

Treatment of Latent Tuberculosis Infection



TB Intensive Workshop

Richmond Virginia

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Disclosures

- Financial –
 - NIH
 - CDC
 - CDC Foundation
 - Revvity, Oxford Immunotec, Ltd
 - UpToDate, LLC
- Therapeutic –
 - 10 medications are approved by the FDA for TB
 - Isoniazid (INH), rifapentine (RIF), Rifapentine, Pyrazinamide (PZA), Ethambutol (EMB), Streptomycin, Cycloserine, Ethionamide, Para-aminosalicylate (PAS), Bedaquiline
 - All other drugs discussed are NOT FDA approved for TB
 - Fluoroquinolone, linezolid, amikacin, clofazamine, meropenem, amox/clav, etc.



Objectives

- Initiating LTBI treatment
- Describe possible adverse effects
- Treatment options (focus on short course options)
- Treatment follow-up
- Cases



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

A GUIDE FOR HEALTH CARE PROVIDERS AND PUBLIC HEALTH PROGRAMS

Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations

[HOME](#) > [GUIDELINES](#) > Mycobacterium tuberculosis Infection and Disease

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

<https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/#.YD5DHq-P6hd>

<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/mycobacterium-tuberculosis-infection-and?view=full>

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w



Pre-LTBI treatment Phase

- Rule out TB disease
 - Symptoms, chest X-ray, AFB smears/culture if indicated
- Ask about 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, ensure it is a priority
- Counsel patient on what to expect
- Weigh risks/benefits for each patient and decide whether to treat
- Consider baseline laboratory testing especially in liver disease, pregnancy/PP, HIV, alcohol use



Rule out TB Disease



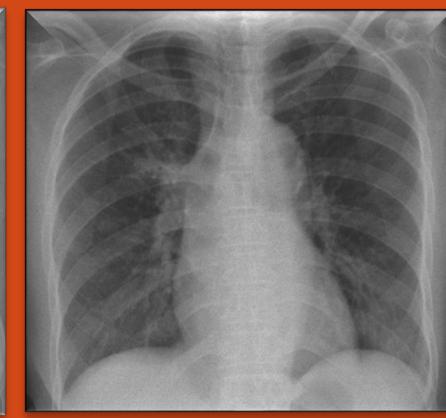
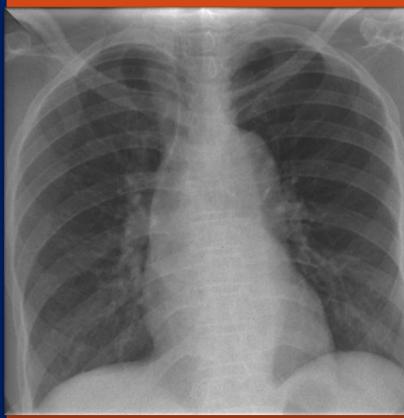
History + Physical

- TB risk factors – region of origin, travel, exposure to TB, immunosuppression, medical conditions, prior treatment
- Sx's – cough, fever, night sweats, weight loss, blood in sputum
- Duration
- Remember - extrapulmonary signs and symptoms (lymph nodes, joint swelling, headache/confusion)
- PE – weight, cachexia, lung findings may be normal, joint effusion, lymph nodes etc



Chest Radiology

- CXR normal or stable
- Compare with prior CXR if possible
- Typically within 3 months of LTBI treatment start (repeat if symptoms)



Microbiology *IF INDICATED*

- If symptoms, exam or imaging raise concern for TB disease, proceed with sputum collection for AFB smear, culture and PCR



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%

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/ SDR (3.8%)
- Orange bodily fluids

Treatment adverse effects => MINIMAL in well selected individuals



Treatment Options

Centers for Disease Control and Prevention

MMWR

Recommendations and Reports / Vol. 69 / No. 1

Morbidity and Mortality Weekly Report

February 14, 2020

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

Shorter treatment
options preferred

Recommendations and Reports

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 Conditional	Very low (HIV negative) Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong [§] Conditional	Moderate (HIV negative) 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 intolerance or drug-drug interactions).



4 months of Rifampin (4R)

Advantages

- Generally well tolerated
- Less hepatotoxicity c/w INH
- Improved adherence/completion
- As effective as INH

Disadvantages

- Multiple drug interactions with oral contraceptives, warfarin, methadone, antiretrovirals, steroids – can be limiting, may need dose adjustment or may need to avoid entirely (certain ART)
 - Can consider 4 months of Rifabutin (weaker P450 inducer) in some settings
- Minimal evidence in people with HIV infection (alternative per HIV guidelines)

DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
RIFAMPIN ^s (4R)		4 months	Daily	120 Adults: 10 mg/kg; 600 mg maximum Children: 15–20 mg/kg; 600 mg maximum

Fregonese, Menzies, et al. NEJM, 2018

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

INH + Rifapentine – 12 dose weekly regimen

Advantages

- Short
- Pills taken weekly
- Non-inferior to 9INH
- Improved adherence and completion
- Less hepatotoxicity

DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
ISONIAZID [†] AND RIFAPENTINE ^{††} (3HP)	3 months	Once weekly	12	Adults and children aged ≥12 yrs INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 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
				Children aged 2–11 yrs INH [†] : 25 mg/kg; 900 mg maximum RPT ^{††} : See above

Disadvantages

- Pill burden – 10 pills at a time
- Not yet approved for children < 2, pregnancy, HIV on ART unless drug-drug interactions are acceptable (eg efavirenz, dolutegravir, raltegravir)
- Drug drug interactions similar to rifampin (hormonal contraceptives, methadone, buprenorphine, warfarin, ART etc)
- Systemic drug reactions/"flu-like" reactions in 4% (usually mild)
- Cost/availability

INH + Rifampin daily for 3 months

- New recommendation in 2020 guidelines
- 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
- Used worldwide

DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
ISONIAZID [†] AND RIFAMPIN [§] (3HR) 	3 months	Daily	90	Adults INH [†] : 5 mg/kg; 300 mg maximum RIF [§] : 10 mg/kg; 600 mg maximum Children INH [†] : 10-20 mg/kg [#] ; 300 mg maximum RIF [§] : 15-20 mg/kg; 600 mg maximum

Isoniazid daily regimens

- 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
- Now considered alternative regimens – can give 6 or 9 months
- Efficacy 12m slightly better than 6m, but lower adherence and more hepatotoxicity of longer treatment ~ favors 6m
- Use INH when drug interactions preclude shorter regimen, contact to case with rifampin monoresistance, or rifamycin intolerance
- If unable to take a preferred regimen:
 - 6m strongly recommended in HIV uninfected; conditional in HIV infected
 - 9m conditional for both
 - Individualize 6m versus longer based on pt risk factors, adherence, liver disease

DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
ISONIAZID [†] (6H/9H) 	6 months	Daily	180	Adults Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
		Twice weekly [¶]	52	
	9 months	Daily	270	Children Daily: 10–20 mg/kg [#] ; 300 mg maximum Twice weekly: 20–40 mg/kg [#] ; 900 mg maximum
		Twice weekly [¶]	76	

Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 2020;69(No. RR-1):1–11.
IUAT, Efficacy of various durations of IPT for TB, Bull WHO, 1982.

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

3HP (12 dose regimen) versus 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

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

Treatment completion:

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

Self-administered once weekly 3HP in the US acceptable

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:

WEEK	Monday	Tuesday	Wednesday
EXAMPLE 5/7 - 5/13	<input type="checkbox"/>	<input checked="" type="checkbox"/> 5/8	<input type="checkbox"/>
Week 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 9	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 11	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Week 12	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SYMPTOM CHECKLIST

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

Patient Name: _____



Normal Side Effects

Most people can take their TB medicine 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: _____



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



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

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Name of the staff caring for you: _____

Phone number: _____

Address: _____

Hours: _____



Centers for Disease
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TB Prevention

www.cdc.gov/tb

<https://www.cdc.gov/tb/topic/treatment/ltdi.htm>

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

One Month of Rifapentine + Isoniazid to Prevent HIV-Related Tuberculosis

RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE 3 NONINFERIORITY TRIAL

3000



HIV-infected
persons at high
risk for TB

Rifapentine + isoniazid
(1 mo)

(N=1488)



Isoniazid alone
(9 mo)

(N=1496)

Incidence of TB
or death per 100
person-yr

0.65

Difference, -0.02; 95% CI, -0.35-0.30; noninferiority shown

Serious adverse
events

83 Patients
(6%)

P=0.07

108 Patients
(7%)

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

- Preferred
 - 3HP – efavirenz, dolutegravir based regimens
 - 3HR – limited by rifampin
- Alternative
 - 6 or 9H
 - 4R – no evidence
 - 1HP (Brief TB trial) - Efavirenz only
 - 4 months rifabutin (not recommended by DHHS guidelines)
- Confirm no drug interactions

LTBI treatment choice – Summary

- 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)

	A	B	C
1	Short Course	INH	
2	Adherence	✓ ✓	
3	Hepatotoxicity	↓	
4	Efficacy	≡	





Treatment Follow-up

- Monitor at least monthly with clinical assessment
 - Ensure adherence
 - Review possible side effects
 - Assess for active TB
 - Lab monitoring if symptoms or risk factors for hepatotoxicity or abnormal baseline testing
 - Identify new medications
 - Prescribe next month of treatment
- Adverse effects
 - Educate patients on side effects to look for, stop medication immediately if signs of hepatitis or other side effects
 - Call
 - Perform clinical assessment

Adverse Effects

- Range from minor to more severe
- If minor, may be able to continue treatment with symptomatic treatment (eg pruritus)
- More severe, require stopping medications and further assessment (LFTs elevated to 3x upper limit normal with symptoms or 5x ULN without symptoms)
 - Once resolved, alternative regimen likely required
 - Referral to specialist – eg persistently elevated LFTs despite stopping treatment, evidence of coagulopathy, significant skin reaction, severe leukopenia



LTBI treatment completion

- Treatment completion
 - # doses in set amount of time (some leeway)
 - Document completion and include in patient record
- Interruption
 - Address reasons
 - Extend treatment for missed doses
 - 6H – 180 doses within 9 months
 - 4R – 120 doses within 6 months
 - 3HP – 12 doses within 16 weeks
 - Based on expert opinion, consider overall risk of progression to TB disease





Discussion

Choosing regimens

50 yo man with atrial fibrillation and LTBI on Coumadin. Work schedule does not allow for frequent visits.	INH for 6 months is likely the best choice as other regimens will require frequent monitoring of INR
40 yo woman with HIV infection on an efavirenz-based antiretroviral regimen and newly diagnosed LTBI	3HP 3HR Alt – INH regimen
25 yo man with newly diagnosed LTBI who had a known exposure to a co-worker with isoniazid resistant TB.	Rifampin for 4 months
67 yo woman with LTBI who does not like taking pills	Requires further discussion Describe regimens, many pills once a week versus fewer pills daily



- Medication tracker
- Alarm
- Text message reminder from clinic

MEDICATION TRACKER

The 4 Months Daily Rifampin Schedule for Latent Tuberculosis (TB) Infection

Your Medication Schedule
(Providers: Indicate the appropriate number of pills)

Medicine	Number of pills per week	Frequency	Duration	Doses
Rifampin: <input type="text"/> mg	TOTAL: <input type="text"/>	Once a day	4 months	120

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 May 4-10	<input checked="" type="checkbox"/> 05/04	<input checked="" type="checkbox"/> 05/05	<input checked="" type="checkbox"/> 05/06	<input checked="" type="checkbox"/> 05/07	<input checked="" type="checkbox"/> 05/08	<input checked="" type="checkbox"/> 05/09/2020	<input checked="" type="checkbox"/> 05/10/2020
Week 1	<input type="checkbox"/>	<input type="checkbox"/>					
Week 2	<input type="checkbox"/>	<input type="checkbox"/>					
Week 3	<input type="checkbox"/>	<input type="checkbox"/>					
Week 4	<input type="checkbox"/>	<input type="checkbox"/>					
Week 5	<input type="checkbox"/>	<input type="checkbox"/>					
Week 6	<input type="checkbox"/>	<input type="checkbox"/>					
Week 7	<input type="checkbox"/>	<input type="checkbox"/>					
Week 8	<input type="checkbox"/>	<input type="checkbox"/>					
Week 9	<input type="checkbox"/>	<input type="checkbox"/>					
Week 10	<input type="checkbox"/>	<input type="checkbox"/>					
Week 11	<input type="checkbox"/>	<input type="checkbox"/>					
Week 12	<input type="checkbox"/>	<input type="checkbox"/>					
Week 13	<input type="checkbox"/>	<input type="checkbox"/>					
Week 14	<input type="checkbox"/>	<input type="checkbox"/>					
Week 15	<input type="checkbox"/>	<input type="checkbox"/>					
Week 16	<input type="checkbox"/>	<input type="checkbox"/>					


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

www.cdc.gov/tb



LTBI Treatment - Summary

- Rule out TB disease
- Provide education and counseling re importance of treatment
- Opt for shorter course treatment
- Monitor periodically