Treatment of TB Infection

TB 101

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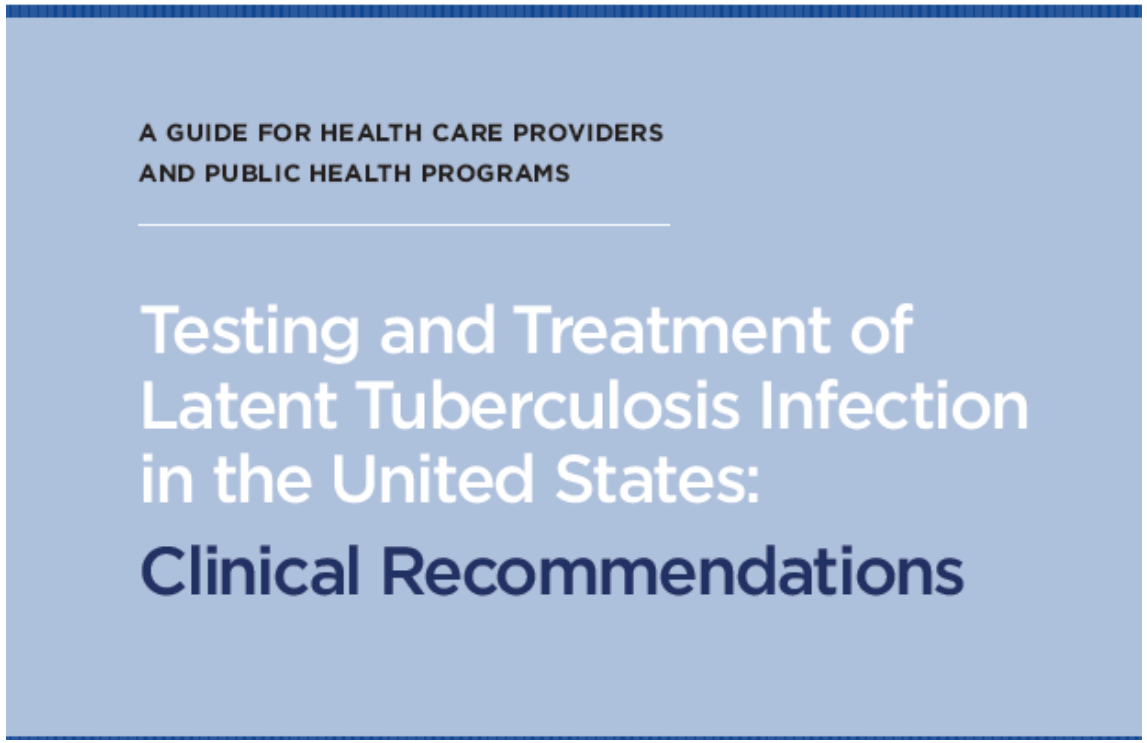
LTBI Treatment – Outline

- Planning LTBI treatment
- Adverse effects
- Treatment options (focus on short-course options)
- Treatment follow-up
- Cases



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-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 entire 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/post-partum, HIV, alcohol use

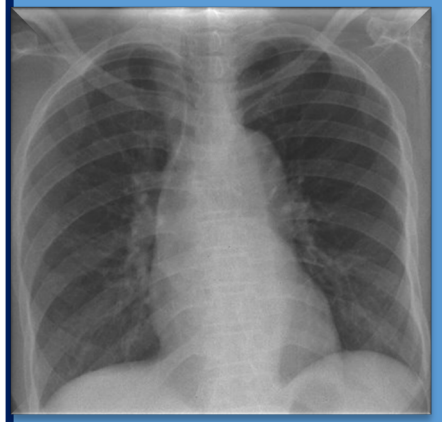
Exclude TB Disease

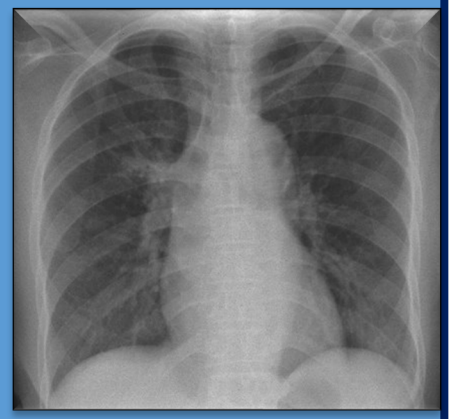
History + Physical

- TB risk factors – region of origin, travel, exposure to TB, immunosuppression, medical conditions, prior treatment
- Symptoms – 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
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

Shorter treatment options preferred

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).

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[§] (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

INH + Rifapentine – 12-dose Weekly Regimen (3HP)

Advantages

- Short
- Pills taken weekly
- Non-inferior to 9 months of INH
- 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
- Method of administration?

https://www.impaact4tb.org/wp-content/uploads/2020/04/5T-eng-DDI-Drugs-Drug-Interactions-Art_RB16.pdf

INH + Rifampin Daily for 3 Months (3HR)

- 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 months of 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

Zenner, AIM, 2017

Isoniazid Daily Regimens (6H or 9H)

- 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 then 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% vs. 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

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 9H 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	Wednesda
EXAMPLE 5/7 - 5/13	☐ _____	☑ 5/9	☐ _____
Week 1	☐ _____	☐ _____	☐ _____
Week 2	☐ _____	☐ _____	☐ _____
Week 3	☐ _____	☐ _____	☐ _____
Week 4	☐ _____	☐ _____	☐ _____
Week 5	☐ _____	☐ _____	☐ _____
Week 6	☐ _____	☐ _____	☐ _____
Week 7	☐ _____	☐ _____	☐ _____
Week 8	☐ _____	☐ _____	☐ _____
Week 9	☐ _____	☐ _____	☐ _____
Week 10	☐ _____	☐ _____	☐ _____
Week 11	☐ _____	☐ _____	☐ _____
Week 12	☐ _____	☐ _____	☐ _____

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

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

https://www.cdc.gov/tb/topic/treatment/ltbi.htm

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	0.627
	Difference, −0.02; 95% CI, −0.35–0.30; noninferiority shown	
Serious adverse events	83 Patients (6%)	108 Patients (7%)
	P=0.07	

The NEW ENGLAND JOURNAL of MEDICINE

Swindells et al. 2019

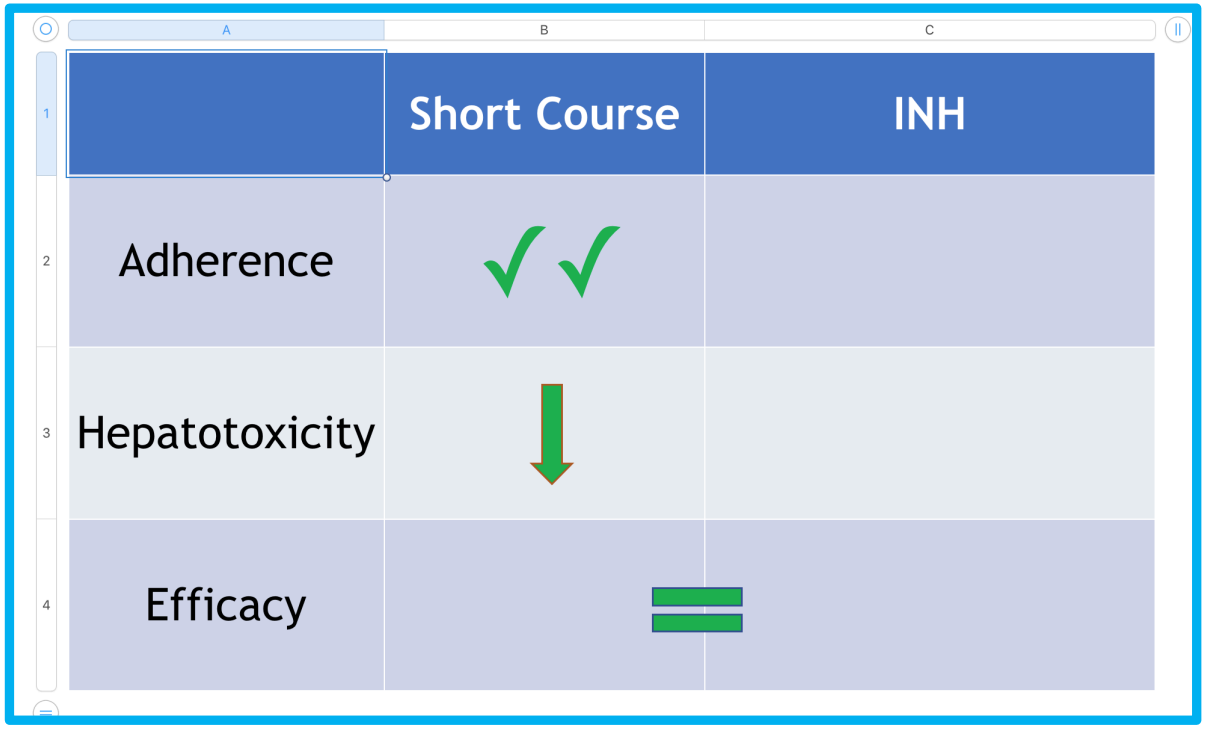
LTBI and HIV infection

- 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

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

LTBI Regimen Selection – Summary

- Short-course RIF-based 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	=	

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 (e.g., 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 – e.g., 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

Poll – Choosing Regimens

50 yo man with atrial fibrillation and LTBI on Coumadin. Work schedule does not allow for frequent visits.	
40 yo woman with HIV infection on an efavirenz-based antiretroviral regimen and newly diagnosed LTBI.	
25 yo man with newly diagnosed LTBI who had a known exposure to a co-worker with isoniazid resistant TB.	
67 yo woman with LTBI who does not like taking pills	

Poll - 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
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

Case

45 yo woman with h/o hypertension and diet-controlled diabetes. Identified as a household contact to her mother with active pulmonary TB. Never treated for TB or LTBI in the past. No cough, fevers, night sweats or weight loss. IGRA positive. CXR normal

Pt is evaluated, counseled and provided education. She elects to start 3HP, self administered. She is given 1 month of medications and clinic contact information

Case (cont.)

After 2nd dose pt reports itching "all over" which subsides by the next day

What else would you want to know? What would you do next?

Case (cont.)

Pt stopped medications and came to clinic. Her physical exam was normal. No rashes or other skin lesions were noted

She takes her 3rd dose on time with no further pruritus

You are also treating the pt's mother who has active pulmonary TB that was smear positive. Xpert MTB/Rif was positive for MTB and no rifampin resistance detected. You receive her final growth based susceptibilities and note INH resistance

How does this impact the patient's (contact) care? Would you want any additional info?

Case (cont.)

After additional assessment you decide the patient most likely became infected recently and that she most likely acquired INH resistant LTBI

Would you make any changes now?

Case (cont.)

The patient is informed of this new information and you recommend changing treatment for rifampin alone for 4 months

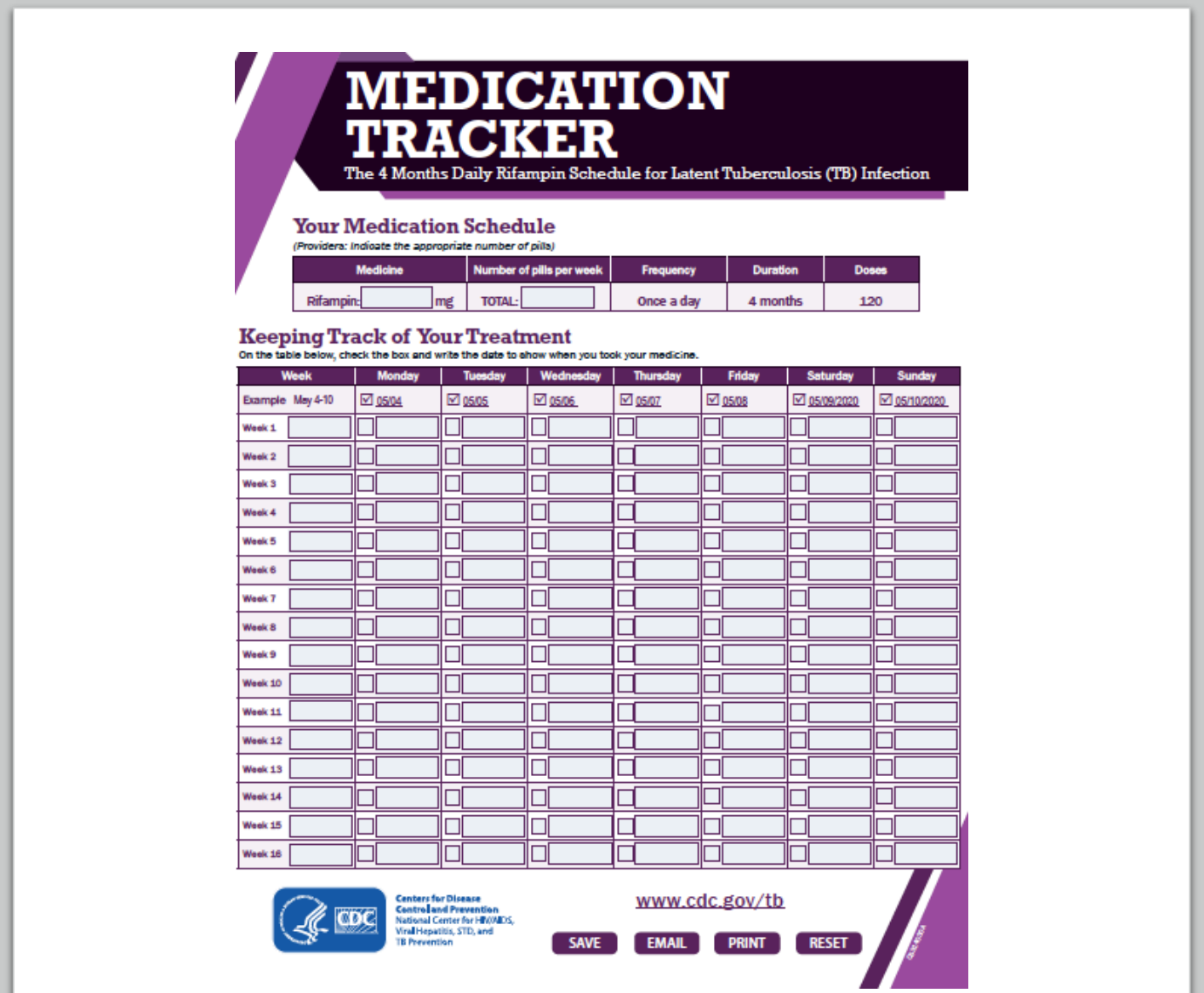
She asks if she needs to take the entire 4 months. What do you think?

What if there was no drug resistance in the index case, but there was a rifapentine shortage after her 3rd dose?

Case (cont.)

The patient's treatment is changed to rifampin daily for an additional 4 months. She is having trouble remembering to take her medication every day. What are some things that might help her?

- 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: ____ mg	TOTAL: ____	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	☑ 05/04	☑ 05/05	☑ 05/06	☑ 05/07	☑ 05/08	☑ 05/09/2020	☑ 05/10/2020
Week 1							
Week 2							
Week 3							
Week 4							
Week 5							
Week 6							
Week 7							
Week 8							
Week 9							
Week 10							
Week 11							
Week 12							
Week 13							
Week 14							
Week 15							
Week 16							

Case (cont.)

The patient completes 1 month of rifampin. She misses her next appointment due to work and childcare and an entire month passes before she is able to come back to clinic. She is feeling well and wants to complete the medication course

What do you advise her about resuming treatment?

LTBI Treatment - Summary

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