LTBI Treatment

Chandler Church, MD, MSc
Vaccine and Infectious Diseases Division
Fred Hutchinson Cancer Center

Public Health
Seattle & King County

Conflict of Interest Disclosure Statement

Neither I, nor my spouse/partner have/had financial or other relationships with ANY commercial interest organizations within the past 24 months.

Objectives

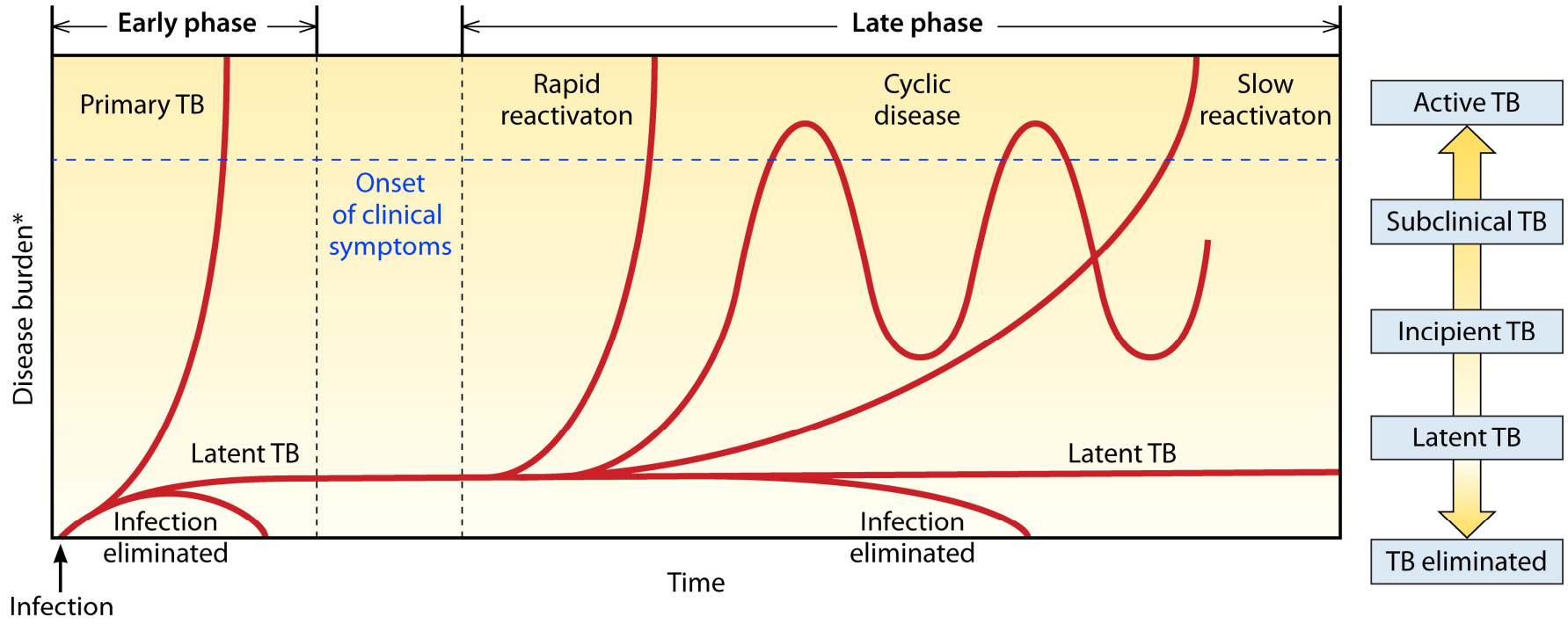
- Understand how to rule out TB disease prior to starting LTBI treatment
- Understand the recommended regimens for LTBI treatment
- Understand the main issues pertinent to each regimen
- Understand how to approach LTBI evaluation/treatment in select special situations

Outline

- Ruling out TB disease
- Recommended LTBI regimens
- Regimen specific issues
- Monitoring during treatment
- Special situations

Ruling Out TB Disease

- Treating TB disease with 1 (or 2) drugs may select for drug resistant TB
- It can be hard to "rule in" or "rule out" TB disease



*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

Drain PK, et al. Clin Micro Rev, 2018

Ruling Out TB Disease

- Negative symptom screen
- Normal CXR
  - CXR within past 3 months
  - Single view (PA) okay, unless < 5 years of age
- Negative sputum evaluation for MTB (as needed based on Sx, CXR)
- Cautions:
  - HIV: subclinical disease more common, CXR can be normal → Practically, if negative symptom screen & CXR, we do not routinely get sputum
  - Immunosuppression, kids: EPTB more common

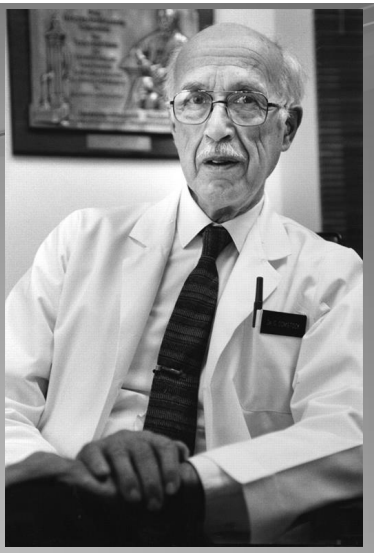
Outline

- Ruling out TB disease
- LTBI regimens
- Regimen specific issues
- Monitoring during treatment
- Special situations

Which regimen is not first-line treatment for LTBI?

A. Rifampin
B. Rifapentine + Isoniazid
C. Isoniazid
D. Levofloxacin

TB Prevention – Recent Hx



- 1957: George Comstock trials of isoniazid
  Bethel, AK
- 2000 Guidelines: regimens include 9H (preferred); 6H, 4R, 2RZ (alternatives)
- 2001: 2RZ fatalities, recommendation rescinded
- 2011: Once-weekly INH/ rifapentine x 12 weeks (3HP) under DOT
- 2018: 3HP may be given self-administered
- 2018: Daily rifampin x 4 months (4R), long used for LTBI treatment→publication of 2 large RCTs

LTBI Regimens

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

Timothy R. Sterling, MD[1]; Gibril Njie, MPH[2]; Dominik Zenner, MD[3]; David L. Cohn, MD[4]; Randall Reves, MD[4]; Amina Ahmed, MD[5]; Dick Menzies, MD[6]; C. Robert Horsburgh, Jr., MD[7]; Charles M. Crane, MD[8]; Marcos Burgos, MD[8,9]; Philip LoBue, MD[2]; Carla A. Winston, PhD[2]; Robert Belknap, MD[4,8]

- Meta-analysis with estimates for regimen effectiveness and hepatoxicity
- Recommended rifamycin based regimens over INH (alone). Compared to INH:
  - Similar efficacy
  - Less hepatotoxicity
  - Better treatment completion

Sterling MMWR 2020

LTBI Regimens: Recommendations

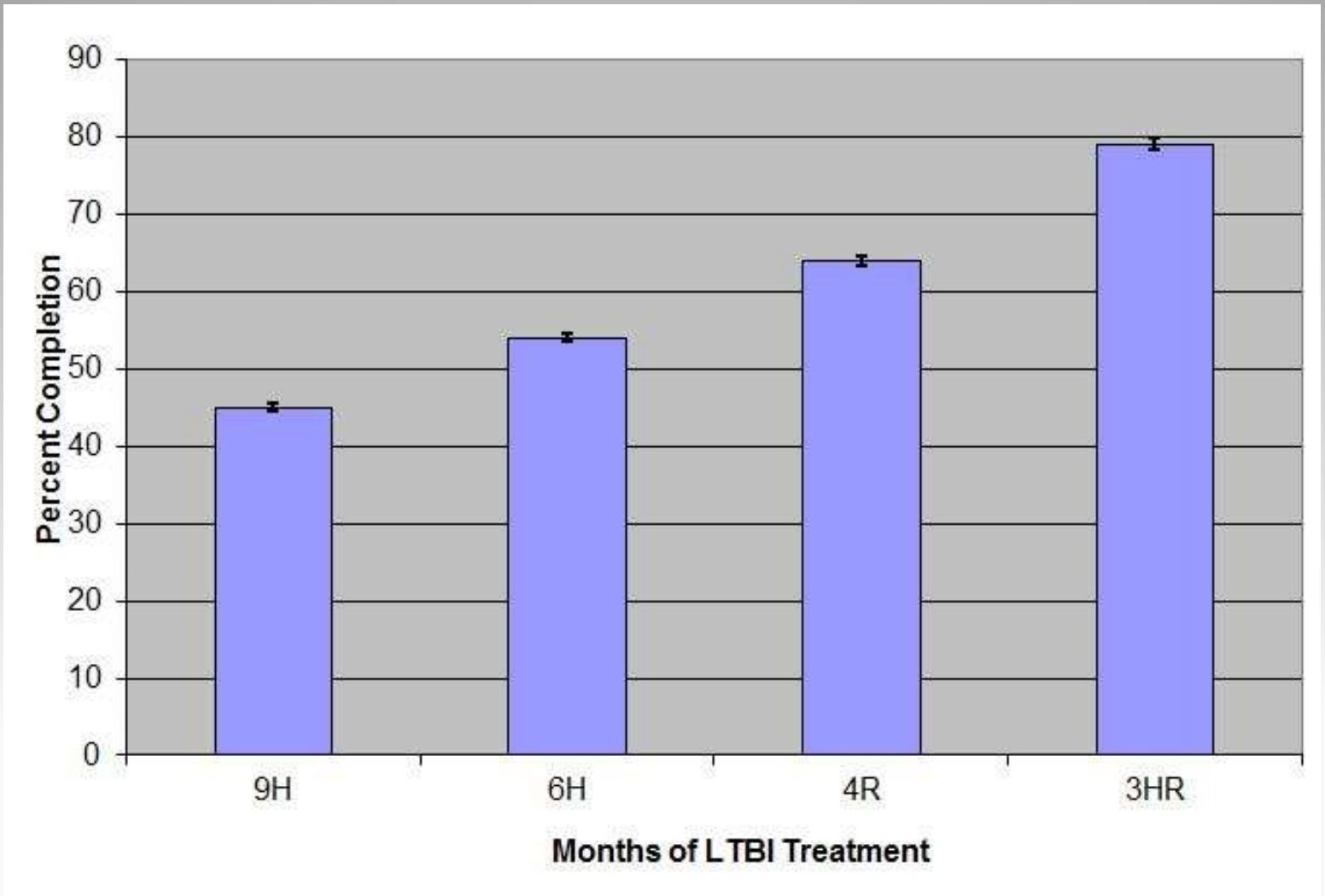
DRUGS AND DURATION	ABBREVIATION	RECOMMENDATION
Rifampin daily for 4 months	4R	Preferred
Rifapentine & INH weekly x 12 weeks	3HP	Preferred
Rifampin & INH daily x 3 months	3HR	Preferred
INH daily for 9 months	9H	Alternative
INH daily for 6 months	6H	Alternative

LTBI REGIMENS: EFFECTIVENESS & HEPATOXICITY

REGIMEN	TB, OR (95% CI)*	HEPATOTOXICY, OR (95% CI)*
4R	0.25 (0.12-0.50)	0.13 (<0.02-0.72)
3HP	0.36 (0.18-0.72)	0.53 (0.13-2.13)
3HR	0.33 (0.20-0.53)	0.73 (0.22-2.38)
9H	0.47 (0.24-0.90)	1.77 (0.35-8.32)
6H	0.40 (0.26-0.59)	1.11 (0.41-3.15)

*Compared to no treatment

Shorter regimens have better completion outcomes



Chest 2010;137:401

Outline

- Ruling out TB disease
- LTBI regimens
- Specific regimens
- Monitoring during treatment
- Special situations

Rifampin (4R)

ORIGINAL ARTICLE

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

	Rifampin	INH
Duration	4 months	9 months daily
Effectiveness	0.05 per 100	0.05 per 100
Completion rate	79%	63%
Hepatotoxicity	0.3%	1.7%

Menzies D.*New Eng J Med*. 2018; 379:440

Safety and Side Effects of Rifampin versus Isoniazid in Children

- Open-label, RCT, 7 countries, N=829 4R vs 9H
- TB: 4R (n=0) vs 9H: (n=2; 1 INH-resistant)
- Completion: 4R (85%) vs. 9H (76%)
- No difference in grade 1 or 2 adverse effects
- No grade 3, 4 or 5 adverse events

4R: Superior completion; efficacy and safety non-inferior

Diallo T. *New Eng J Med*. 2018; 379:454-63

Rifampin- Drug Interactions

- **Potent inducer of cytochrome P450**
  - rifampin>rifapentine>rifabutin
- **Antiretrovirals**
  - NRTIs → tenofovir alafenamide; NNRTIs→ NO except efavirenz; Integrase inhibitors: double dose, beware fixed dose combinations; Protease inhibitors: avoid
- **Anti-convulsants**: phenytoin, carbamazepine, valproic acid
- **Anti-coagulation**: warfarin, DOACs
- **Immunosuppressants**: Calcineurin inhibitors, **corticosteroids**, mycophenolate
- **Chemotherapy** (tamoxifen, bortezomib, imatinib, others)
- **Anti-HCV agents** (sofosbuvir, velpatasvir)
- **Methadone**
- Other: **Contraceptives**, BP meds, oral DM meds, levothyroxine

Rifampin- Adverse effects

- Hepatotoxicity
  - Rare severe hepatitis, more common when combined with other medications
  - Asymptomatic hyperbilirubinemia (0.6%)
- Dermatologic: Pruritus, rash (up to 6%)
- Hypersensitivity reaction (0.07-0.3%)
- GI: nausea, anorexia, abdominal pain
- Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)

Rifampin - Summary

4 months of rifampin – Adults & Children

- Adults: 10mg/kg/d (600mg/d max)
  - <45kg: 450mg
- Children: 15-20mg/kg/d (600mg/d max)*
- Duration: 120 doses within 180 days
- Preferred if contact to INH-monoresistant case
- Not recommended in:
  - Difficult to manage drug interactions
  - Presumed infection with RIF-resistant MTB
  - Rifamycin allergy

*The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers

Isoniazid/Rifapentine (3HP)

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D.,

	INH-RPT	INH	P-value
Effectiveness	**1.9 per 1,000**	**4.3 per 1,000**	**Non-inferior**
Completion rate	**82.1%**	**69.0%**	**P<0.001**
Hepatotoxicity	**0.4%**	**2.7%**	**P<0.001**

Prevent TB Study Results

Table 3. Adverse Events.*

Outcome	Isoniazid Only (N=3759)	Combination Therapy (N=4040)	P Value†
Related to drug	206 (5.5)	332 (8.2)	<0.001
Hepatotoxicity‖	103 (2.7)	18 (0.4)	<0.001
Rash	21 (0.6)	31 (0.8)	0.26
Possible hypersensitivity**	17 (0.5)	152 (3.8)	<0.001
Other drug reaction	65 (1.7)	131 (3.2)	<0.001

Sterling TR. *NEJM* 2011; 365(23):2155;

3HP Administration: DOT vs SA

- 3HP originally studied as DOT regimen
- CDC approved SA 3HP based on one study
  - Study population: Median age 36; all age >18; 5% homeless; 7% alcohol abuse; 5% drug use
  - Completion rates (US patients only):
    - DOT: 85.4% (CI 80.4% to 89.4%)
    - SA: 77.9% (CI 77.9% to 82.6%)
  - No increased adverse events in SA group

Belknap Ann Int Med 2017

3HP Issues

- Drug interactions (less than rifampin, but still significant)
- Large pill burden (usually 10 pills)
- Non hepatotoxic adverse effects: Rash, thrombocytopenia, GI upset

- **Flu like syndrome (2-4%)**
  - Flu like symptoms, hypotension, syncope
  - Poorly understood and difficult to predict
  - Can often safely rechallenge (use clinical judgement)

Sterling TR. *Clin Inf Dis.* 2015; 61:527

Table 2. Characterization of the 153 Systemic Drug Reactions According to Syndrome

	3HP (n = 138)	9H (n = 15)
Cutaneous[a]	23 (17%)	9 (60%)
Severe	3	1
Nonsevere	20	8
Flu-like[b]	87 (63%)	2 (13%)
Severe	6	0
Nonsevere	81	2
Gastrointestinal[c]	7 (5%)	1 (7%)
Severe	2	0
Nonsevere	5	1
Respiratory[d]	5 (4%)	0 (0%)
Severe	1	0
Nonsevere	4	0
Not defined[e]	16 (12%)	3 (20%)
Severe	1	0
Nonsevere	15	3

Isoniazid (6H/9H)

Isoniazid

- Adult dose - 300 mg/d x 6 or 9 months
  - Children 10-15 mg/kg, not to exceed 300 mg
  - 200 mg daily for adults < 40 kg
  - General: **6 or 9 month** incl children, HIV, abnl CXR
- Intermittent twice weekly dosing under **DOT**
  - Adults 15 mg/kg (900 mg max)
  - Children 20-30 mg/kg (900 mg max)
- Completion based on total number of doses
  - 270 doses for daily 9 month regimen

INH: DILI

- Hepatic accommodation: asymptomatic mild elevation in LFTs (10-20% of patients); difficult to distinguish this from early serious hepatoxicity
- Drug-induced liver injury (DILI)
  - 10-20% mild LFT abnormality - tends to resolve despite continuation
  - DILI incidence lower than previously thought (0.1 -0.15%)
- Hepatitis risk increases with age
  - Uncommon in persons <20 years old
  - Nearly 2% in persons 50 to 64 years old
- Other DILI risk factors: liver disease, heavy alcohol, baseline transaminitis, peripartum

INH

Least likely to be completed

- ~10% of TB isolates in the US are INH resistant
- Non hepatotoxic adverse events
  - Peripheral neuropathy (up to 2%), give B6 to minimize risk for certain at risk populations

    Rash
  - GI upset
  - Increases phenytoin, carbamazepine levels

3HR

- Same as those for INH and RIF monotherapy
- Older studies suggested this regimen may be more hepatotoxic that INH alone, but this was not borne out in CDC/NTCA meta-analysis

Selecting LTBI Regimen

- **<u>In general</u>, 3HP or 4R preferred due to shorter length, better adherence, and better safety profile than 9H/6H**

<u>Special considerations</u>

- Drug-susceptibility results of the presumed source case
  - INH-monoresistant? → 4R preferred
  - MDR-TB? Consult expert
- Age < 2 years? INH x 9 months preferred, 4R increasingly used
- Ages 2-11 years? Can use any of the 3 options, although most experts prefer 3HP

Selecting LTBI Regimen

- <u>Special considerations</u>
- Potential drug-drug interactions w/rifampin or rifapentine?
  - Manageable - e.g., BP medications, contraception
  - Not manageable - (e.g., protease inhibitor for HIV)→INH
- HIV-infection – No evidence for 4R
- Pregnancy – Guidelines say usually delay until 3 months post-partum. May be safer to treat during pregnancy with new less hepatotoxic regimens than with 6H/9H

Outline

- Ruling out TB disease
- LTBI regimens
- Regimen specific issues
- Evaluation & Monitoring
- Special situations

Evaluation before LTBI Treatment

- HIV-infection: Is the patient on ART or soon starting?
- Risk of liver injury? Alcohol, liver disease, viral hepatitis, medications, pregnant/<3 months post-partum
- Neuropathy risk? Increased in diabetes mellitus, ESRD, alcoholism, malnutrition, HIV infection, pregnancy/breastfeeding, seizure disorders
- Weight

Evaluation before LTBI Treatment

- **Rule out active TB disease** – CXR, symptoms
- History of previous treatment?
  - If treated, was it adequate? What was the regimen and were there adverse effects?
- List patient's medications
  - Note rifamycin interactions, e.g. anti-epileptics, blood thinners, immunosuppressants, methadone, OCPs

Treatment Monitoring

- Baseline & monthly education about adverse effects and what to do if they occur (**Communication**!!!)
  - Fatigue or weakness
  - Anorexia, nausea, vomiting, dark urine, jaundice, rash
  - Numbness/tingling in hands &/or feet
- Laboratory monitoring not routinely indicated

Treatment Monitoring

- Consider baseline LFTs & monitoring if at high risk
  - HIV
  - Daily alcohol
  - Chronic liver disease, recent abnormal LFTs
  - Pregnant or recent delivery (< 3 months),
  - Taking medications with potential for liver toxicity
- As indicated LFTs, if signs/symptoms of liver injury
- If hematologic issues (anemia, neutropenia, thrombocytopenia) & rifamycin-containing regimen→ monitor CBC

When to Interrupt LTBI Treatment

- If symptomatic for liver injury and transaminases > 3x upper limit of normal
- If asymptomatic & transaminases > 5x upper limit of normal
- If total bilirubin > 2.5 mg/dL

Outline

- Ruling out TB disease
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Case

27 yo boyfriend of smear + case with newly positive IGRA. He is on methadone and starts daily INH. He completes 3 months of therapy but stops coming to appointments. Returns 9 weeks later to restart therapy

What should you do?

A) Re-start INH after evaluating for TB – gets credit for completed treatment

B) Re-start INH from the beginning after evaluating for TB

C) He is adequately treated for LTBI

D) Since he was not compliant with therapy he should not be offered further INH

Treatment completion / Missed Doses

Based on total number of doses

Regimen	# doses	Timeframe to complete
RIF daily x 4 months	120	6 months
INH+RFP	12	16 weeks
INH daily x 9 months	270	12 months
INH daily x 6 months	180	9 months

CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000.

Pregnancy

- Treatment for LTBI controversial - Risk of increas hepatotoxicity during pregnancy and early post-partum
  - Persons **at higher risk** for TB (HIV, converter, contact)

    Recommend to <u>treat now</u> even in first trimester

  - If **lower risk** of TB - **<u>Wait until 3 months</u> postpartum**
- INH = preferred treatment
  - Crosses placental barrier, but no teratogenicity
  - Supplement with Vitamin B6
- RIF likely safe
  - Lacks efficacy data
  - Some experts prefer RIF to decrease risk of hepatotoxicity

<u>Breastfeeding</u>: medications found in low-levels in breast milk – all 3 likely safe

CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000.

Case

3 year old boy, father newly diagnosed with smear+, cavitary TB

- Evaluation: No past medical history or medications. No obvious symptoms. Exam normal. CXR normal. QFT negative.

What is the next best step?

A. Start 4 drug therapy for TB disease
B. Leave the kid alone. He's not infected
C. Repeat the QFT in ~ 8 weeks after father is no longer infectious
D. Start rifampin daily, repeat QFT ~ 8 weeks after father is no longer infectious

Window prophylaxis

After exposure, may take up to 8 weeks for TST or IGRA to turn positive

- During that time, if infected young children (age <5) are at high risk for TB disease

- "Window prophylaxis": Empiric LTBI treatment for contacts as you give the test time to turn positive
  - Rule out TB disease

    Start LTBI treatment at same time as initial test
  - If initial test is negative, retest 8 weeks after last infectious exposure; If 2nd test negative, stop treatment
- For immunosuppressed contacts with possibility of false negative TST/IGRA, consider entire course of empiric treatment

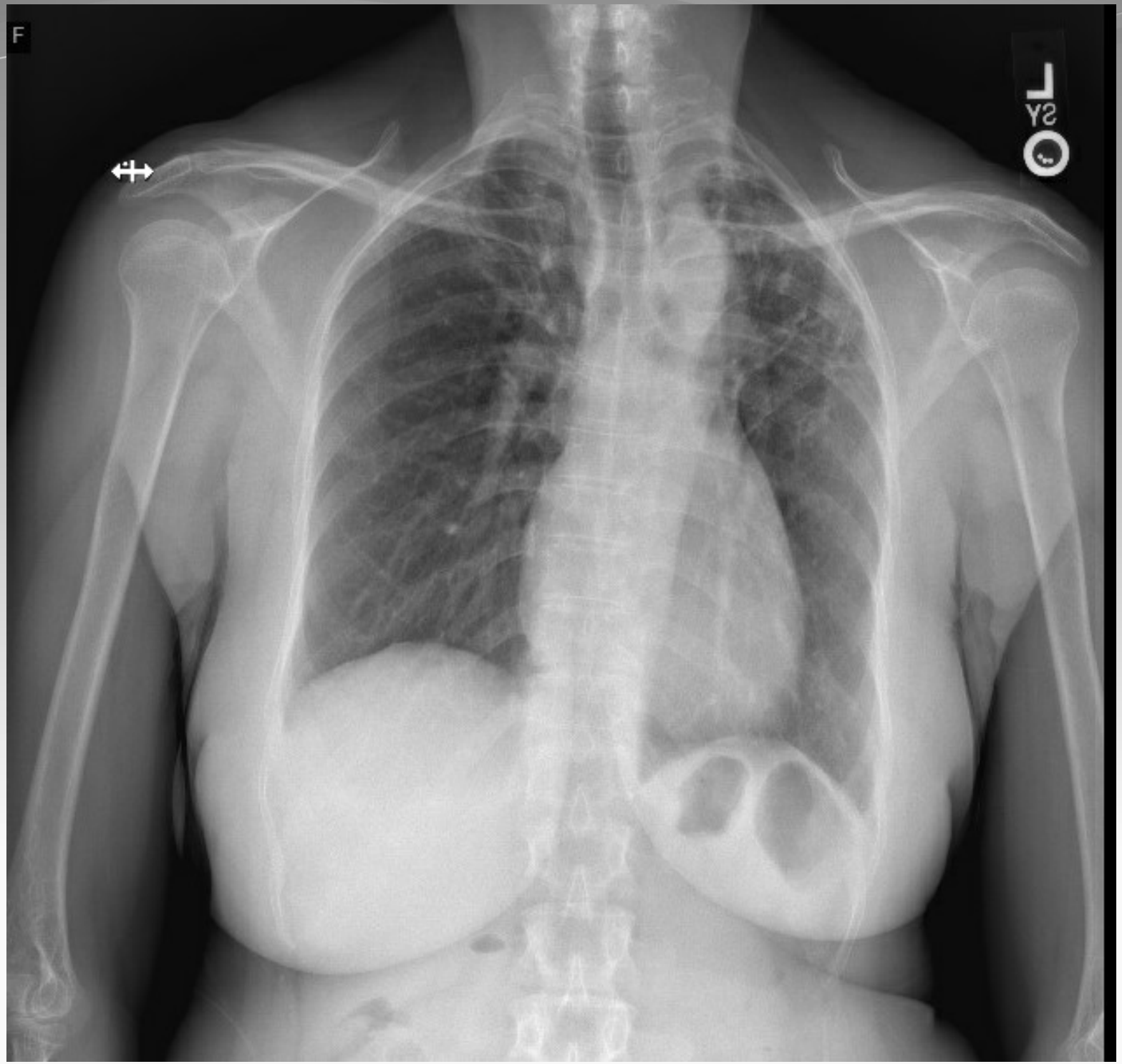
PEDIATRICS

- Children < 5 (and especially those < 1) are at increased risk for TB disease, severe disease, and CNS disease
  - Are always recently infected

    Immature immune system
- Risk of hepatitis is low, even with INH
- 3HP not recommended for those < 2 years old
- Weight based dosing, tricks to get meds into kids

Case

- 55 yo F who recently immigrated from India.
- Denies any prior TB testing or treatment. Denies any known TB disease episodes
- No other medical problems. No medications. LFTs and hepatitis serologies recently normal.
- Lives with 3 grandchildren, all under age 5
- QFT positive.
- Mild intermittent cough for > 5 years, unchanged. Otherwise asymptomatic.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Case

All of the following options are reasonable next steps EXCEPT:

A. Start rifampin daily for LTBI
B. Obtain sputum for AFB smear/culture and MTB PCR
C. Obtain sputum and start empiric 4 drug TB disease treatment
D. Isolate the patient

FIBROTIC CHANGES ON CXR

- Patients with “old healed TB” on CXR (i.e., upper lobe fibrotic changes) without prior treatment→ increased risk for TB (especially if CXR lesions are > 2 cm) and should be prioritized for LTBI treatment

- Need to rule out TB disease first:
  - Asymptomatic, prior sputum evaluation negative, and CXR is stable → No need for sputum evaluation

    Symptomatic and/or CXR changed from prior→ collect sputum, consider empiric TB disease treatment initiation

  - Asymptomatic, no prior CXR, no imaging features highly suggestive of active disease→ collect sputum and wait

PREVIOUSLY TREATED LTBI

- A test for LTBI remains positive after treatment
- After re-exposure to infectious TB, no way to know if a positive TST/IGRA indicates reinfection
- In general, it is not recommended to retreat
- Consider retreatment for those at high risk of progression if reinfected (weight risks/benefits), especially if source case is highly infectious (ie smear positive, cavitary, multiple other positive contacts)
  - HIV and other immunosuppression
  - Children < 5

LOW TB DISEASE SUSPECTS

- rifampin + pyrazinamide for 2 months has been shown to be an effective regimen for LTBI, but is not recommended due to high rates of hepatotoxicity

- In patients empirically treated for TB disease with standard 4 drug therapy (rifampin, pyrazinamide, ethambutol, and isoniazid), if they complete 2 months this is adequate LTBI treatment

MDR Contacts – Expert opinion

- Select drugs based on source case DST results
- Fluoroquinolone (levo, moxi) +/- ethambutol
  - Micronesia: 104 MDR-contacts→12-month FQN (+/- EMB)
    - Treated: no progression to TB over 36-month f/u
    - Untreated: 3/15 + 15 unidentified contacts → MDR TB

- Immunocompetent:
  - Follow without treatment; OR
  - Treat for 6-12 months & Follow x 2 yrs
- Immunocompromised→Treat 12 months & Follow x 2 yr
- Surveillance = Evaluation/Symptom review every 3-6 months x 2 years +/- CXR; sputum as indicated

** Bamrah S, et al. Int J Tuberc Lung Dis. 2014 Aug;18(8):912-8.

https://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/Tuberculosis/TBProviderToolkit#Treatment (DOH TB page->TB Provider Toolkit)

Latent tuberculosis infection (LTBI) treatment guidance in Washington State

Promoting rifamycin-based, shorter-course regimens

Latent Tuberculosis Infection (LTBI) Treatment Regimens

Regimen	Dosages	Comments
Rifampin Daily x 4 months	*Preparation*: 150mg or 300mg capsules. *Adult Dosage*: generally 600 mg Consider 450 mg once daily for adults who weigh less than 50 kg. Pediatric dosage: 15-20mg/kg/d (600mg maximum) *Target Duration:* 120 doses within 180 days	• Higher rates of treatment completion • Lower rates of side effects, especially drug-induced hepatitis • Self-administered • Caution: drug-drug interactions • Monthly symptom review for side effects
Isoniazid (INH) and *Rifapentine* Once weekly x 12 weeks 3HP "12 dose regimen"	**Isoniazid** 15 mg/kg per dose once weekly, rounded up to the nearest 50 or 100 mg (max 900 mg). For example, using 300-mg tablets Kg / Lbs / Dosage: Less than 45 kg / 98 or less / 600 mg 45 – 55 kg / 99 - 120 / 750 mg 55 kg or more / 121 or more / 900 mg max **Rifapentine** once weekly dosage *Preparation*: 150 mg tablets Kg / Lbs / Dosage: 10.0–14.0 kg / 22-31 / 300mg 14.1–25.0 kg / 32-55 / 450mg 25.1–32.0 kg / 56-71 / 600mg 32.1–49.9 kg / 72-110 / 750mg ≥50.0 kg / 111 or more / 900mg max *Target Duration:* 12 doses within 16 weeks	• Higher rates of treatment completion • Lower rates of side effects, especially drug-induced hepatitis • Can be self-administered • Shortest LTBI regimen • Caution: drug-drug interactions due to rifapentine • Monthly symptom review for side effects • If patient has diabetes, HIV, renal failure, alcoholism, poor nutrition or is pregnant/breast-feeding, administer vitamin B6 50 mg weekly
Isoniazid Daily x 6 – 9 months	*Preparation*: 100mg or 300mg tablets. *Dosage*: Adults: 5 mg/kg per dose (300 mg max) Children: 10-15mg/kg per dose (300mg max) Consider 200 mg once daily for adults 40 kg or less *Target duration:* >180 doses within 9 months acceptable; 270 doses within 12 months preferred.	• First choice for children < 2 years (crush pills as suspension is poorly tolerated) • Be aware of INH-related hepatotoxicity • Poor adherence due to longer duration of INH • Self-administered • Monthly symptom review for side effects • If patient has diabetes, HIV, renal failure, alcoholism, poor nutrition or is pregnant/breast-feeding, administer vitamin B6 25-50 mg daily
Isoniazid Twice Weekly x 6 – 9 months	*Dosage:* *Adults:* 15mg/kg per dose (900 mg max) Children: 20-30mg/kg/dose (900 mg max) *Target duration:* >52 doses acceptable within 9 months; 76 doses preferred within 12 months.	• Be aware of INH-related hepatotoxicity • The use of directly observed therapy is highly recommended and thus it requires sustained resource utilization for 6 – 9 months • Consider 3HP instead for children > 2 years and adults • Monthly symptom review for side effects • If patient has diabetes, HIV, renal failure, heavy alcohol use, poor nutrition or is pregnant/breast-feeding, administer vitamin B6 50 mg with INH

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Resources

- CDC/MMWR, Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, 2009
- Guidelines on the management of latent tuberculosis infection, WHO, 2015
- CDC. Tuberculosis associated with blocking agents against tumor necrosis factor - alpha - California, 2002–2003. MMWR 2004; 53 (No.30).
- CDC. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection – United States - 2010. MMWR 2010;59(RR05).
- Treating LTBI in Special Situations. http://sntc.medicine.ufl.edu/TrainingOnline.aspx#.VB9z7CtdVro
- 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.

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