Federation) account for 49% of the global burden
  - Need to be aware of the country of origin, work, or travel to increase suspicion of resistance

Source: WHO Global Tuberculosis Reports 2020
Reported Tuberculosis (TB) Cases United States, 1982–2016*

No. of cases

Year

*As of June 21, 2017.
Factors Contributing to the Increase in TB Morbidity: 1985-1992

• Deterioration of the TB public health infrastructure
• HIV/AIDS epidemic
• Immigration from countries where TB is common
• Transmission of TB in congregate settings
  ◦ Homeless shelters, prisons, etc.
Tuberculosis Case Rates by Reporting Area
United States, 2019

TB Incidence Rate (per 100,000 persons)

- 7.9
- 4.0
- 3.9
- 2.9
- 2.8

*Includes NYC

NJ (3.5)
MD (3.5)
District of Columbia (3.4)

0 - 1.4
1.4 to 2.7
> 2.7

TB Incidence Rate (per 100,000 persons)
Countries of Birth Among Non-U.S.-Born Persons Reported with TB, United States, 2019

- Mexico: 19%
- Philippines: 12%
- India: 9%
- Vietnam: 8%
- China: 6%
- Guatemala: 4%
- Honduras: 3%
- Other countries: 39%

Percentage of TB cases among non-U.S.-born persons.
Number of Tuberculosis Cases and Incidence Rate, Indiana, 2011-2020

Indiana TB 10-Year Trend, 2011-2020

Cases = 92
Incidence Rate = 1.4/100,000

Contrast to:
U.S. – 2.7* (2.8)
Global – 130**

* Per CDC 2019 TB Data
** Per WHO Global TB Report 2020
Indiana TB Cases by County, Indiana, 2020
TB Cases by Country of Birth, Indiana, 2020

- UNITED STATES: 42.4%
- Other: 15.2%
- BURMA/MYANMAR: 7.6%
- PHILIPPINES: 5.4%
- MEXICO: 4.3%
- INDIA: 4.3%
- NIGERIA: 20.9%

N=92
Percentages of Tuberculosis Cases Estimated to be Attributed and Not Attributed to Recent Transmission, by Origin of Birth*, 2018–2019

This is why we screen and treat Latent TB Infection!

The opportunity to screen is a chance to treat TB.

* Cases with unknown origin of birth not shown (n=11).
† A TB case is designated as attributed to recent transmission if a plausible source case can be identified in a person who i) has the same M. tuberculosis genotype, ii) has an infectious form of TB disease, iii) resides within 10 miles of the TB case, iv) is 10 years of age or older, and v) was diagnosed within 2 years before the TB case.
‡Cases not attributed to recent transmission may be misclassified in children <5 years old or indeterminate in persons with a recent U.S. arrival due to limitations of the plausible-source case method.
~ 30% of heavily exposed persons will become infected

Transmission

Primary Tuberculosis

Skin-test conversion in 6 to 8 weeks

Spontaneous healing in 6 months

Latent Tuberculosis

Progression within 2 years, 5%

"Reactivation" Tuberculosis

Progression with concurrent HIV infection, 10% each year

~ 30% of heavily exposed persons will become infected

Properly treated LTBI can prevent development of active tuberculosis disease.

Progression after 2 years, 5%
Screening for TB Infection

• Who is at risk / Who do we screen?
• How do we screen?
  • Tuberculin Skin Test (TST) or Quantiferon Release Assay
  • Both test for past exposure to TB
  • Both tests are only ~ 75% sensitive (25% false negative)
  • Neither test differentiates between active or latent ds.
• What evaluations are done with a positive screen?
  • History and physical exam
  • CXR
  • Sputum or tissue samples if suspicion of active disease
TB Cases by Site of Disease, Indiana, 2020

Extrapulmonary sites include:

- Lymphatic (38.1%)
- Bone and/or joint (23.8%)
- Eye and/or ear (9.5%)
- Genitourinary (9.5%)
- Peritoneal (4.8%)
- Breast (4.8%)
- Colon (4.8%)
- Spinal Cord (4.8%)
Latent TB Infection (LTBI)

- LTBI is the presence of *M. tuberculosis* infection *without* symptoms or radiographic evidence of TB disease (active TB).
- “Treatment of latent TB infection” replaces the terms “preventive” and “chemoprophylaxis”.
- Targeted tuberculosis testing is key to detect LTBI:
  - Groups at the *highest* risk for TB
  - “Decision to test is a decision to treat”
Persons at Higher Risk for Exposure to or Infection with TB

- Close contacts of known or suspected TB
- Persons from high TB endemic areas
- Residents and employees of high-risk congregate settings
- Health care personnel (HCPs)
  - High-risk clients
Persons at Higher Risk for Exposure to or Infection with TB (continued)

- Medically underserved, low-income populations
- High-risk ethnic minority populations
- Children exposed to high-risk adults
  - Under age 4, poorly developed cellular immunity
  - More rapid rate of progression and severe disease in young
- Persons who inject illicit drugs
LTBI Treatment Regimens

• An optimal LTBI treatment is minimally toxic and as short as possible to enhance completion rates.
• Until recently, 6 – 9 months of INH monotherapy was recommended.
• Recommendations now give shorter alternatives:
  o 3 months once weekly INH plus rifapentine (3HP)
  o 4 months daily rifampin alone (4R)
  o 3 months daily INH plus rifampin (3HR)

LTBI is REPORTABLE to the Indiana Department of Health!

# LTBI Treatment Regimens

## Latent Tuberculosis Infection Treatment Regimens

Treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). CDC and the National Tuberculosis Controllers Association preferentially recommend short-course, rifampin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.

Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), existing medical conditions (e.g., HIV*), and potential for drug-drug interactions.

https://www.cdc.gov/mmwr/volumes/69/rfr6901a1.htm?_cid=rfr6901a1_w

### DRUG

#### Preferred

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DURATION</th>
<th>FREQUENCY</th>
<th>TOTAL DOSES</th>
<th>DOSE AND AGE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAXID(^1) AND RIFAPENTINE(^2) (3HP)</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
<td>Adults and children aged ≤12 yrs</td>
</tr>
<tr>
<td></td>
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<td>INH: 35 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RIF: 10-14.0 kg; 300 mg 14.1-25.0 kg; 450 mg 25.1-32.0 kg; 600 mg 32.1-49.9 kg; 750 mg ≥50.0 kg; 900 mg maximum</td>
</tr>
<tr>
<td>RIFAPENTINE(^3) (4R)</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
<td>Adults: 10 mg/kg; 600 mg maximum</td>
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<td></td>
<td></td>
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<td>Children: 15-26 mg/kg; 600 mg maximum</td>
</tr>
<tr>
<td>ISONIAXID(^1) AND RIFAPENTINE(^4) (3HR)</td>
<td>3 months</td>
<td>Daily</td>
<td>90</td>
<td>Adults: INH: 5 mg/kg; 300 mg maximum RIF: 10 mg/kg; 600 mg maximum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Children: INH: 10-20 mg/kg; 280 mg maximum RIF: 15-20 mg/kg; 600 mg maximum</td>
</tr>
</tbody>
</table>

### Alternative

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DURATION</th>
<th>FREQUENCY</th>
<th>TOTAL DOSES</th>
<th>DOSE AND AGE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAXID(^1) (6H/9H)</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
<td>Adults: 5 mg/kg; 300 mg maximum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
<td>Children: 10-20 mg/kg; 280 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 months</td>
<td>270</td>
<td>Children: 10-20 mg/kg; 280 mg maximum Twice weekly: 20-40 mg/kg; 900 mg maximum</td>
</tr>
</tbody>
</table>


**Please refer to the LTBI Treatment Regimens for a comprehensive list of regimens.**

### References

1. *Cochrane Database Syst Rev.* 2014;10:CD008299. [Link](https://www.cdc.gov/mmwr/volumes/69/rfr6901a1.htm?cid=rfr6901a1_w)
2. *Journal of the American Medical Association.* 1994;272:1443-1447. [Link](https://www.cdc.gov/mmwr/volumes/69/rfr6901a1.htm?cid=rfr6901a1_w)
5. *Am J Respir Crit Care Med.* 2016;194:67-74. [Link](https://www.cdc.gov/mmwr/volumes/69/rfr6901a1.htm?cid=rfr6901a1_w)

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Current Challenges with Supply of Rifamycins

Rifamycins – Recent FDA investigations of many classes of medications for nitrosamine contamination (potential carcinogen). Levels in rifamycins have not met the threshold for recall, but the FDA is still working with manufacturers to lower levels.

As a result, supplies have been short at times for this drug class, including:

• **Rifampin** – Still recommended part of active and LTBI regimens if you are able to identify the supply needed
Current Challenges with Supply of Rifamycins (continued)

- **Rifapentine** – FDA concerns on top of already short supplies, but if supplies can be obtained it is still recommended as part of 3HP LTBI regimen (weekly INH/Rifapentine for 3 months, 12 doses)
- Link to CDC’s Division of TB Elimination September 2020 dear colleague letter with update on Rifamycin issues
- Please contact your **regional nurse consultant** for supply updates or any additional questions!
Reporting LTBI

• LTBI is a reportable condition in the state of Indiana per State Code 410 IAC 1-2.5-111
  ◦ “All newly diagnosed cases of LTBI shall be reported to the local health officer or the department within five business days.”

• Local health departments can report LTBI cases directly in the National Electronic Disease Surveillance System (NBS)

• Providers can access a reporting form at this link.
  ◦ Completed forms can be sent directly to the applicable local health department
Reporting LTBI continued

• Questions on reporting
• Reach out to Indiana Department of Health TB Control Program
  ◦ Phone: 317-233-7434
  ◦ E-mail: tbcontrol@isdh.in.gov
Thank You!

Questions?

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References

• https://www.cdc.gov/tb/topic/treatment/ltbi.htm#:~:text=CDC%20and%20the%20National%20Tuberculosis%20Controllers%20Association%20NTCA%29,rifapentine%203HP%29%20Four%20months%20of%20daily%20rifampin%20R%29 Accessed Sept 2020

• https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w#F1_down Accessed Sept 2020