Treatment of Latent TB Infection

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LTBI - Outline

- Why focus on LTBI?
- LTBI review
- LTBI management in 2021
  - Planning LTBI treatment
  - Adverse effects
  - Treatment options (focus on short course options)
  - Treatment completion

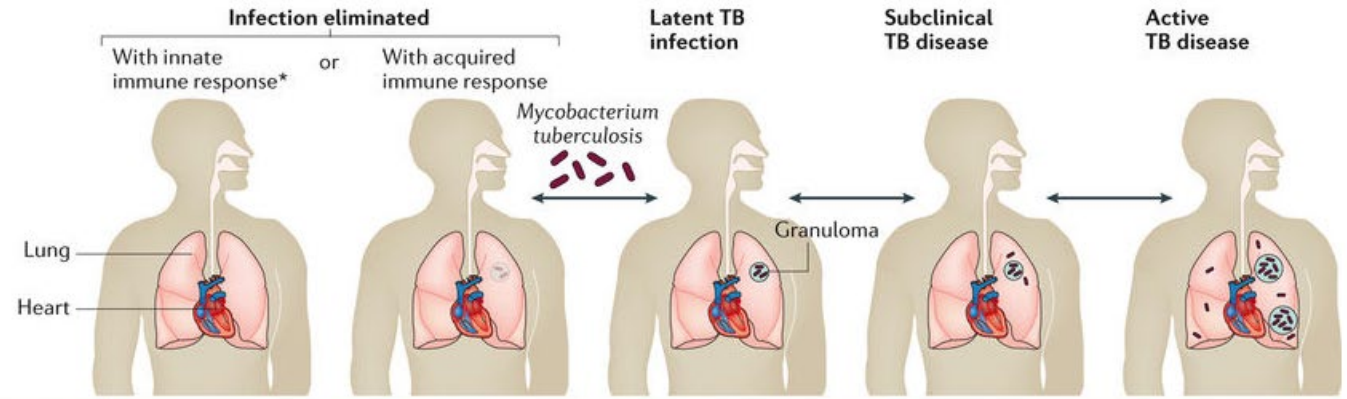
TB in the US – Focus on LTBI

- Decline in TB rate in US is slowing
- 28 times the threshold for TB elimination
- More then 80% of TB disease in the US is due to reactivation
- Up to 13 million (4.5%) in US have TB infection or LTBI (not declining)
- LTBI treatment less costly than TB disease
- Progress towards TB elimination (<1 case/million) requires:
  - Continued identification/curing those with infectious TB
  - Expanded detection and treatment of LTBI, especially in high-risk groups
  - Public health + private practitioners + CHCs

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

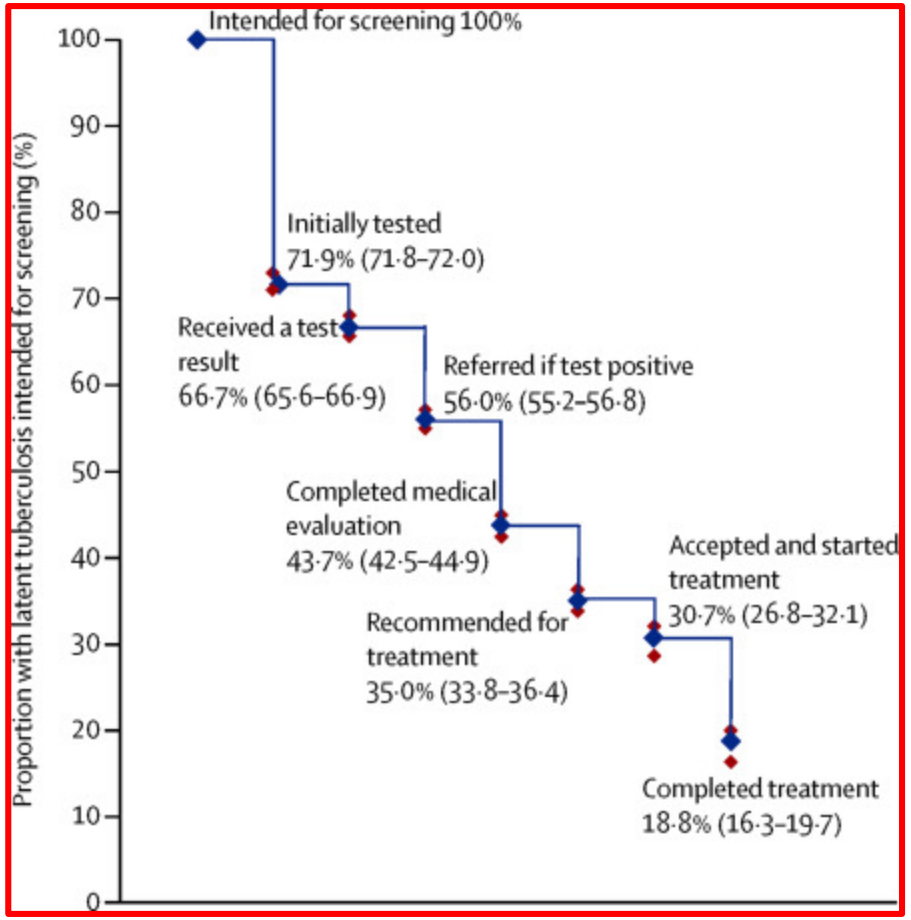
Pai et al., Nature Reviews 2016

TB Infection vs. TB Disease

A Person with Latent TB Infection	A Person with Active TB Disease
✓ Has no symptoms ✓ Does not feel sick ✓ Cannot spread TB to others ✓ Usually has a positive TST or IGRA ✓ Has a normal CXR and sputum test	✓ Has symptoms that may include: • a bad cough that lasts > 2 weeks • pain in the chest • coughing up blood or sputum • weakness or fatigue • weight loss • no appetite • chills • fever • night sweats ✓ May spread TB to others ✓ Usually has a positive TST or IGRA ✓ May have an abnormal chest x-ray, or positive sputum smear or culture

LTBI – and why its complicated

- Identification of those infected
  - Who to test? How to test?
  - No test of cure
- Adverse effects/perception of risk influencing patient and provider agreement
- Lengthy treatment leading to limited adherence



Alsdurf et al Lancet ID 2016

LTBI management in 2021

- Pre-treatment evaluation
- Adverse effects
- Treatment options
- Ensuring treatment completion

LTBI (Pre) Treatment

- Rule out TB disease
  - Symptoms, chest X-ray, AFB smears/culture if indicated
- History of prior TB exposure or treatment
- Identify risks factors for hepatotoxicity (alcohol use, liver disease, medications)
- Ensure patient willing to complete treatment course
- Educate patient on importance, treatment of an infection, make it a priority
- Counsel patient on what to expect
- Weigh risks/benefits for each patient
- Consider baseline laboratory testing especially in liver disease, pregnancy/PP, HIV, alcohol use; follow-up testing for high-risk individuals

Treatment adverse effects => MINIMAL in well selected individuals

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%

Rifampin

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

INH + Rifapentine weekly

- Lower rates of hepatotoxicity (0.4%)
- Possible hypersensitivity (3.8%)
- Orange

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 69 / No. 1
February 14, 2020

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.

* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.

† No evidence reported in HIV-positive persons.

§ Strong recommendation for those persons unable to take a preferred regimen (e.g., due to drug intolerability or drug-drug interactions).

INH for 9 months is too long..

- 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
- 2020 guidelines = reiterate INH as an alternative regimen, and 6 months is acceptable

A 25 y/o woman on oral contraceptives has a positive QFT Plus and a known prior exposure to a TB case. Which is least likely to interfere with her current medications?

A. 4R
B. 3HP
C. 6H
D. 3HR

Rifampin for 4 months: preferred regimen

Comparison of Regimen Features: 9H and 4R

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

Methadone	Phenytoin
Hormonal contraception	Steroids
Warfarin	*PI

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

Efficacy of 9H versus 4R

- Indirect data supporting 4R – in guidelines since 2000
- 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

Fregonese, Menzies, 4RIF v (INH trials team, Montreal Chest Institute, NEJM, 2018

4 months of Rifampin (4R)

- Drug interactions with oral contraceptives, warfarin, methadone, certain antiretrovirals, steroids – can be limiting, may need dose adjustment
  - Can consider 4 months of Rifabutin instead
- Patient education on reddening of bodily fluids, adherence, when to hold medications and report to clinic
- AE – less hepatotoxicity, skin reactions up to 6%; hypersensitivity type reactions; thrombocytopenia - uncommon
- Patient education materials

https://www.cdc.gov/tb/publications/pdf/RIF_508.pdf

- Antiretrovirals + Rifampin

https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations02.htm

Who should not receive Isoniazid and Rifapentine weekly for 12 weeks?

A. 50 y/o man with HIV and LTBI on efavirenz based treatment
B. 4 y/o child who is a contact to an active case
C. 24 y/o woman who is 11 weeks pregnant

INH + Rifapentine 12 dose regimen: preferred regimen

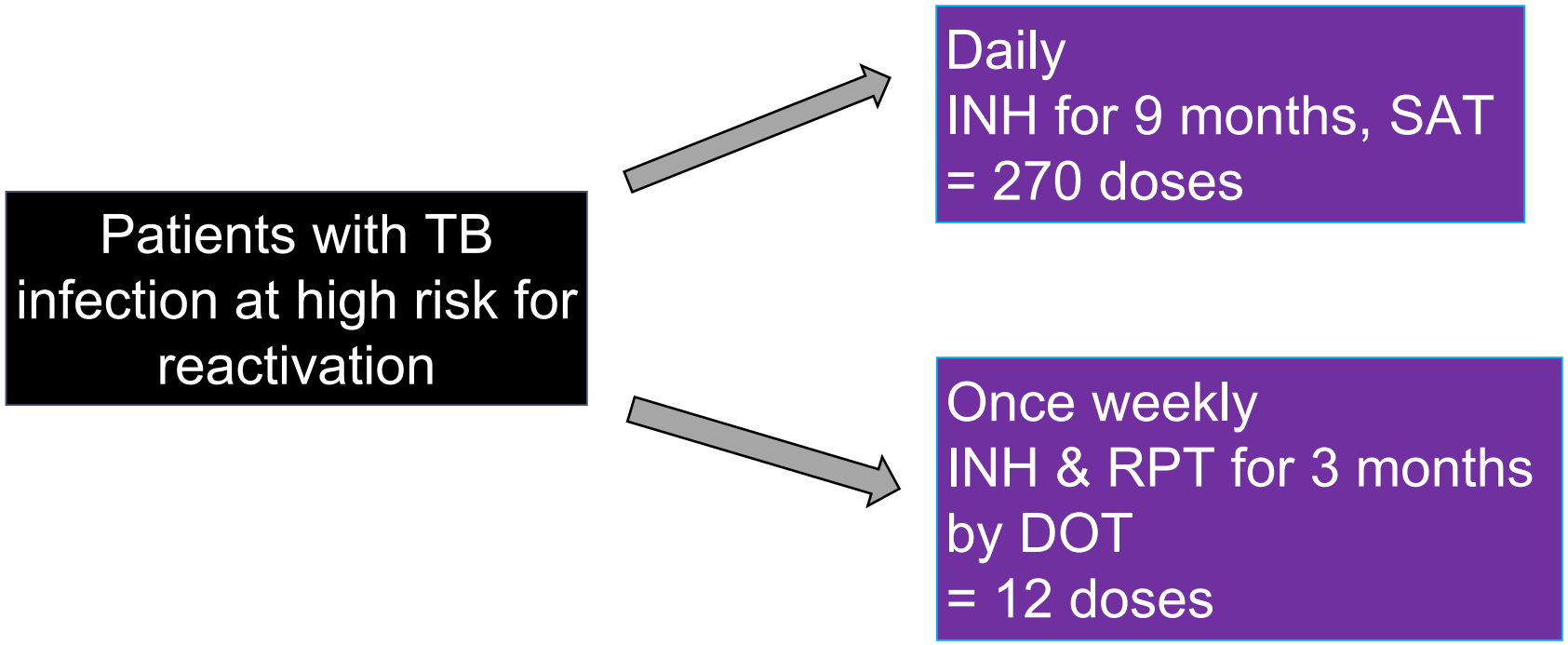
Pros

- INH + Rifapentine + B6 once a week x 12 weeks
- Short course = better completion = better efficacy

Cons

- Pill burden (10 pills)
- (DOT)
- Rifapentine information lacking for some groups (HIV, pregnancy, children < 2)
- RPT availability/cost

PREVENT TB (TBTC Study 26): 12 dose INH + RPT + B6



Followed for development of TB disease for 33 months

Sterling et al. NEJM. 2011

You are discussing various TB infection treatment options with a 45 yo man with diabetes. He asks you about the 12 dose option and its side effects. Which of the following is true?

- A. The 12 dose regimen is shorter but not as effective as an isoniazid monotherapy option
- B. The 12 dose regimen must be administered via DOT
- C. 9 months of isoniazid has a higher risk of hepatotoxicity then 3HP
- D. Mild flu-like illnesses can occur with 3HP and necessitate halting the treatment

3HP – 12 dose regimen - compared with 9H

- Efficacy similar - 0.19% vs 0.43% developed TB disease
- Adherence better - 82% 3HP vs. 69% INH (9H)
- Adverse events
  - More hepatotoxicity in 9m INH group (2.7% v 0.4%)
  - More systemic drug reactions ("flu-like" or rash) 3.5% 3HP (0.3% severe) vs 0.4% INH
    - Occurs after 3-4 doses and ~4 hours after dose
    - Symptoms resolve within 24 hours; pre-hydrate
    - Severe reactions – syncope/hypotension – rare → **STOP**
    - Mild/moderate reactions → can usually continue w/ close observation

Sterling et al. CID, 2015

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

- Treatment completion:

	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

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

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 Treat

On the table below, check the box and write the date to

WEEK	Monday	Tuesday	Wednesd
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	☐ _____	☐ _____	☐ _____
Week 12	☐ _____	☐ _____	☐ _____

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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: _____

Hours: _____

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

www.cdc.gov/tb

12-DOSE REGIMEN (3HP)

for Latent Tuberculosis Infection Treatment

CDC continues to recommend the use of the short-course combination regimen of once-weekly isoniazid-rifapentine for 12 weeks (3HP) for treatment of latent tuberculosis infection (LTBI) in adults.

CDC now also recommends use of 3HP:

- by directly observed therapy (DOT) **or self-administered therapy (SAT)***
- in persons aged **2–11 years**
- in persons with LTBI who are **living with HIV infection** including AIDS and taking antiretroviral medications with acceptable drug-drug interactions with rifapentine

Shorter treatment regimens, like 3HP, **have higher treatment completion rates** and **lower costs**.

* Healthcare providers should choose the mode of administration (DOT vs. SAT) based on local practice, individual patient attributes and preferences, and other considerations, including risk of progression to severe forms of tuberculosis disease.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

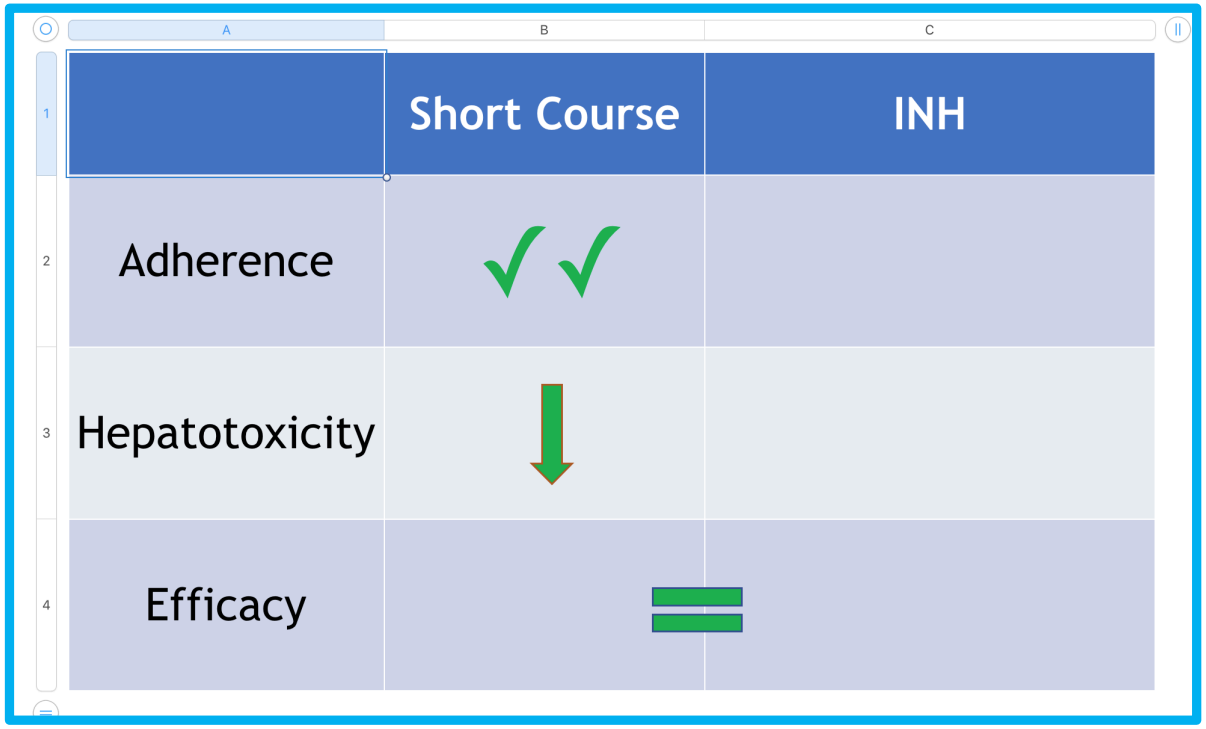
3 months daily INH & Rifampin (3HR): new in 2020 guidelines, preferred regimen

- Similar efficacy to 6-12 months INH with limited data especially in HIV uninfected
- Adherence equal or better
- Hepatotoxicity likely similar to 6-9 month INH
- Drug interactions issues
- Used worldwide

Zenner, AIM, 2017

LTBI treatment choice

- Short course regimens are preferable to INH for 6-9 months
- Reserve INH regimen for those unable to tolerate rifamycin or on essential medications which rifamycin would interfere with
- INH + RIF if evidence of prior TB disease (e.g., upper lobe fibrosis)



	Short Course	INH
Adherence	✓✓	
Hepatotoxicity	↓	
Efficacy	=	

LTBI Treatment – Follow-up

- Monitor at least monthly with visit
  - Ensure adherence
  - Review possible side effects
  - Lab monitoring if new symptoms or risk factors for hepatotoxicity or abnormal baseline testing
  - Identify any new medications
  - Prescribe next month of treatment
- Adverse effects
  - Educate patients on side effects to look for, stop medication immediately if signs of hepatitis
  - Call clinic
  - Stop if transaminases 3x ULN and has symptoms, 5x ULN and asymptomatic

A 31 y/o woman with TB infection is started on rifampin in February. Due to the pandemic and limited clinic hours she was unable to fill her 2nd month of rifampin. She completed her 1st month of treatment. The clinic reopens and she comes to her next appt. She has missed 6 weeks of rifampin. What do you advise?

A. Start treatment over again from the beginning

B. Restart rifampin and ensure completion of 120 daily doses by August

C Restart rifampin and ensure completion of 120 doses by November

D. Restart rifampin for 1 more month.

LTBI Treatment – Follow-up

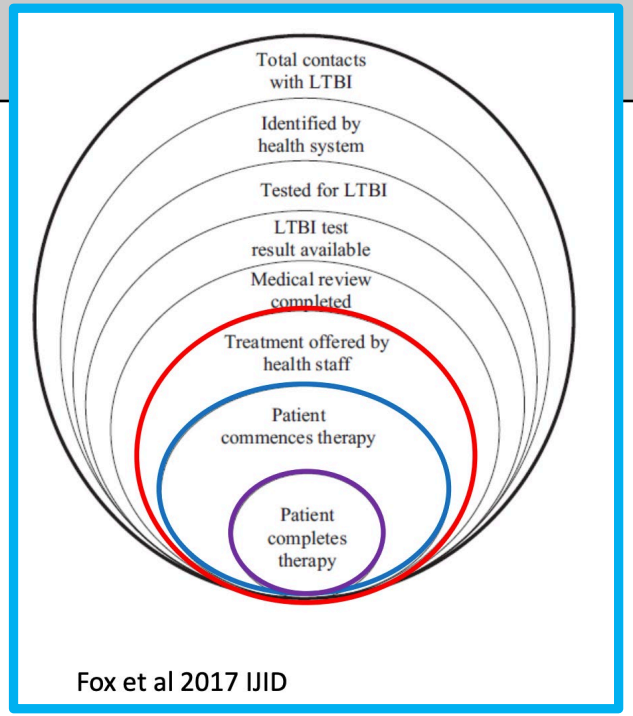
- Treatment completion
  - # doses in set amount of time (some leeway)
    - 3HP – 12 doses in 16 weeks
    - 4R – 120 doses in 6 months
  - Document completion
- Consider referral
  - Liver disease, HIV, pregnant, close contact, TNF blocker, young child, abnormal CXR, adverse effects

LTBI – Future

- Brief TB trial - NEJM 2019
  - 1 month daily INH and Rifapentine (1HR) versus 9H in HIV-infected individuals in high TB prevalence areas - noninferior, better adherence
- 3HP in pregnancy
- Risk assessment, better tests
- Leveraging EHRs
- Ehealth

LTBI – Summary

		Changes
Who to test	Birth, travel, residence in high-risk country Immunosuppression Close contact	No < 5 year arrival cut-off for non-U.S.-born No absolute age cut-off, weigh risks/benefits
How to test	TST or IGRA, latter if had BCG	QFT plus replaced QFT Gold
How to treat	Shorter course encouraged unless on essential interacting medications	Preferred: 3HP (SAT or DOT), 4R (SAT), 3HR Alternate: 6H, 9H



Fox et al 2017 IJID