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Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

Treatment of TB Infection

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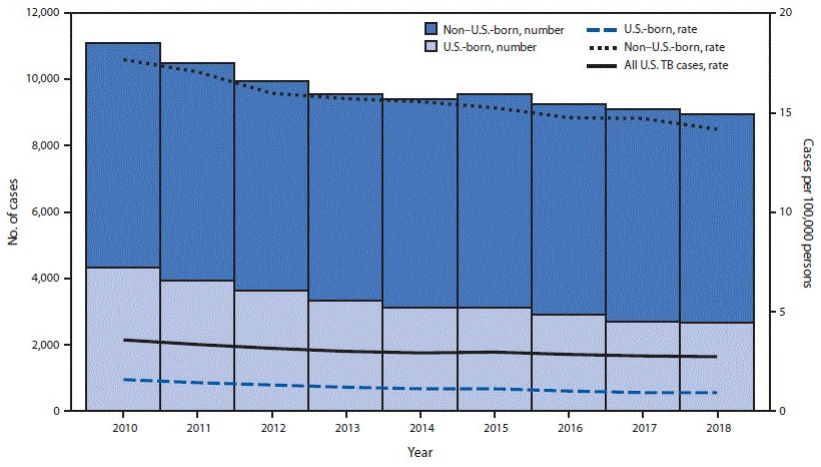
Number of tuberculosis (TB) cases and TB incidence, by national origin*,† — United States, 2010–2018



Talwar A, Tsang CA, Price SF, et al. Tuberculosis — United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68:257–262.

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Summary of TB Trends in US (2018)

- Number of cases/case rate decreased slightly in 2018
- 70% of all cases are in people born outside the US
  - 46% of these cases received diagnosis >= 10 years in US
  - Most common countries of birth include Mexico, Philippines, India, Vietnam and China
- Highest TB rates among US born – Hawaiians/PI
- HIV coinfection remains < 6%
- Though US born account for < 30% cases, 61% cases among homeless are US born
- In the US >80% cases are felt to be from reactivation

Talwar A, Tsang CA, Price SF, et al. Tuberculosis — United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68:257–262.

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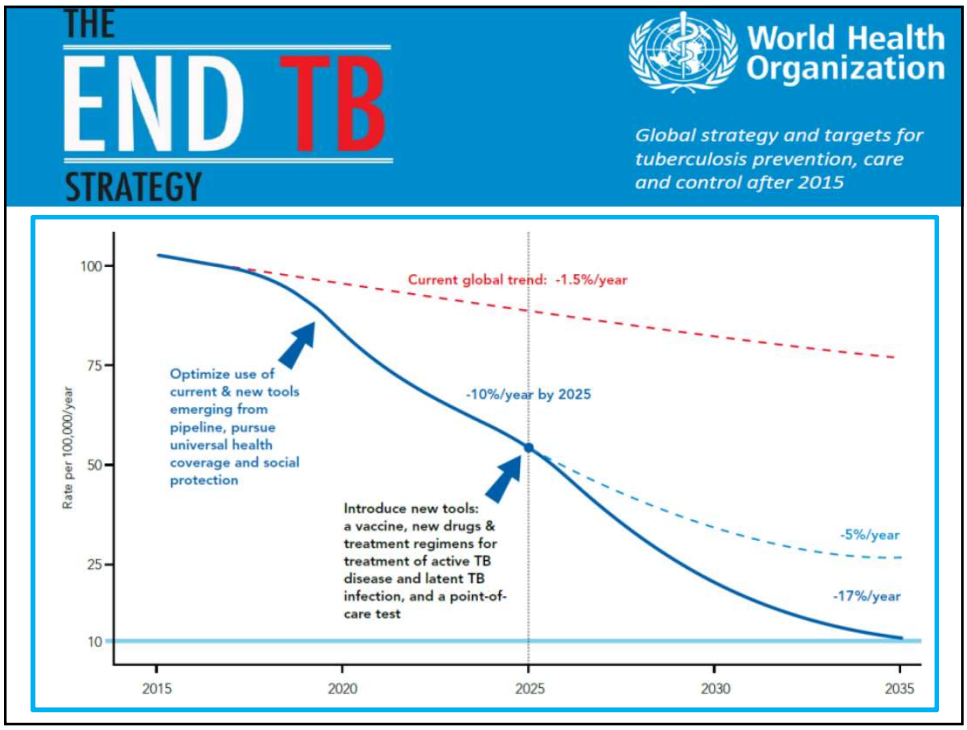
(Latent) TB Infection in the US

- Infection with *Mycobacterium tuberculosis* without manifestations of active disease
  - Asymptomatic
  - Normal or stable chest radiography
- Up to 13 million people in US infected; ~ 4.5%
- 5-10% may go on to have active TB if untreated
- ~ 70% of LTBI in foreign born individuals
- 19% of US born with LTBI treated; 10% of foreign born
- Treatment 90% effective
- No significant decline in TST or IGRA positivity over past decade

Mancuso et al, AJRCCM, 2016



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(Latent) TB Infection in the US

- A large reservoir of LTBI remains, and continues to be a barrier to TB elimination (≤ 1 case/million)
  - Preventing transmission is essential
  - Testing and treating LTBI, especially in high risk groups, must be increased if TB elimination is the goal
- Clinicians, health care agencies, community organizations, esp those serving at-risk patients, are critical to success

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LTBI Treatment Challenges

- Identification of those infected
- Lengthy treatment leading to limited adherence
- Adverse effects influencing patient and provider agreement
- Perception of risk
- Cost

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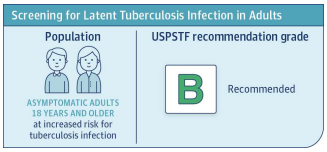
Addressing Barriers: CDC & USPSTF



Targeted testing and treatment

- CDC and USPSTF recommend testing in those at increased risk
  - USPSTF
    - Those from countries with increased TB prevalence
    - Those in high risk congregate settings
    - Consult with L/SHD regarding populations at risk
  - CDC still recommends testing
    - HCW (update forthcoming)
    - Close contacts
    - Certain medical illnesses (HIV, DM, etc.)
    - Before starting medications such as TNFα blocker

Clinicians and community organizations critical to TB elimination in these groups

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LTBI Treatment Challenges

- Identification of those infected
- Lengthy treatment leading to limited adherence
- Perception of risk (high) and benefit (low)
- Adverse effects influencing patient and provider agreement
- Cost

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Why is there a debate about treating LTBI?

Hypertension	Latent TB infection
• Asymptomatic condition	• Asymptomatic condition
• Very serious complications – Death – Major disability	• Very serious complications – Death, – Major disability – AND transmission
• Treatment is for years – Expensive medications – Potential serious side effects – Requires close monitoring and follow up	• Treatment is max 9 months – Cheap medications – Potential serious side effects – Requires close monitoring and follow up
• BUT – no debate about Treating	• WHY the debate about Treating??

Menzies et al., Indian Jnal of Medical Research, 2011

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LTBI Treatment Adverse Effects

Isoniazid

- Asymptomatic LFT elevation in 10-20% on INH
  - Generally return to normal even if medication continued
- Clinical hepatitis – 0.1-1% on INH
  - Can increase depending on age, other risk factors and medications
  - Severe/fatal very rare but have been reported
- Peripheral neuropathy <0.2%

Rifamycin

- Asymptomatic hyperbilirubinemia 0.6%
- Clinical hepatitis increases when INH + RIF
- Cutaneous – up to 6% of people, usually self limited
- Hypersensitivity reactions - rare

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LTBI Treatment Challenges

- Identification of those infected
- Lengthy treatment leading to limited adherence
- Perception of risk (high) and benefit (low)
- Adverse effects influencing patient and provider agreement
- Cost

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TB Infection Treatment and Duration: INH 9 months

- Completion of Isoniazid for 9 months (9H) is variable, but poor even in controlled situations
  - 53% in NJ (Lardizabal et al., 2006)
  - 69% in CDC INH – RPT trial

- Follow up costs

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Short Course Regimen: Rifampin 4 months

Comparison of Regimen Features: 9H and 4R

Regimen Feature	9H	4R
High efficacy	X	*
Lower hepatotoxicity		X
Lower overall cost		X
Higher adherence		X
More effective against INH-resistant strains *(e.g., among foreign-born persons)*		X
Shorter duration		X
Fewer drug-drug interactions	X	

* Good evidence that 3R is at least as efficacious as 6H. Inferential reasoning from other evidence suggests that efficacy of 4R may approach that of 9H.

***AJRCCM* 170; 832-835, 2004**

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Short course regimen: INH + Rifapentine 12 dose regimen

PROs

- INH + Rifapentine + B6 once a week x 12 weeks
- Adherence better

CONs

- Pill burden per dose (10 pills)
- DOT
- Rifapentine information lacking for some groups

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Treatment Adherence

- Treatment efficacy increases with amount of drug taken
- Many do not complete therapy, regardless of whether adverse effects are present
- Shorter course regimens may have better adherence

Trajman, IJTLD, 2010
Goswami, BMC Public Health, 2012

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LTBI Treatment

1. Initiating treatment
2. Choosing a treatment regimen
3. Monitoring
4. Completion

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Prior to Treatment Initiation

- Rule out TB disease
  - Assess/evaluate for symptoms
  - CXR
  - Microbiology (AFB smear/culture) if suspicion for TB disease
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
  - E.g. active liver disease, alcoholism
- Ascertain current and previous drug therapy and side effects

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Baseline Laboratory Evaluation

- Not indicated routinely
- Indicated for:
  - Persons with HIV infection
  - Pregnant & postpartum women (up to 2-3 mos. after delivery)
  - Individuals with history/risk of liver disease
    - Heavy alcohol use
    - Chronic hepatitis
    - History of injection drug use
  - Consider in older individuals with other chronic medical conditions/medications

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High risk – CXR consistent with prior TB disease

- i.e., old fibrotic lesions consistent with prior tuberculosis – e.g. dense nodules, scar, volume loss, sharp margins, 'hard', bronchiectasis
- Lack of change from prior CXR
- TST reaction 5mm or greater

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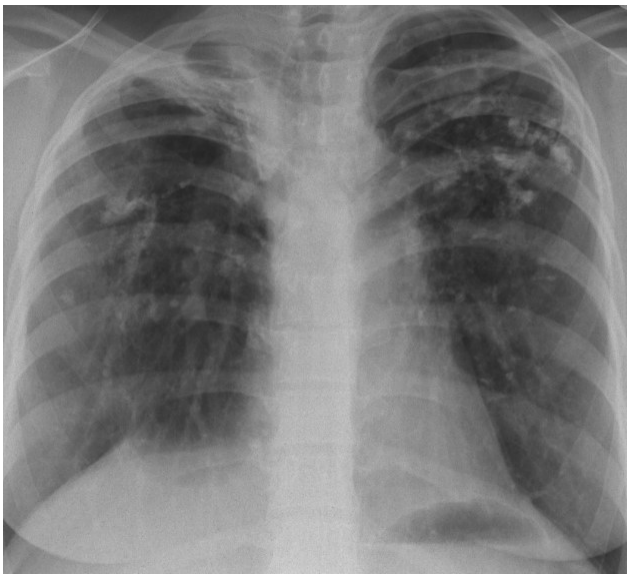

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Lower risk – CXR consistent with healed primary TB

- i.e., calcified solitary pulmonary nodule, apical pleural capping, calcified hilar lymph node
- Not at increased risk of developing TB disease
  - Treat as though CXR normal
- Use other risk factors and appropriate TST size to determine treatment with standard regimen

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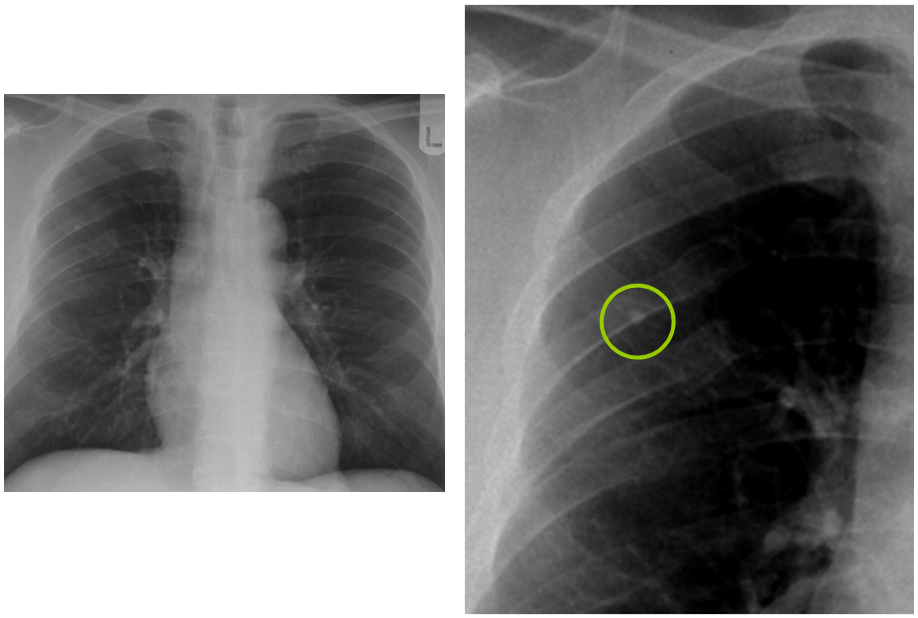

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Recent literature – Pregnancy

- Randomized trial of safety of IPT during or after pregnancy
  - HIV positive pregnant women randomized to immediate treatment v deferred to 12 weeks post partum
  - Gupta et al. CROI 2018
  - Immediate group had higher adverse pregnancy outcomes; final analysis pending
  - Recommendation for immediate treatment in HIV positive pregnant women may need re-evaluation, except in very high risk (eg recent contact)

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Treatment Initiation: Patient Education

- Counsel and educate patient
  - Discuss patient's risk for progressing to TB disease
  - Emphasize benefits of treatment
  - Assess whether patient willing to be treated for full treatment period
- Review common side effects
- Establish treatment and monitoring plan

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Treatment Regimens for LTBI

Drugs	Months of Duration	Interval	Minimum Doses
INH	9*	Daily	270
		2x wkly**	76
INH	6	Daily	180
		2x wkly**	52
RIF	4	Daily	120
INH-RPT	3	Weekly**	12

*Preferred ** Intermittent treatment only with DOT

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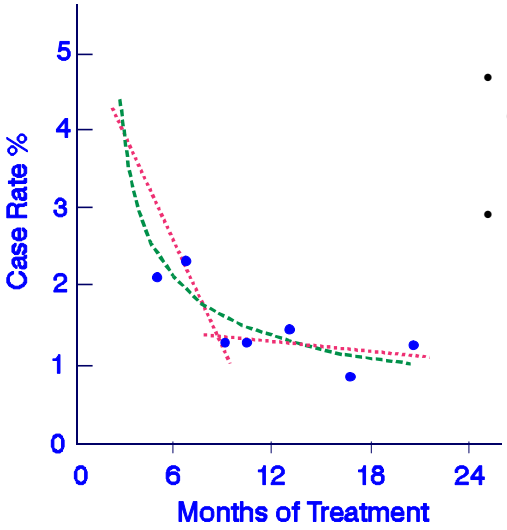
How Much INH Needed for Prevention of TB?



- Longer duration corresponded to lower TB rates if took 0 – 9 mos.
- No extra increase in protection if took > 9-10 mos.

Comstock GW, Int. J Tuberc Lung Dis 1999; 3:847-50

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Isoniazid Regimens

Regimen	Doses	Ideal Duration	Complete Within	
Daily	270	9 months	12 months	
Twice weekly*	76	9 months	12 months	
Daily	180	6 months	9 months	Avoid: HIV infected, fibrotic lesion on CXR, children
Twice weekly*	52	6 months	9 months	

**via Directly Observed Therapy*

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Rifampin Regimens

- RIF daily for 4 months is preferred when:
  - INH resistant or intolerant
  - Patient unlikely to be adherent for longer treatment period

  → **4R is the first choice in many practices**
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted
- Be aware of predictable drug interactions (opiates, corticosteroids, oral contraceptives, PI, warfarin etc)
- Orange discoloration urine, tears etc; may stain contact lenses
- ~~RIF + PZA~~ for 2 months

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Efficacy of 9H versus 4R

- Multicenter RCT of ~ 6000 adults
  - 2/3 close contacts
  - 4% HIV positive
  - 3% other immunosuppressed
- Treatment Completion (>80% doses) – 9H 54% v 4R 69%
- No different in (low) incidence of active TB
- Adverse events – fewer grade 3-4 with 4R (hepatotoxicity)
- 4R non-inferior to 9H in terms of efficacy

Menzies et al., N Engl J Med 2018; 379:440-453, 2018

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12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)

- Rifapentine (RPT) is a rifamycin with a long half-life
  - Used as part of weekly continuation phase regimen in selected patients with TB disease
- INH + RPT for 3 months v Standard INH for 9 months

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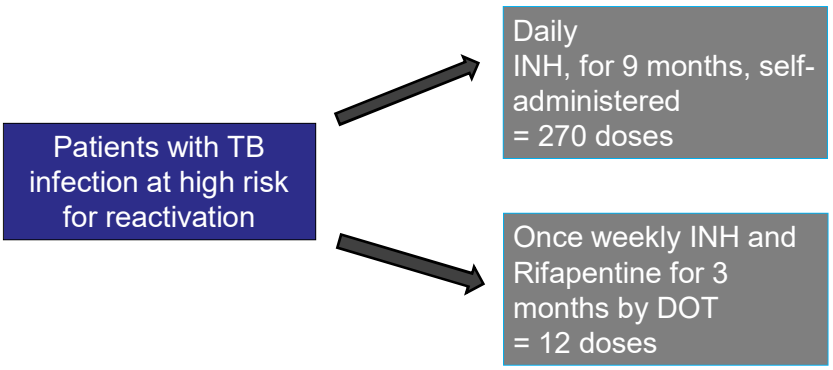
12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)



Followed for development of TB disease for 33 months

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12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)

Study Population (n = 7731)	
TST+ close contacts	71%
Converters	25%
TST+ HIV or HIV+close contact	2%
TST+ with fibrotic changes	2%

Sterling et al., NEJM, 2011

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12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)

- Efficacy was similar
  - 0.19% v 0.43% developed TB disease
- Adherence better - 82% INH-RPT vs. 69% INH
- Permanent drug discontinuation due to adverse effect higher in INH-RPT group, but overall fewer adverse events in INH-RPT
- More hepatotoxicity in INH alone group
- More ‘possible hypersensitivity’ reactions in INH-RPT group

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12 Dose INH + RPT (3HP) Initial Recommendations

- Equal alternative to 9 months INH in otherwise healthy individuals ≥ 12 years old + high risk for TB disease:
  - Close contact
  - Converter
  - Fibrotic changes on CXR
  - HIV *not* on ART, otherwise healthy
- Others considered on an individual basis if circumstances deem INH-RPT to be a better choice (likelihood of completion should be considered)
  - Now also recommended down to age 2
  - HIV infected individuals on compatible HIV treatment regimens

Recommendations for Use of an INH-RPT Regimen with DOT to Treat LTBI. MMWR / December 9, 2011 / Vol. 60 / No. 48

Villarino et al., JAMA Pediatrics, 2015

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INH-RPT NOT Recommended – Need additional studies

- Children < 2 years old
- HIV on ART (other then efavirenz/raltegravir)
- Pregnancy, or likely to become pregnant during treatment
- Presumed INH or RIF resistance
- Prior AE with INH or rifamycin

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Cautions with INH-RPT

- Ensure TB disease is not present
- Patients with fibrotic or 'old healed' lesions on CXR
- HIV infected patients
  - CXR may appear normal despite presence of TB disease
  - More extra-pulmonary disease

Recommendations for Use of an INH-RPT Regimen with DOT to Treat LTBI. MMWR / December 9, 2011 / Vol. 60 / No. 48

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RPT Adverse Effects

- Reddening of secretions
- Less common
  - Hepatotoxicity
  - Leukopenia
  - Thrombocytopenia
  - Hypersensitivity seen with other rifamycins
    - Fever, 'flu-like', pruritus, hypotension, headache, dizziness
    - Systemic reactions may occur more frequently with 3HP
- Hepatic induction of drug metabolism
- Reporting: ltbidrugevents@cdc.gov; MedWatch http://www.fda.gov/safety/medwatch/howtoreport/default.htm

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INH-RPT Monitoring

- Assess for fever, dizziness, rash, jaundice, muscle aches, abdominal pain, nausea, vomiting, loss of appetite at each encounter
- Educate patients to report above symptoms
- Monthly clinical assessment at a minimum

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Dosing for INH-RPT with DOT

Isoniazid
15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum

Rifapentine

10.0–14.0 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

Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT)is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

Source: Three months of weekly rifapentine and isoniazid for *Mycobacterium tuberculosis* infection (PREVENT TB). Information available at http://clinicaltrials.gov/ct2/show/nct00023452?term=rifapentine&rank=9.

Recommendations for Use of an INH-RPT Regimen with DOT to Treat LTBI. MMWR / December 9, 2011 / Vol. 60 / No. 48

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Choosing INH-RPT

- Drug availability and resources
- Cost of regimen v cost-effectiveness
- Program operations
- Expectance of treatment completion
- Patient/Provider preferences
- (DOT/eDOT/SAT)

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3HP DOT vs Self administered (SAT) vs Self administered with text message reminder (eSAT): iAdhere Study

- Treatment Completion in adults >=18

	All	US group
DOT	87.2%	85.4%
SAT	74%	77.9%
eSAT	76.4%	76.7%

Non-inferior

- Self administered once weekly 3HP in the US acceptable (>=2)

Belknap et al., *Annals of Internal Medicine*, 2017

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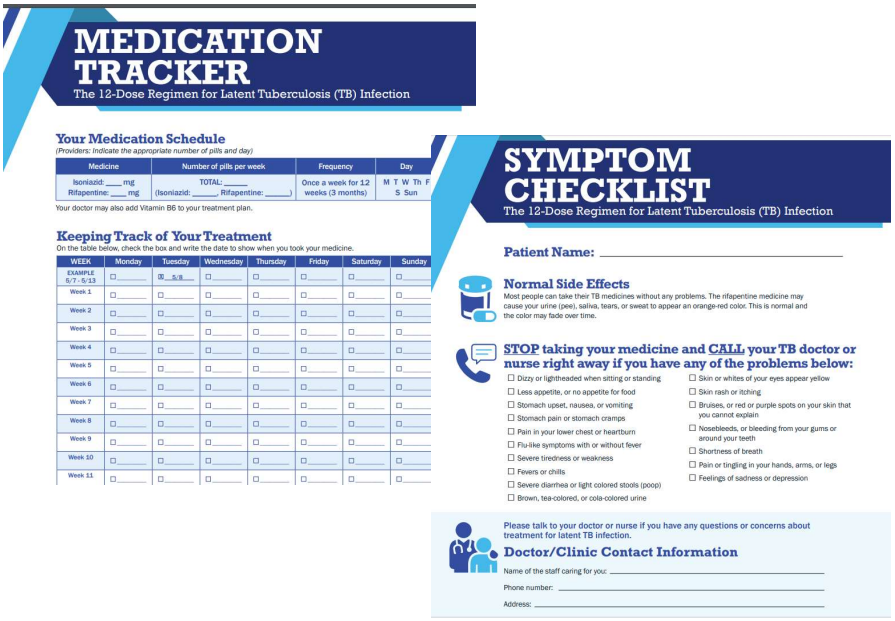

MEDICATION TRACKER

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Your Medication Schedule

(Providers: Indicate the appropriate number of pills and day)

Medicine	Number of pills per week	Frequency	Day
Isoniazid: ___ mg Rifapentine: ___ mg	TOTAL: ____ (Isoniazid: ____, Rifapentine: ____)	Once a week for 12 weeks (3 months)	M T W Th F S Sun

Your doctor may also add Vitamin B6 to your treatment plan.

Keeping Track of Your Treatment

On the table below, check the box and write the date to show when you took your medicine.

WEEK	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
EXAMPLE 5/7 - 5/13	☐	☒ 5/8	☐	☐	☐	☐	☐
Week 1	☐	☐	☐	☐	☐	☐	☐
Week 2	☐	☐	☐	☐	☐	☐	☐
Week 3	☐	☐	☐	☐	☐	☐	☐
Week 4	☐	☐	☐	☐	☐	☐	☐
Week 5	☐	☐	☐	☐	☐	☐	☐
Week 6	☐	☐	☐	☐	☐	☐	☐
Week 7	☐	☐	☐	☐	☐	☐	☐
Week 8	☐	☐	☐	☐	☐	☐	☐
Week 9	☐	☐	☐	☐	☐	☐	☐
Week 10	☐	☐	☐	☐	☐	☐	☐
Week 11	☐	☐	☐	☐	☐	☐	☐

SYMPTOM CHECKLIST

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Patient Name: _____

Normal Side Effects

Most people can take their TB medicines without any problems. The rifapentine medicine may cause your urine (pee), saliva, tears, or sweat to appear an orange-red color. This is normal and the color may fade over time.

STOP taking your medicine and CALL your TB doctor or nurse right away if you have any of the problems below:

- ☐ Dizzy or lightheaded when sitting or standing
- ☐ Less appetite, or no appetite for food
- ☐ Stomach upset, nausea, or vomiting
- ☐ Stomach pain or stomach cramps
- ☐ Pain in your lower chest or heartburn
- ☐ Flu-like symptoms with or without fever
- ☐ Severe tiredness or weakness
- ☐ Fevers or chills
- ☐ Severe diarrhea or light colored stools (poop)
- ☐ Brown, tea-colored, or cola-colored urine
- ☐ Skin or whites of your eyes appear yellow
- ☐ Skin rash or itching
- ☐ Bruises, or red or purple spots on your skin that you cannot explain
- ☐ Nosebleeds, or bleeding from your gums or around your teeth
- ☐ Shortness of breath
- ☐ Pain or tingling in your hands, arms, or legs
- ☐ Feelings of sadness or depression

Please talk to your doctor or nurse if you have any questions or concerns about treatment for latent TB infection.

Doctor/Clinic Contact Information

Name of the staff caring for you: _____

Phone number: _____

Address: _____

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Shorter treatment regimens on the horizon (?)

- 9H versus 1 month daily INH and Rifapentine in HIV infected individuals
  - 1HP v 9H in patients with HIV (efavirenz/nevirapine) deemed non-inferior with fewer side effects and higher completion in 1HP
  - Completion 97% v 90%
  - Similar efficacy and safety

Chaisson, CROI 2018
Swindells et al, N Engl J Med 2019; 380:1001-1011, 2019

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Comparing regimens

- Menzies 4R v 9H
- Retrospective study in Seattle
  - 85% completion 4R and 3HP
  - 52% 9H
- 16 US programs, observational study of 3HP
  - 87% completed 3HP
  - 94.5% children completed 3HP
  - 35% reported side effects, with 76% still completing treatment

Sandul et al, *CID*, Volume 65, Issue 7, 1 October 2017, 1085–1093
McClintock et al. *BMC ID*, V17, 2017.

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Choice of treatment regimen summarized

- Short course (4R or 3HP) preferred over 9H
- 3HP populations expanded, DOT not required
- Patients/providers have choices
- Education, follow-up, completion of treatment

- 9H *only* if on essential medications, which rifampin would interfere with, or other contraindication to rifamycin

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Monthly Monitoring During LTBI Treatment

- Reinforce patient's understanding of LTBI and its treatment
- Evaluate for signs and symptoms of active TB and drug reactions
- Monitor adherence to prescribed regimen
- Educate patient about signs and symptoms of hepatotoxicity, adverse effects
- Review all medications and assess for potential drug interactions

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Monthly Monitoring During LTBI Treatment

- Repeat liver function tests for
  - Patients with abnormal baseline
  - HIV infection
  - Pregnant and post-partum women
  - History/risk of liver disease

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Management of the Patient Who Misses Doses

- Extend or re-start treatment for frequent or prolonged interruptions that preclude completion within recommended time frame
- Examine patients to rule out TB disease when treatment interruption > 2 months
- Recommend and arrange for DOT as needed

  Completion of therapy is based on the total number of doses administered, not on duration alone

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Completion of Therapy

Regimen	Duration	Doses	Complete Within
Daily INH	9 months	270	12 months
Twice weekly INH	9 months	76	12 months
Daily INH	6 months	180	9 months
Twice weekly INH	6 months	52	9 months
Rifampin	4 months	120	6 months
INH-RPT	3 months	11-12	16 weeks

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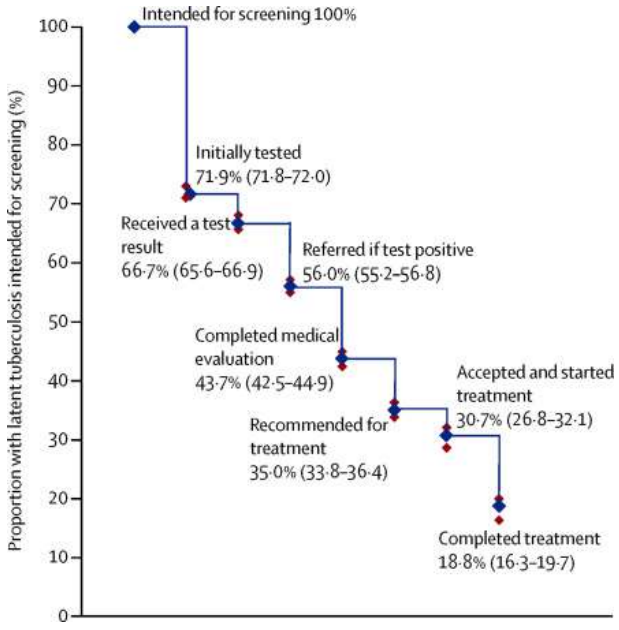
LTBI "Cascade of Care"



Alsdurf et al Lancet ID 2016

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Summary

- Prior to initiating LTBI treatment, assess for presence of TB disease
- Patient centered approach to treatment choice
- Monthly clinical assessments and ongoing patient education important
- Use DOT for high-priority patients