Treating LTBI in Special Situations

Table of Contents

MODULES
Contact to a Drug-Resistant Case
Hepatitis
HIV/AIDS
Infants & Children
Pregnancy
Renal Failure
TNF Antagonists
Transplantation

REFERENCE BOOKS
Course Review & References
Managing Common Adverse Effects
LTBI Treatment Options (including short course therapy)
Interferon Gamma Release Assays (IGRAs)
LTBI Resources
Contact to Drug-Resistant Case File
Case Presentation

Mr. I is a close contact to an individual with INH-resistant TB. His TST is 11 mm induration, his chest x-ray is normal, and HIV testing is negative. Mr. I is a smoker and describes having a “smoker’s cough” for a year prior to last contact with no other associated symptoms.

TST rollover text: Tuberculin Skin Test. Note that Interferon-Gamma Release Assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
At this point, you:

Select one of the options below.

a. Consider Mr. I a TB suspect and start treatment with rifampin, pyrazinamide, and ethambutol.

b. Initiate treatment for LTBI.

c. Collect sputum for smear, nucleic acid amplification, and culture and initiate LTBI treatment.

d. Collect sputum for smear, nucleic acid amplification, and culture and follow Mr. I clinically pending culture results.
Response a: Not quite. Given Mr. I’s cough, you need to exclude active TB prior to starting LTBI treatment. However, further work-up is indicated prior to initiating treatment for active TB. Try again.

Response b: Be careful. Given Mr. I’s cough, you need to exclude active TB prior to starting LTBI treatment. Treatment of unsuspected active TB with a single drug could contribute to the development of further resistance. Try again.

Response c: Incorrect. Given Mr. I’s cough, you need to exclude active TB prior to starting LTBI treatment. LTBI treatment should not be started until you have confidently excluded active TB. Try again.

Response d: That’s right. Given Mr. I’s cough, you need to exclude active TB prior to starting LTBI treatment. It is good practice to follow Mr. I clinically while you await final culture results and make any decisions about LTBI treatment.
Treating unsuspected active TB with a single drug intended for LTBI treatment could contribute to the development of further resistance.
Smear, nucleic acid amplification, and cultures are negative for M.TB. Mr. I’s cough has resolved completely with treatment of asthma with an inhaled corticosteroid.

At this point, you offer Mr. I treatment for LTBI with:

Select one of the options below.

- a. High-dose INH for 9 months (do we want consistency with bullets?)
- b. Rifampin for 4 months
- c. High-dose INH and rifampin for 4 months
- d. Moxifloxacin for 6 months
- e. INH and Rifapentine for 12 weeks
Case Summary

+ Contact to INH-resistant case
  - TST 11 mm
  - Normal CXR
  - HIV negative
  - cough resolved with asthma treatment
  - smear, NAA, cultures negative

Response a: Incorrect. High-dose INH would not be recommended for LTBI treatment in a contact to an INH-resistant case. Try again.

Response b: Correct. Rifampin 600 mg daily (for 4 months in adults, 6 months in infants and children) is the treatment of choice for LTBI treatment in a contact to an INH-resistant case. CDC/ATS guidelines also recommend a regimen of rifampin and PZA for 2 months; however, there is a much higher risk of hepatotoxicity and is therefore rarely used in this situation.

Let’s review what you just learned.

CDC/ATS rollover text: Centers for Disease Control and Prevention/ American Thoracic Society

Response c: Incorrect. There is no added benefit of INH in this situation. Try again.

Response d: Incorrect. Moxifloxacin is not the drug of choice for LTBI treatment in a contact to an INH-resistant case. Try again.

Response e: Incorrect. Although INH and rifapentine weekly for 12 weeks is an acceptable short-course regimen for LTBI treatment, it is not recommended in the setting of known INH resistance. Try again.
Review

- Given the high morbidity and mortality associated with TB disease in close contacts, treatment of LTBI should be considered.
- Consider the possibility of active TB disease and evaluate, as clinically indicated, prior to starting any treatment to avoid development of further resistance.
Case Summary

+ Contact to INH-resistant case
  - TST 11 mm
  - Normal CXR
  - HIV negative
  - cough resolved with asthma treatment
  - smear, NAA, cultures negative
Let’s take a look at another contact to a drug-resistant case.

Mrs. R is a 30-year-old contact to a case of multidrug-resistant TB and has a TST of 13 mm induration. Her chest x-ray is normal, and she has no symptoms compatible with TB disease.

Case Summary

+ Contact to multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - Normal CXR
Which of the following is not an accepted treatment option for a contact to a case of MDR-TB?

Select one of the options below.

a. PZA and ethambutol

b. A fluoroquinolone (levofloxacin or moxifloxacin) and a second drug to which the isolate is susceptible

c. A fluoroquinolone (levofloxacin or moxifloxacin) alone

d. Clinical monitoring

e. Ethambutol and INH
MDR-TB rollover text: TB resistant to at least INH and rifampin.

Clinical monitoring rollover text: Symptom screen every 3 months for a minimum of 2 years, along with chest x-ray and/or sputum analysis, if clinically indicated.

Case Summary

+ Contact to multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - Normal CXR

Response a: Actually, this option follows CDC/ATS recommendations to use two drugs to which the index case’s isolate is susceptible. As is the case with all regimens for treatment of MDR-LTBI, there is no data on efficacy in preventing progression to disease. This regimen may be better tolerated than fluoroquinolone-containing regimens.

Response b: Actually, this option follows CDC/ATS recommendations to use two drugs to which the index case’s isolate is susceptible. As is the case with all regimens for treatment of MDR-LTBI, there is no data on efficacy in preventing progression to disease. There appear to be high rates of hepatitis and intolerance with levofloxacin/PZA; levofloxacin/ethambutol may be better tolerated. Try again.

Response c: Although CDC/ATS guidelines recommend treating MDR-LTBI with two drugs to which the isolate is susceptible, many experts recommend a fluoroquinolone alone, because of the known in vitro anti-tuberculosis activity of the quinolones and the higher likelihood of completion of this regimen. Try again.

Response d: Incorrect. Given the lack of proven efficacy of any treatment for MDR-LTBI and the high likelihood of side effects, clinical monitoring without treatment is a reasonable alternative. All contacts should be educated on the signs and symptoms of TB disease. This option is most appropriate when a contact fails to tolerate an LTBI
treatment regimen and is not HIV-infected, under 5 years of age, a documented TST/IGRA converter, or otherwise at high risk of progression to TB disease. Try again.

IGRA rollover text: Interferon-Gamma Release Assays

Response e: Good job. The combination of INH and ethambutol is not a regimen recommended for treatment of MDR-LTBI.

Let’s review what you just learned.
Review

- Although there is limited data to support any single approach, CDC/ATS guidelines advocate treatment of MDR-LTBI with two drugs to which the index case’s isolate is susceptible; however, many experts advocate treatment with a fluoroquinolone alone if the index case isolate is susceptible to a fluoroquinolone.

CDC/ATS rollover text: Centers for Disease Control and Prevention/ American Thoracic Society

- The regimen should be tailored for each individual based on the susceptibility results of the source case isolate.
- Most experts recommend treatment for a duration of 6-12 months.
- Transmission of MDR-TB is well documented, and therefore full evaluation of all contacts should be pursued.
MDR-TB rollover text: TB resistant to at least INH and rifampin.

- As in LTBI with a pansensitive isolate, TB disease must be excluded prior to starting an LTBI regimen to minimize the potential for development of further resistance.

- If the option of no drug treatment is selected, close and active clinical monitoring is essential.

Clinical monitoring rollover text: Symptom screen every 3 months for a minimum of 2 years, along with chest x-ray and/or sputum analysis, if clinically indicated.

- Expert consultation to assist in treatment choices for contacts to MDR cases is recommended.

Expert consultation rollover text: Each of the four TB Regional Training and Medical Consultation Centers (RTMCC) is available to assist in the treatment of challenging cases. Contact information for each center is listed in the LTBI Resources reference book.
On further history, you learn that Mrs. R was first told that she had a positive TST (13 mm) at the time of her immigration from Honduras four years ago. She had deferred LTBI treatment at that time. She has no other medical problems and is not HIV-infected. She is breastfeeding her 4-month-old infant. The index MDR-TB case was non-cavitary and smear-negative, and only two of eight household contacts are documented TST converters. Mrs. R’s contact to the case was casual, one hour per day for three weeks in a well-ventilated area of her office.
Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
Taking all of Mrs. R’s reported history into account, you decide to treat her with:

Select one of the options below:

a. No treatment, as Mrs. R is unlikely to be infected with TB. Her TST of 13 mm likely reflects BCG vaccination.

b. No treatment, as LTBI treatment is strictly contraindicated in the nursing mother.

c. INH alone now, or INH and moxifloxacin after Mrs. R stops breastfeeding.

d. Moxifloxacin, pyrazinamide, and ethambutol, as Mrs. R may have MDR-LTBI and needs to protect her nursing infant.

Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
- TST 13 mm
- CXR normal
- HIV negative
- currently nursing

Response a: Be careful. Mrs. R meets criteria for treatment of LTBI, as she is a recent immigrant from a country where TB is endemic and has a TST of 10 mm or greater. Screening for LTBI with an IGRA might also be considered in this case, given the higher specificity of IGRA in individuals who received BCG in their country of origin. Try again.

Response b: Actually, Mrs. R meets criteria for treatment of LTBI, as she is a recent immigrant from a country where TB is endemic and has a TST of 10 mm or greater. LTBI treatment is not contraindicated in the nursing mother. Try again.

Response c: Correct. CDC/ATS guidelines advocate treatment of MDR-LTBI with two drugs to which the isolate is susceptible, and some experts recommend a fluoroquinolone alone. Based on epidemiologic risk in this case, Mrs. R is more likely to have been infected with a drug-sensitive strain in her country of origin than with MDR-TB from her limited contact with a case with a low level of infectiousness. Furthermore, Mrs. R likely has some degree of innate immunity related to exposure prior to immigration conferring relative protection against reinfection. Thus, treatment with INH alone now is one possible approach to this case.

Response d: Incorrect. Treatment for MDR-LTBI does not require all three drugs; CDC/ATS guidelines advocate treatment with two drugs to which the isolate is susceptible, and some experts recommend a fluoroquinolone alone. While moxifloxacin, pyrazinamide, and ethambutol are not strictly contraindicated in the nursing mother, the risks to the nursing infant are not well understood. In an animal model, fluoroquinolones have adverse effects on growing cartilage. Therefore, ATS guidelines advocate its use only when the potential benefit is high in the setting of active MDR-TB or if alternative regimens are not available. Try again.
If there is concern that Mrs. R may have been reinfected with the MDR strain, INH and moxifloxacin (to treat LTBI due to both a pansensitive and a multi-drug resistant organism) could be considered, once she is no longer breastfeeding. ATS guidelines do not recommend fluoroquinolones in the nursing mother due to possible effects on cartilage growth.

Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
Overall, there are several variables to consider when selecting treatment regimens for contacts to drug-resistant cases:

- Drug susceptibility of the M.TB isolate of the presumed source case

- **Infectiousness** of the source MDR-TB case

  **Infectiousness** rollover text: The infectiousness of a case is determined by smear and culture status, presence or absence of cavitary disease, site of TB involvement, and evidence of transmission to other contacts.

- **Intensity** of exposure

  **Intensity** rollover text: Intensity of exposure is determined by the cumulative hours spent with the source case and the setting of the exposure.

- Contact’s likelihood of prior exposure to drug-sensitive TB
Likelihood of prior exposure rollover text: Likelihood of prior exposure is determined by considering the contact’s TST/IGRA history, history of foreign residence, and history of prior exposures to TB disease.

- Likelihood of progression to TB disease

Likelihood of progression rollover text: Likelihood of progression is determined by the contact’s immunosuppression, age, documented TST/IGRA conversion, and whether they have diabetes, renal failure, and other medical conditions.

- Tolerability and toxicity of drugs to be used for LTBI treatment

Consider the use of an IGRA for individuals from areas where they were likely to have received BCG vaccination.

Select the most effective, best-tolerated regimen to which the TB is likely to be sensitive.

Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
Let’s take a look at the household contacts to the MDR-TB case. As previously mentioned, there was evidence of transmission to two of eight household contacts. These two contacts are US-born with no history of prior contact to a TB case:

- a 4-year-old boy with a TST of 0 mm at baseline, and a TST of 10 mm after 8 weeks
- a 50-year-old woman with diabetes, a documented TST of 0 mm 2 years ago, and a current TST of 12 mm

The case is known to be sensitive to moxifloxacin, pyrazinamide, and ethambutol.
Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
Which of the following is an acceptable option for treatment of these two contacts? Select one of the options below.

a. PZA and ethambutol for both, with window prophylaxis for the child
b. Moxifloxacin for both, with window prophylaxis for both
c. Moxifloxacin for both, with window prophylaxis for neither
d. PZA alone for both, with window prophylaxis for the boy

Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - negative multi
  - 4 years ago at immigration
  - OK normal
  - HIV negative
  - currently nursing
- CXR normal
- HIV negative
- currently nursing

Response a: Correct. The regimen of PZA and ethambutol satisfies CDC/ATS recommendations to treat MDR-TB contacts with two drugs to which the isolate is susceptible. Because the child is under 5, window prophylaxis would be recommended pending repeat TST at 8-12 weeks after last exposure to the case. The 50-year-old woman is a documented TST converter with diabetes, an additional risk factor for progression; however, window prophylaxis is generally reserved for very young children and HIV-infected individuals with very close contact to a highly infectious case.

Response b: Incorrect. Although monotherapy with moxifloxacin would be recommended by many experts for the woman, prolonged treatment with fluoroquinolones is generally avoided in very young children due to the potential adverse effects on growing cartilage, especially if there are alternative regimens available. Window prophylaxis is not indicated for the mother. Try again.

Response c: Incorrect. Although monotherapy with moxifloxacin would be recommended by many experts for the woman, prolonged treatment with fluoroquinolones is generally avoided in children when possible due to the potential adverse effects on growing cartilage, especially if there are alternative regimens available. Window prophylaxis would be recommended for the child under 5 years of age. Try again.

Response d: Monotherapy with PZA is not an accepted treatment regimen for MDR-LTBI. Although the index case is sensitive to PZA, CDC/ATS guidelines recommend treatment with at least two drugs to which the organism is susceptible. Monotherapy with a fluoroquinolone but not PZA is recommended by many experts. Window prophylaxis is recommended in children under 5 or in individuals with HIV with very close contact to a highly infectious case. Try again.
Although emerging data is beginning to suggest that fluoroquinolones may be safe even in children, there are concerns that fluoroquinolones may cause arthropathy in very young children (based on extrapolation from animal data). While many experts would recommend monotherapy with moxifloxacin for the woman, fluoroquinolones have been reserved historically for children (with parental informed consent) when the benefit of treatment clearly outweighs the risk, and there is no reasonable alternative.

Let’s review what you just learned
Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
Review

- Window prophylaxis should be considered in very high-risk contacts who are TST-negative when exposure is intimate and prolonged, and transmission to other contacts has been documented.
- Immunosuppressed contacts should be treated with a multi-drug MDR-LTBI regimen rather than monotherapy.
- Every contact to a drug-resistant case should be followed clinically for two years at a minimum and should be educated about the signs and symptoms of TB disease.
Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
How long do you plan to treat the two contacts with the MDR-LTBI regimen?

Select one of the options below.

a. 4 months

b. 12 months

c. 2 years

d. Indefinitely

Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
- CXR normal
- HIV negative
- currently nursing

Response a: Incorrect. Despite the lack of efficacy data, most experts agree that 4 months of treatment would not be considered adequate for MDR-LTBI treatment. Try again.

Response b: Correct. Recommendations are to treat MDR-LTBI for 6-12 months. Young children and immunosuppressed patients should be treated for 12 months at a minimum.

Response c: Careful. Contacts to a drug-resistant case should be followed clinically for a minimum of two years. That is not the recommended length of treatment. Try again.

Response d: Incorrect. Indefinite treatment would not be recommended, given the lack of data on efficacy and the potential for adverse effects over time. Try again.
All contacts, regardless of the selected treatment regimen, should be educated on the signs and symptoms of TB disease and should understand the need for prompt medical attention if symptoms occur. Most experts recommend clinical follow up, with symptom review at a minimum, every 3-6 months for 2 years after MDR-LTBI treatment is completed. Special emphasis (and possibly more detailed evaluation with physical examination, radiographs, and sputa) should be placed on contacts who have not received MDR-LTBI treatment as well as treated high-risk contacts.

High-risk contacts rollover text: Those with HIV or other immunocompromising conditions, under age 5, and TST converters.

- MDR-LTBI for 6-12 months, with longer durations for immunosuppressed individuals.
Case Summary

+ Casual contact to smear-negative multi-drug resistant case
  - asymptomatic
  - TST 13 mm
  - CXR normal
  - HIV negative
  - currently nursing
Let’s take a look at one more contact to a drug-resistant case.

Mr. X is a 40-year-old man who is a contact to a case of TB resistant to rifampin, INH, ethambutol, PZA, moxifloxacin, and amikacin. His TST is 13 mm induration, his chest x-ray is normal, and he is asymptomatic.

Case summary:
+ Contact to case resistant to rifampin, INH, ethambutol, PZA, moxifloxacin and amikacin
  - TST 13 mm
  - CXR normal
  - asymptomatic
Which of the following is an acceptable treatment option for Mr. X?

Select one of the options below.

a. Close observation or a multi-drug regimen including rifampin and INH

b. Close observation or a multi-drug regimen including oral second-line drugs

c. Close observation or a multi-drug regimen including more than one injectable drug

d. Close observation or monotherapy with moxifloxacin
Case summary:

+ Contact to case resistant to rifampin, INH, ethambutol, PZA, moxifloxacin and amikacin

-TST 13 mm

-CXR normal

-asymptomatic

Response a: Incorrect. Given the limited treatment options for contacts to an XDR case, close clinical observation is always a reasonable alternative to treatment. Depending on the risk/benefit ratio in a given patient, drug therapy is also a possibility. The index case is resistant to INH and rifampin. As such, neither INH nor rifampin would be expected to be effective for LTBI treatment in contacts to such cases. Try again.

Response b: Correct. Extensively-drug resistant TB is, by definition, TB resistant to at least INH, rifampin, fluoroquinolones and an aminoglycoside. As such, monotherapy with a fluoroquinolone would not be expected to be effective for LTBI treatment in contacts to such cases. Although a multi-drug regimen of oral second line agents may be considered, there is no data to support this approach. Most experts recommend close clinical monitoring in the vast majority of patients.

Response c: Incorrect. Given the limited treatment options for contacts to an XDR case, close clinical observation is always a reasonable alternative to treatment. Although second-line injectables might be considered in contacts with very high risk of progression to active disease, most experts would not recommend injectables for preventive treatment, given the adverse effects and discomfort associated with these drugs. Try again.

Response d: Incorrect. Given the limited treatment options for contacts to an XDR case, close clinical observation is always a reasonable alternative. Depending on the
risk/benefit ratio in a given patient, drug therapy is also a possibility. Extensively-drug resistant TB is, by definition, TB resistant to at least INH, rifampin, fluoroquinolones and an aminoglycoside. Even if the index case had in-vitro susceptibility to other fluoroquinolones, the possibility of cross-resistance in vivo among the fluoroquinolones renders fluoroquinolone monotherapy a poor choice for LTBI treatment in contacts to such cases. Try again.
Review

- Given the limited data and experience in treating LTBI due to contact to an XDR case, drug therapy is frequently not recommended, depending on the risk/benefit ratio in a given patient. In these cases, close clinical observation is essential.
- Expert consultation is recommended.
Now that you’ve learned about LTBI treatment in contacts to a drug-resistant case, try to answer a few review questions.
Review questions:

Is close clinical observation an appropriate management option for contacts to MDR or XDR TB cases?

a. Yes

b. No

Response a: That’s right. Given the limited data and experience on treatment, close clinical observation is frequently an appropriate management option for contacts to MDR or XDR TB cases. Risks and benefits need to be weighed in each individual case.

Response b: Actually, given the limited data and experience on treatment, close clinical observation is frequently an appropriate management option for contacts to MDR or XDR TB cases. Risks and benefits need to be weighed in each individual case.
Review questions:
Should every contact to a drug-resistant case be educated on the signs and symptoms of TB disease and undergo regular clinical follow up for at least two years following exposure?

  a. Yes
  b. No

Response a: Regardless of the selected treatment option, patient education and regular clinical follow up are the mainstay of management of contacts to drug-resistant cases of TB.

Response b: Actually, regardless of the selected treatment option, patient education and regular clinical follow up are the mainstay of management of contacts to drug-resistant cases of TB.
Review questions:

Should an adult contact to an MDR-TB case be treated with either PZA and ethambutol or moxifloxacin monotherapy?

a. Yes
b. no

Response a: Correct. PZA and ethambutol or moxifloxacin monotherapy are both acceptable treatment options for adult contacts to an MDR-TB case.

Response b: Actually, PZA and ethambutol or moxifloxacin monotherapy are both acceptable treatment options for adult contacts to an MDR-TB case.
Congratulations! You have completed the LTBI Treatment in Contacts to a Drug-Resistant Case module. Click here to view the references for this module and a list of all Contacts to a Drug-Resistant Case Review Points.

Click MENU to return to the main menu.
Hepatitis File
Case Presentation

Mr. H is a 45-year-old man from Mexico. He immigrated last year. Following the CDC guidelines for targeted tuberculin testing, you perform a TST. Induration is 13 mm. He has no signs or symptoms of active TB, and chest x-ray is normal. On screening for a history of liver disease, he states he believes he was once told he had hepatitis. You perform hepatitis screening and discover that he has hepatitis C.

TST rollover text: Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
At this point, you:

Select one of the options below.

a. Screen for signs and symptoms of active hepatitis and draw baseline liver function tests.

b. Refer the patient to a hepatologist for treatment of hepatitis C, and defer treatment of LTBI for now.

c. Reassure Mr. H that his risk of progression to active TB is low and that in the setting of hepatitis C, the risk of hepatotoxicity outweighs the benefit.

d. Begin treatment with rifampin.

e. Screen for signs and symptoms of active hepatitis and begin treatment with INH if the screen is negative.
Response a: That’s right. Immigration within the past 5 years from a country where TB is endemic represents a risk of progression to active disease; hence treatment of LTBI is recommended.

Response b: Not quite. Most patients with hepatitis C will tolerate treatment with INH. Treatment of hepatitis C may be recommended in cases where LTBI treatment is not tolerated and the risk of progression to active disease is high. Try again.

Response c: Not exactly. Most patients with hepatitis C will tolerate treatment with INH. Immigration within the past 5 years from a country where TB is endemic is a risk factor for progression to active disease. For that reason, treatment of LTBI is recommended. Try again.

Response d: Actually, most patients with hepatitis C will tolerate treatment with INH, which remains the treatment of choice in this population. Try again.

Response e: Be careful. Even in the absence of signs or symptoms of hepatitis, baseline liver function tests are recommended in the setting of known hepatitis. Try again.
Even in the absence of signs and symptoms, baseline liver function tests are recommended for patients with a possible liver disorder, those with a history of chronic liver disease, and those who use alcohol regularly. However, studies have failed to show a clear association between the presence of hepatitis C alone and INH hepatotoxicity risk. The vast majority of patients with hepatitis C will tolerate treatment with INH, and this drug remains the treatment of choice in this population.

Liver function tests text rollover: Liver function tests should include serum ALT and bilirubin, at a minimum.

Chronic liver disease text rollover: Examples include chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis.
Mr. H has no symptoms of active hepatitis. Baseline liver function tests results are:

- total bilirubin 0.5
- direct bilirubin 0.1
- AST 45
- ALT 50
- ALKP 100.

Mr. H is taking acetaminophen every 6 hours for osteoarthritis of the right knee.
Case Summary:

45-yo man
- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- at baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100

Symptoms of active hepatitis text rollover: Symptoms include abdominal pain, nausea, and jaundice.
At this point, should you defer LTBI treatment?

Select one of the options below.

a. Yes  
b. No

Case summary:

45-uo man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- at baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
Response a: Actually, you do not need to defer LTBI treatment at this time. Because liver function is only minimally elevated and Mr. H has no symptoms of active hepatitis, you can still treat him for LTBI with a low risk of complications.

Response b: You’re right. You do not need to defer LTBI treatment at this time. Because liver function is only minimally elevated and Mr. H has no symptoms of active hepatitis, you can still treat him for LTBI with a low risk of complications.
It is essential that Mr. H discontinue use of acetaminophen and any other hepatotoxic medications and abstain from alcohol while being treated for LTBI. It is also crucial that you educate Mr. H on the signs and symptoms of hepatitis and advise him to discontinue treatment of LTBI and seek medical attention immediately should such signs or symptoms develop on therapy. Consultation with a hepatologist could also be considered, although it is not absolutely necessary at this point.

Case summary:

45-yo man
- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- at baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
You educate Mr. H on the signs and symptoms of hepatotoxicity and counsel him to discontinue treatment and seek medical attention should such signs or symptoms develop. You also explain the importance of abstaining from alcohol and discontinuing use of acetaminophen and any other hepatotoxic medications.

Case summary:

45-yr old man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- at baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
Following your consultation with Mr. H, you recommend:

a. treatment with rifampin, with regular clinical and laboratory monitoring
b. treatment with rifabutin, with regular clinical and laboratory monitoring
c. treatment with INH, with regular clinical and laboratory monitoring
d. treatment with INH, with regular clinical monitoring alone; regular laboratory monitoring is not required.

Case summary:

45-yo man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- at baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100

Response a: Incorrect. Although the patient has hepatitis C, the ALT is minimally elevated, and INH remains the treatment of choice. Treatment with rifampin should be reserved for patients with INH resistance or intolerance to INH.

Response b: Not exactly. Although the patient has hepatitis C, the ALT is minimally elevated, and INH remains the treatment of choice.

Response c: That’s right. Although Mr. H has hepatitis C, the ALT is minimally elevated. INH remains the treatment of choice. However, liver function testing at baseline and follow-up are recommended in addition to patient education and regular clinical monitoring. The frequency of monitoring is debated; however, monthly monitoring at a minimum is suggested. Let’s review what you’ve just learned.

Response d: Incorrect. In the presence of known hepatitis, baseline and follow-up liver function testing is recommended.
Review

- Presence of hepatitis C alone is not a contraindication to LTBI treatment.
- Even in the absence of signs and symptoms, baseline and follow-up liver function tests are recommended for patients with a possible liver disorder, those with a history of chronic liver disease, and those who use alcohol regularly.
- Patient education and monitoring is the mainstay of prevention of drug-related hepatotoxicity. Patients should be educated on the signs and symptoms of hepatitis with strict instructions to avoid alcohol and hepatotoxic medications and to discontinue treatment and seek medical attention should signs and symptoms of hepatitis develop.
- INH remains the treatment of choice in asymptomatic patients with hepatitis C and normal or minimally elevated liver function.
Liver function tests text rollover: Liver function tests should include serum ALT and bilirubin, at a minimum.

Chronic liver disease text rollover: Examples include chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis.
On clinical follow-up at 1 month of treatment, liver function is stable. At 2 months, however, liver function is as follows:

- **total bilirubin** 0.6
- **direct bilirubin** 0.2
- **AST** 300
- **ALT** 100
- **ALKP** 180

**Case summary:**

45-yo man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180
Mr. H is asymptomatic. At this point, you:

Select one of the options below.

a. advise Mr. H that he is not a candidate for LTBI treatment and refer him for liver transplantation

b. ask Mr. H about alcohol use

c. ask Mr. H about a history of symptoms of biliary colic

d. reassure Mr. H that elevation of liver enzymes is common with hepatitis C and is not a cause for concern

Case summary:

45-yo man
- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180

Response a: Be careful. You need to consider potential causes of the transaminase elevation before deciding on a course of action. Try again.

Response b: Correct. A disproportionate elevation of AST relative to ALT is the most common biochemical abnormality seen in alcoholic hepatitis.

Response c: Incorrect. The pattern of liver function abnormality here is hepatocellular, not cholestatic. There is little in this presentation to suggest biliary obstruction from a gallstone. Try again.

Response d: Be careful. Any significant elevation of liver enzymes needs to be taken seriously, and you need to do more to elucidate the cause of the abnormality before deciding to continue treatment with INH. Try again.
You need to have a candid discussion with Mr. H about alcohol use and the serious risks of continued use. If he abstains from alcohol and any other hepatotoxins, INH may be resumed once liver function returns to baseline.

Case summary:

45-ya man
- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180
Mr. H admits to recent alcohol use. After a productive conversation with you, he has a better understanding of the necessity of abstinence from alcohol and avoidance of all hepatotoxins. Liver function returns to baseline.

However, at 3 months of treatment, liver function is as follows:

- total bilirubin 0.5
- direct bilirubin 0.1
- AST 300
- ALT 274
- ALKP 200
Case summary:

45-yo man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180
- EtOH use discontinued
- at 3 months of Tx: tbili 0.5, dbili 0.1, AST 300, ALT 274, ALKP 200
Mr. H is asymptomatic and denies any alcohol use. At this point, you:

Select one of the options below:

a. Discontinue INH and explain to Mr. H that the risk of treatment of LTBI outweighs the benefit and that any further attempts at treatment are likely to result in progressive hepatic failure.

b. Discontinue INH and consider treatment of LTBI with a rifamycin for 4 months once liver function returns to baseline.

c. Discontinue INH and consider treatment of LTBI with moxifloxacin for 4 months once liver function returns to baseline.

d. Continue INH but perform clinical and laboratory monitoring more frequently (e.g. weekly).
Case summary:

45-yo man
- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180
- EtOH use discontinued
- at 3 months of Tx: tbili 0.5, dbili 0.1, AST 300, ALT 274, ALKP 200

Response a: Incorrect. At this point, Mr. H has had an asymptomatic elevation of ALT > 5x the upper limit of normal (ULN) on INH, but you do not need to abandon LTBI treatment entirely. Mr. H does have a risk factor for progression to active TB disease (recent arrival from a country where TB is endemic), and there may be ways to minimize the risk of hepatotoxicity. Try again.

Response b: Correct. The ATS statement on hepatotoxicity of anti-TB therapy suggests rifampin as a treatment option for LTBI when INH hepatotoxicity becomes a treatment-limiting factor. Despite limited data on efficacy, many experts suggest that rifabutin is also an option in this situation, with an even lower risk of liver toxicity than rifampin.

ATS text rollover - American Thoracic Society.

Treatment-limited factor text rollover - ALT increases to 5 times the ULN without associated symptoms, to 3 times the ULN with associated symptoms of hepatitis (nausea, vomiting, abdominal pain, jaundice or unexplained fatigue), or 2-3 times baseline if the baseline is 3 times the ULN or greater.
Response c: Moxifloxacin for 4 months is not a recommended treatment regimen for LTBI. Try again.

Response d: Be careful. Because Mr. H has experienced a treatment-limiting side effect (asymptomatic elevation of ALT > 5x the ULN) on INH and has known hepatitis C, rechallenge with INH would not be advised in this case. Try again.
You decide to offer Mr. H treatment with rifabutin for 4 months for treatment of LTBI. He experiences no adverse effects for the first few weeks. He then calls your office complaining of nausea, vomiting, and abdominal pain.

Liver function tests for Mr. H are as follows:

- total bilirubin 5.0
- direct bilirubin 3.0
- AST 150
- ALT 175
- ALKP 600

Abdominal ultrasound is unremarkable.
Case summary:

45-yo man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180
- EtOH use discontinued
- at 3 months of Tx: tbili 0.5, dbili 0.1, AST 300, ALT 274, ALKP 200
- switch INH to rifanutin
- within 1 month of Tx: tbili 5.0, dbili 3.0, AST 150, ALT 175, ALKP 600 with normal liver u/s
At this point, you:

Select one of the options below.

a. Discontinue rifabutin and defer LTBI treatment for now.
b. Hold rifabutin and rechallenge with rifabutin 300 mg biweekly by DOT once liver function is back to baseline.
c. Discontinue rifabutin and begin LTBI treatment with moxifloxacin 400 mg daily once liver function is back to baseline.
d. Hold rifabutin and rechallenge with INH 300 mg orally triweekly once liver function is back to baseline.
e. Discontinue rifabutin and refer the patient to a hepatologist for immediate treatment of hepatitis C.
Case summary:

45-yo man

- from Mexico  
- TST 13 mm  
- asymptomatic  
- CXR normal  
- hepatitis C  
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100  
- Tx with INH started  
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180  
- EtOH use discontinued  
- at 3 months of Tx: tbili 0.5, dbili 0.1, AST 300, ALT 274, ALKP 200  
- switch INH to rifanutin  
- within 1 month of Tx: tbili 5.0, dbili 3.0, AST 150, ALT 175, ALKP 600 with normal liver u/s

Response a: Correct. While the rifamycins most frequently produce a cholestatic pattern of hepatotoxicity (unlike INH, which produces primarily a hepatocellular pattern), the pattern may be mixed, as in this case. It is important to exclude biliary obstruction by performing an ultrasound of the liver.

Response b: Be careful. Given that Mr. H has developed symptoms with transaminases > 3x ULN, rifabutin should be discontinued. Try again.

Response c: Not quite. Given that Mr. H has developed symptoms with transaminases > 3x ULN, rifabutin should be discontinued. However, moxifloxacin is not a recommended regimen for LTBI treatment in this case. Try again.

Response d: Not exactly. Given that Mr. H has developed symptoms with transaminases > 3x ULN, rifabutin should be discontinued. However, given that the patient has had an
increase in transaminases to above 5x the ULN on INH, rechallenge with INH is not recommended in this case. Try again.

Response e: Incorrect. Laboratory testing for HCV RNA and referral to a hepatologist is appropriate in this case. However, given that Mr. H is not immunosuppressed and was not a close contact to a case, treatment of LTBI is not urgent, and it is likely that the risk of hepatotoxicity outweighs the benefit of treatment in this case. Try again.
Given that Mr. H has developed symptoms with transaminases > 3x ULN, rifabutin should be discontinued. Laboratory testing for HCV RNA and referral to a hepatologist would not be inappropriate. However, given that Mr. H is not immunosuppressed and was not a close contact to a case, treatment of LTBI is not urgent, and it is likely that the risk of hepatotoxicity outweighs the benefit of treatment at this time. If Mr. H had a history of HIV, severe immunosuppression, or if he was a recent contact to an active TB case, referral for treatment of hepatitis C would be considered more urgent.

Let’s review what you just learned.

Case summary:

45- yo man

- from Mexico
- TST 13 mm
- asymptomatic
- CXR normal
- hepatitis C
- baseline: tbili 0.5, dbili 0.1, AST 45, ALT 50, ALKP 100
- Tx with INH started
- at 1 month of Tx: tbili 0.6, dbili 0.2, AST 300, ALT 100, ALKP 180
- EtOH use discontinued
- at 3 months of Tx: tbili 0.5, dbili 0.1, AST 300, ALT 274, ALKP 200
- switch INH to rifanutin
- within 1 month of Tx: tbili 5.0, dbili 3.0, AST 150, ALT 175, ALKP 600 with normal liver u/s
Review

- While INH hepatotoxicity usually occurs in a hepatocellular pattern, the pattern with the rifamycins is often cholestatic, although a mixed pattern can also be seen, especially in the setting of viral hepatitis.

- When the AST/ALT ratio is greater than 2, alcohol use should be suspected, and the patient should be re-educated regarding the importance of avoidance of alcohol and any other hepatotoxins.

- In the setting of known viral hepatitis, it is not recommended to rechallenge with a drug on which a treatment-limiting threshold was reached.

- Rifampin or rifabutin for 4 months may be considered when treatment-limiting thresholds are reached on INH.

- When treatment-limiting thresholds are reached on a rifamycin, decisions regarding treatment of LTBI depend on a careful assessment of risks and benefits.
Let’s take a look at another case.

Mrs. B is a close contact to her husband, who was recently diagnosed with smear-positive cavitary pulmonary TB. She is a 50-year-old caregiver at a children’s daycare. TST was 0 mm at the time of her employment physical last year. TST is now 20 mm induration. Chest x-ray is normal. When you ask her about a history of prior liver disease in preparation to initiate LTBI treatment, she says that she thinks she may have hepatitis B.

Case summary:

50-yo woman
- daycare caregiver
- close contact to TB case
- TST 0 mm last year
- TST 20 mm today
- asymptomatic
- CXR normal
- hepatitis B
What is your next step?

Select one of the options below.

- Offer treatment with INH for 9 months.
- Offer treatment with rifampin for 4 months.
- Screen for signs and symptoms of active hepatitis and draw baseline liver function tests.
- Induce sputum for smear and culture.
- Refer Mrs. B to a hepatologist for immediate treatment of hepatitis B

Case summary:

50-yo woman
- daycare caregiver
- close contact to TB case
- TST 0 mm last year
- TST 20 mm today
- asymptomatic
- CXR normal
- hepatitis B

Response a: Incorrect. While INH may be an option in this case, you need to do more to assess Mrs. B prior to making decisions about LTBI treatment. Try again.

Response b: Incorrect. Depending on the status of Mrs. B’s hepatitis, INH may still be an option for treatment. You need to do more to assess Mrs. B prior to making decisions about LTBI treatment. Try again.

Response c: Correct. The first step is to assess the activity of Mrs. B’s hepatitis. Even in the absence of signs and symptoms, baseline liver function tests (serum ALT and bilirubin at a minimum) are recommended for patients with a history of chronic liver disease.

Response d: Incorrect. Sputum induction for smear and culture would be appropriate if the Mrs. B had any symptoms or radiologic findings to suggest active pulmonary TB. Mrs. B has no symptoms and a normal chest x-ray. Try again.

Response e: Incorrect. While Mrs. B might benefit from consultation with a hepatologist, there is no clear indication for treatment of hepatitis B at this time. Try again.
Liver function testing reveals the following:

- total bilirubin 0.5
- direct bilirubin 0.1
- ALT 200.

You confirm that Mrs. B does not drink alcohol and is not taking any hepatotoxic drugs. HBeAg is positive.

Case summary:

- 50-yo woman
- daycare caregiver
- close contact to TB case
- TST 0 mm last year
- CXR normal
- hepatitis B
- HBsAg positive
- TST 20 mm today
- asymptomatic
- CXR normal
- hepatitis B
- baseline: tbili 0.5, dbili 0.1, ALT 200
- HBeAg positive
At this point, you:

Select one of the options below.

a. Refer Mrs. B to a hepatologist for consideration of hepatitis B treatment and plan for LTBI treatment with a rifamycin with followup liver function testing every 2 weeks.

b. Initiate treatment with INH 300 mg biweekly via DOT with followup liver function testing every 2 weeks.

c. Initiate treatment with rifampin 600 mg daily for 4 months with monthly clinical and laboratory monitoring.

d. Defer LTBI treatment, as the risks of hepatotoxicity clearly outweigh potential benefits.
Case summary:

50-yo woman
- daycare caregiver
- close contact to TB case
- TST 0 mm last year
- TST 20 mm today
- asymptomatic
- CXR normal
- hepatitis B
- baseline: tbili 0.5, dbili 0.1, ALT 200
- HBeAg positive

Response a: Correct. The ATS statement on hepatotoxicity of anti-TB therapy recommends HBeAg testing in hepatitis B surface antigen-positive individuals with elevated ALT. Those who are HBeAg seropositive have a higher risk of INH-related hepatotoxicity, and a rifamycin is preferred for LTBI treatment.

Response b: Incorrect. Mrs. B is at high risk of INH-related hepatotoxicity. Treatment with INH, even with DOT and frequent laboratory monitoring, would not be advisable in this case. Try again.

Response c: Incorrect. There is a high risk of hepatotoxicity in this case. Try again.

Response d: Incorrect. Because she is a documented TST converter and a close contact to a highly infectious case, Mrs. B is at high risk of progression to active TB disease. Try again.
Additionally, if the HBeAg is positive and ALT is > 2 times the ULN or there are other factors increasing the risk of drug-related hepatotoxicity, consultation with a hepatologist is suggested for possible pretreatment of hepatitis B. Clinical and laboratory monitoring should occur on a frequent basis (e.g. every 2-4 weeks).

Factors increasing the risk of drug-related hepatotoxicity text rollover: age, alcohol consumption, evidence of active viral replication

Case summary:

50-yo woman

- daycare caregiver

- close contact to TB case

- TST 0 mm last year
- TST 20 mm today

- asymptomatic

- CXR normal

- hepatitis B

- baseline: tbili 0.5, dbili 0.1, ALT 200

- HBeAg positive
Given that Mrs. B was a close contact to a highly infectious case and is a documented TST converter, she is at high risk of progression to TB disease; therefore, all efforts to initiate and complete LTBI treatment should be made in this case.

Let’s review.

Case summary:

50-yo woman

- daycare caregiver
- close contact to TB case
- TST 0 mm last year
- TST 20 mm today
- CXR normal
- hepatitis B
- S1-electrolyte L.5, Hb10.1, A1C 7.0
- HIV IgG positive
- CXR normal

- hepatitis B

- baseline: tbili 0.5, dbili 0.1, ALT 200

- HBeAg positive
Review

- Active, but not quiescent, hepatitis B increases the risk of INH-related hepatotoxicity.
- Treatment with a rifamycin is preferred in individuals who are HBeAg seropositive with elevated ALT.
- Decisions to treat LTBI should be made based on an individualized assessment of risk of progression to TB disease and risk of drug-related hepatotoxicity.
- When the risk of progression to TB disease is high and LTBI treatment is felt to be important, consultation with a hepatologist and consideration of pre-treatment of viral hepatitis are advised.
Here is another case to review.

Mr. R is a 25-year-old contact to an INH-resistant TB case. He has no history of liver disease. He began LTBI treatment with rifampin one month ago. Routine blood work done as part of a pre-employment physical revealed liver function as follows:

total bilirubin 2.5

direct bilirubin 0.2

AST 30

ALT 35

ALKP 90
Mr. R has no abdominal pain or jaundice. The complete blood count, reticulocyte count, and blood smear are normal.
At this point, you?

Select one of the options below.

a. Discontinue treatment with rifampin.

b. Reassure the patient and continue treatment with rifampin.

Response a: Actually, the clinical and laboratory findings are highly suggestive of Gilbert’s syndrome, a common inherited disorder of bilirubin glucuronidation, often diagnosed in young adults who present with mild unconjugated hyperbilirubinemia. Even one dose of rifampin can result in a significant rise in total bilirubin. In fact, “rifampin testing” using certain thresholds for total and unconjugated bilirubin elevations has been reported to have a high sensitivity and specificity for the diagnosis of Gilbert’s syndrome. The condition is benign, and thus, treatment with rifampin may be continued.
Response b: Correct. The clinical and laboratory findings are highly suggestive of Gilbert’s syndrome, a common inherited disorder of bilirubin glucuronidation, often diagnosed in young adults who present with mild unconjugated hyperbilirubinemia. Even one dose of rifampin can result in a significant rise in total bilirubin. In fact, “rifampin testing” using certain thresholds for total and unconjugated bilirubin elevations has been reported to have a high sensitivity and specificity for the diagnosis of Gilbert’s syndrome. The condition is benign, and thus, treatment with rifampin may be continued.
Now that you’ve learned about LTBI treatment in patients with hepatitis, try to answer a few review questions.
Review questions:

Treatment of LTBI with INH is contraindicated in the setting of viral hepatitis.

Select one of the options below.

a. True  
b. False

Response a: Actually, LTBI treatment, even with INH, is frequently well tolerated in individuals with viral hepatitis.

Response b: That's right. LTBI treatment, even with INH, is frequently well tolerated in individuals with viral hepatitis.
Review questions:

Individuals with a history of viral hepatitis should undergo liver function testing at baseline and followup during LTBI treatment.

Select one of the options below.

a. True
b. False

Response a: While clinical monitoring is sufficient in patients without a history of liver disease or additional risk factors for drug-related hepatotoxicity, baseline and followup laboratory monitoring is recommended in those with viral hepatitis.
Response b: Actually, while clinical monitoring is sufficient in patients without a history of liver disease or additional risk factors for drug-related hepatotoxicity, baseline and followup laboratory monitoring is recommended in those with viral hepatitis.
Review questions:

Which of the following procedures is not always required when treatment of LTBI is being undertaken in an individual with known viral hepatitis?

Select one of the options below:

a. Clear instructions to discontinue treatment and seek immediate medical attention if symptoms of hepatitis develop
b. Patient education on avoidance of alcohol and hepatotoxic drugs
c. Baseline and followup liver function testing
d. Measurement of viral replication
e. Individualized assessment of risks and benefits

Response a: The correct answer is d. Measurement of viral replication is not indicated in all candidates for LTBI therapy with a history of viral hepatitis; if liver function is normal.
or mildly elevated, most patients will tolerate LTBI treatment, even with INH. However, all patients with viral hepatitis should undergo an individualized assessment of risks and benefits of LTBI treatment and baseline and follow-up liver function testing. They should be educated on avoidance of alcohol and hepatotoxins, hepatitis symptoms, and the need to discontinue treatment and seek medical attention should such symptoms develop.

Response b: The correct answer is d. Measurement of viral replication is not indicated in all candidates for LTBI therapy with a history of viral hepatitis; if liver function is normal or mildly elevated, most patients will tolerate LTBI treatment, even with INH. However, all patients with viral hepatitis should undergo an individualized assessment of risks and benefits of LTBI treatment and baseline and follow-up liver function testing. They should be educated on avoidance of alcohol and hepatotoxins, hepatitis symptoms, and the need to discontinue treatment and seek medical attention should such symptoms develop.

Response c: The correct answer is d. Measurement of viral replication is not indicated in all candidates for LTBI therapy with a history of viral hepatitis; if liver function is normal or mildly elevated, most patients will tolerate LTBI treatment, even with INH. However, all patients with viral hepatitis should undergo an individualized assessment of risks and benefits of LTBI treatment and baseline and follow-up liver function testing. They should be educated on avoidance of alcohol and hepatotoxins, hepatitis symptoms, and the need to discontinue treatment and seek medical attention should such symptoms develop.

Response d: Measurement of viral replication is not indicated in all candidates for LTBI therapy with a history of viral hepatitis; if liver function is normal or mildly elevated, most patients will tolerate LTBI treatment, even with INH. However, all patients with viral hepatitis should undergo an individualized assessment of risks and benefits of LTBI treatment and baseline and follow-up liver function testing. They should be educated on
avoidance of alcohol and hepatotoxins, hepatitis symptoms, and the need to
discontinue treatment and seek medical attention should such symptoms
develop.

Response e: The correct answer is d. Measurement of viral replication is not indicated in
all candidates for LTBI therapy with a history of viral hepatitis; if liver function is normal
or mildly elevated, most patients will tolerate LTBI treatment, even with INH. However,
all patients with viral hepatitis should undergo an individualized assessment of risks and
benefits of LTBI treatment and baseline and follow-up liver function testing. They should
be educated on avoidance of alcohol and hepatotoxins, hepatitis symptoms, and the
need to discontinue treatment and seek medical attention should such symptoms
develop.
Congratulations!

You have completed the LTBI Treatment in Patients with Hepatitis module.

Click here to view the references for this module and list of all Hepatitis Review Points.

Click MENU to return to the main menu.
HIV/AIDS File
Mr. H is a 50-year-old man who was diagnosed with HIV within the past year. He is originally from Haiti. He immigrated 12 years ago and travels to Haiti every year to visit family.

Mr. H has been a heavy smoker for many years. CD4 count is 150 cells/mm3. There is no prior history of TB disease or treatment and no other known risk factors for TB. Mr. H denies ever having had a TB skin test. He reports “a smoker’s cough” with morning sputum production for the past year. His chest x-ray is normal.
How would you evaluate Mr. H for TB at this time?

Select one of the options below.

a. Place a TST and schedule a follow-up in 48-72 hours.

b. Place a TST, schedule a follow-up in 48-72 hours, collect sputum for smear, nucleic acid amplification test (NAA), and culture.

c. Place a TST and perform anergy testing, and schedule a follow-up in 48-72 hours.

d. Place a TST and perform anergy testing, schedule a follow-up in 48-72 hours, and collect sputum for smear, NAA, and culture.

e. Defer TST placement until after antiretroviral therapy is initiated, as a false-negative result is likely with CD4 counts under 200 cells/mm3.
TST rollover text: Tuberculin skin test. Note that Interferon Gamma Release Assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.

Anergy testing rollover text: Testing for delayed type hypersensitivity reactions to certain common antigens.

Response a: Be careful. You should place a TST and schedule a follow-up, but that’s not enough. Given that Mr. H reports a productive cough, you need to exclude active disease. Try again.

Response b: Correct. Regardless of CD4 count, anyone not already known to be reactive should receive a TST as soon as HIV is diagnosed. In addition, you should also collect sputum because patients with CD4 counts under 200 cells/mm3 have a 20% incidence of normal chest radiographs during active TB. This is especially important since Mr. H reports a productive cough.

Let’s take a look inside Mr. H’s chart.

Response c: Incorrect. Routine testing for anergy is no longer recommended based on studies that failed to show a correlation between anergy testing and TST response. Furthermore, there is no survival benefit in anergic patients who received LTBI therapy. In addition, you need to do more to exclude active TB in Mr. H. Try Again.

Response d: Incorrect. Routine testing for anergy is no longer recommended based on studies that failed to show a survival benefit in anergic patients who received preventive therapy. Try again.

Response e: Not quite. Although the CD4 count under 200 cells/mm3 could result in a false-negative TST, you should not defer TB screening. Regardless of CD4 count, anyone not already known to be reactive should be screened for TB infection as soon as possible after HIV is diagnosed. Try again.
Smear and NAA results should be available to you by the time Mr. H follows up with you in 48-72 hours. While a negative TST does not exclude TB infection or disease and a positive TST does not establish the diagnosis, a positive test can help establish an epidemiologic link to TB. As the CD4 count drops, the frequency of false-negative TST increases. Even in HIV-negative patients, 15-20% of patients with active disease will have negative TSTs.

Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
- smoker’s cough
- Normal CXR
It's important to understand the risk of progression from LTBI to TB disease for those who are infected with HIV.

In patients with HIV, the risk of progressing from LTBI to active disease is higher than in the normal population. For a person with HIV infection and LTBI, the risk of progressing to active TB is 7-10% each year. For a person with a normal immune system, the risk of progression is 5-10% over a lifetime.

There is a high mortality rate from TB in patients with HIV. Worldwide, 13% of patients with AIDS die from TB.

HIV infection is the strongest known risk factor for progressing to TB disease. Therefore, all persons not already known to be reactive should receive a TST as soon as HIV is diagnosed.

This has been a lot of information. Let’s take a moment to review.
Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker's cough
  - Normal CXR
Review

- Patients infected with HIV are at high risk of developing active disease after infection with *M. tuberculosis*. HIV-infected patients who are TST positive have a 7-10% yearly risk of progression to active TB. Non-HIV-infected patients have a 10% lifetime risk.

- As soon as HIV is diagnosed and regardless of CD4 count, patients should receive a TST unless they are already known to be reactive.

- Because patients with CD4 counts under 200 cells/mm3 have up to a 20% incidence of normal chest radiographs during active TB, sputum should be collected if any symptoms or additional risk factors are present.

- Routine anergy testing is no longer recommended.

*M.tb.* rollover text: *Mycobacterium tuberculosis*

TST rollover text: *Tuberculin skin test.*
Anergy testing rollover text: Testing for delayed type hypersensitivity reactions to certain common antigens.
Mr. H returns to your clinic 48 hours later and has a TST of 2 mm induration. Sputum smears and NAA test are negative. He now states that his productive cough is unchanged for the past 5 years. You plan to follow sputum cultures.

NAA rollover text: Nucleic Acid Amplification

You educate Mr. H on the symptoms of active disease in HIV-infected people and advise him to return to your office immediately if new symptoms or risk factors develop.

Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
- Normal CXR
- Smoker's cough, unchanged x5 years
- TST 2 mm
- Sputum smear and NAA negative
At this point, you consider whether to perform two-step testing, which involves performing a second TST on the patient 1-3 weeks after the initial test. In some people with LTBI, the delayed type hypersensitivity responsible for TST reactions wanes over time. The "booster phenomenon" occurs when an initial TST result is falsely negative, but a subsequent TST placed 1-3 weeks after the first is positive. This occurs because of “boosting” of the immune response to tuberculin rather than to recent infection with M. *tuberculosis*.

**Case Summary**

+ 50-year-old man
  - HIV +
  - from Haiti
  - smoker
- CD4 < 150
- smoker’s cough
- Normal CXR
- smoker’s cough, unchanged x5 years
- TST 2 mm
- sputum smear and NAA negative
Two-step testing helps to establish a baseline TST status and is recommended for initial LTBI screening any time periodic screening for LTBI is anticipated. Periodic screening is common for healthcare workers, chronic dialysis patients, people living in high-risk congregate settings, people with HIV, and those at risk of ongoing TB exposure.

With the advent of IGRA, some experts recommend a single IGRA instead of two-step testing because booster effects are not believed to occur with IGRA.

IGRAs rollover text: Interferon-Gamma Release Assays

Case Summary

+ 50-year-old-man
- HIV +
- from Haiti
- smoker
- CD4 < 150
- smoker’s cough
- Normal CXR
- smoker’s cough, unchanged x5 years
- TST 2 mm
- sputum smear and NAA negative
Should you perform two-step testing on Mr. H?

Select one of the options below.

a. Yes
b. No

Case Summary

+ 50-year-old man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
  - smoker’s cough, unchanged x 5 years
  - TST 2 mm
  - Sputum smear and NAA negative
- Normal CXR
- smoker’s cough, unchanged x5 years
- TST 2 mm
- Sputum smear and NAA negative

Response a: You’re right. Annual screening for LTBI is appropriate because Mr. H has HIV and he travels yearly to a country where TB is endemic. Two-step testing will help establish a baseline TST status for Mr. H.

Response b: Actually, annual screening for LTBI is appropriate because Mr. H has HIV and he travels yearly to a country where TB is endemic. Two-step testing will help establish a baseline TST status for Mr. H.
You conduct the two-step testing and Mr. H’s repeat TST is 3 mm induration. You initiate antiretroviral therapy.

What is your next step?

Select one of the options below.

a. Once final sputum cultures return as negative, prescribe INH 300 mg daily along with vitamin B6 25 mg daily for 9 months.

b. Once final sputum cultures return as negative, initiate treatment for LTBI with a short-course regimen of rifampin and PZA.

c. Schedule a follow up in approximately 2 months for repeat CD4 count and repeat testing for LTBI.

d. Schedule a follow up in one year for repeat CD4 count and repeat testing for LTBI.
Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
  - Normal CXR
  - smoker’s cough, unchanged x5 years
  - TST 2 mm
  - sputum smear and NAA negative
  - On 2-step TST 3 mm

Response a: Incorrect. The TST is considered positive in an HIV-infected patient if the size of induration is 5 mm or greater. Since Mr. H has a 2mm induration, his test is not considered positive. You are reassured by the patient’s history, resolution of cough, and negative smears. However, were LTBI indicated in this case, it would be appropriate to await final culture results prior to starting INH, first-line therapy for LTBI.

Response b: Be careful. The TST is considered positive in an HIV-infected patient if the size of induration is 5 mm or greater. Since Mr. H has a 2-mm induration, his test is not considered positive. You are reassured by the patient’s history, resolution of cough, and negative smears. However, were LTBI indicated in this case, it would not be appropriate to initiate rifampin and PZA.. Although a 2-month regimen of PZA and rifampin may be effective in HIV-positive individuals, it has been associated with an unacceptably high risk of hepatotoxicity and is no longer recommended in any situation.

Response c: Correct. Mr. H’s TST is under the 5 mm threshold for positivity in an HIV-infected individual. Given Mr. H’s negative diagnostic tests for LTBI, CD4 counts < 200 cells/mm3, and no indication for empiric LTBI treatment, he should be retested for LTBI.
once he shows a response to antiretroviral therapy. As the immune system reconstitutes, the TST may become positive.

Response d: Not quite. Mr. H’s TST is under the 5 mm threshold for positivity in an HIV-infected individual. Given Mr. H’s negative diagnostic tests for LTBI, CD4 counts < 200 cells/mm³, and no indication for empiric LTBI treatment, he should be retested for LTBI once he shows a response to antiretroviral therapy. As the immune system reconstitutes, the TST may become positive. Therefore, you should not wait a year to reevaluate Mr. H.

Let’s review.
Review

- A TST is considered positive in an HIV-infected individual if the induration is 5 mm or greater.
- Two-step testing helps to establish a baseline TST status and is recommended for initial LTBI screening any time periodic screening for LTBI is anticipated (e.g. in health care workers, chronic dialysis patients, people living in high-risk congregate settings, people with HIV, and those at risk of ongoing TB exposure).
- Some experts recommend a single IGRA as an alternative to two-step testing.
- HIV-positive individuals with negative diagnostic tests for LTBI, CD4 counts < 200 cells/mm³, and without indication for empiric LTBI treatment should be retested for LTBI once they show a response to antiretroviral therapy.
• If CD4 counts are > 200 cells/mm³ and no other risk factors develop in the interim, patients with HIV should be screened for LTBI annually.
• INH is first-line therapy for LTBI in patients with HIV.
• A short-course regimen of rifampin and PZA is not recommended due to unacceptably high risk of hepatotoxicity.
At a visit with you three months later, Mr. H is doing well. CD4 count is 400 cells/mm³. He continues to abstain from cigarettes, and his cough has resolved completely. He denies any other symptoms. TST is now 4 mm induration. Chest x-ray remains normal. However, he reports that his roommate has been diagnosed with pansensitive smear-positive cavitary pulmonary tuberculosis in the past week.

Do you initiate LTBI treatment with INH at this time?

Select one of the options below.

a. Yes
b. No
Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
  - Normal CXR
  - smoker’s cough, unchanged x5 years
  - TST 2 mm
  - sputum smear and NAA negative
  - On 2-step TST 3 mm

3 months later:
  - CD4 400 on antiretrovirals
  - cough resolved
  - Normal CXR
  - roommate with pansensitive smear-positive pulmonary TB

Response a: That’s right. Mr. H should be treated for LTBI even though his TST is under the 5 mm threshold, because he is a close contact to a case. This contact puts him at high risk of progressing to disease if left untreated.

Response b: Actually, you should start treatment for LTBI at this time. Mr. H should be treated for LTBI regardless of his TST status because he is a close contact to a case. This contact puts him at high risk of progressing to disease if left untreated.
There are several situations in which patients with HIV should be treated for LTBI (once active disease is excluded) regardless of TST status:

- recent contact to a case
- a history of prior untreated or partially treated active TB
- CD4 count < 200 cells/mm³ with fibrotic lesions consistent with TB on a chest x-ray and no prior history of TB treatment.

In contrast, adult contacts who are not HIV-infected and have an initial negative TST should have the TST repeated 8-12 weeks after last exposure but should not be started on LTBI treatment unless the 2nd TST is positive (i.e. TST of 5 mm or greater).
Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
  - Normal CXR
  - smoker’s cough, unchanged x5 years
  - TST 2 mm
  - sputum smear and NAA negative
  - On 2-step TST 3 mm

3 months later:
  - CD4 400 on antiretrovirals
  - cough resolved
  - Normal CXR
  - roommate with pansensitive smear-positive pulmonary TB
Because Mr. H is a close contact to an active case and has no evidence of active tuberculosis, you plan to initiate treatment for LTBI. You ask Mr. H about prior liver disease, and he denies any history of hepatitis, jaundice, right upper quadrant pain, or jaundice, right upper quadrant pain, or exposure to alcohol or other hepatotoxins. Testing for hepatitis B and C is negative.

Case Summary

+ 50-year-old man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
  - Normal CXR
  - smoker’s cough, unchanged x5 years
- TST 2 mm
- sputum smear and NAA negative
- On 2-step TST 3 mm

3 months later:
- CD4 400 on antiretrovirals
- cough resolved
- Normal CXR
- roommate with pansensitive smear-positive pulmonary TB
At this point, you counsel Mr. H on symptoms of hepatitis and avoidance of hepatotoxins. After confirming that Mr. H’s roommate had TB sensitive to INH, you:

a. Draw baseline LFTs, initiate treatment with INH, consider DOT, and repeat LFTs monthly at a minimum.

b. Initiate treatment with INH, consider DOT, and repeat LFTs weekly for the duration of treatment.

c. Initiate treatment with rifampin, consider DOT, and repeat LFTs at one month at a minimum and again if symptoms of hepatitis develop.

d. Initiate treatment with rifampin, consider DOT, and repeat LFTs monthly.

e. Initiate treatment with rifampin and PZA, consider DOT, and repeat LFTs weekly.
When treating LTBI in contacts, it is important to verify that the index case had TB sensitive to INH. In cases of INH resistance, contacts with LTBI should be treated with rifampin.

Liver function tests include transaminases and bilirubin.

Directly Observed Therapy

Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
  - smoker
  - CD4 < 150
  - smoker’s cough
  - Normal CXR
  - smoker’s cough, unchanged x5 years
  - TST 2 mm
  - sputum smear and NAA negative
  - On 2-step TST 3 mm

3 months later:
  - CD4 400 on antiretrovirals
  - cough resolved
  - Normal CXR
  - roommate with pansensitive smear-positive pulmonary TB

Response a: That’s correct. HIV confers an increased risk for INH hepatotoxicity. Therefore DOT is advised both for monitoring for adverse effects and to ensure adherence and completion in this high-risk contact. More frequent laboratory monitoring is recommended, particularly if additional risk factors for hepatotoxicity are present.
Response b: Not quite. While more frequent laboratory monitoring is recommended, weekly monitoring is not required in most cases. Try again.

Response c: Be careful. Rifampin should generally be reserved for contacts of INH-resistant cases or intolerance to INH. Try again.

Response d: Be careful. Rifampin should generally be reserved for contacts of INH-resistant cases or intolerance to INH. Try again.

Response e: Although a 2-month regimen of PZA and rifampin was found to be effective in HIV-positive individuals, it has been shown to be associated with an unacceptably high risk of hepatotoxicity and is no longer recommended in any situation. Try again.
Mr. H’s initial liver function tests are normal. You start him on INH 900 mg along with vitamin B6 50 mg biweekly via DOT and schedule monthly follow up for clinical and laboratory monitoring for hepatotoxicity and other side effects. If there is mild elevation of transaminases, you plan to conduct more frequent monitoring to confirm stability.

You also instruct Mr. H to avoid hepatotoxins and to discontinue treatment and contact your officer if symptoms of hepatitis develop.

It’s time for one more review of the information you’ve just learned.

Case Summary

+ 50-year-old-man
  - HIV +
  - from Haiti
- smoker
- CD4 < 150
- smoker's cough
- Normal CXR
- smoker's cough, unchanged x5 years
- TST 2 mm
- sputum smear and NAA negative
- On 2-step TST 3 mm

3 months later:
- CD4 400 on antiretrovirals
- cough resolved
- Normal CXR
- roommate with pansensitive smear-positive pulmonary TB
Review

- Rifampin should be reserved for contacts to INH-resistant cases or with intolerance to INH.

- Because of loss of TST sensitivity (anergy), LTBI therapy is recommended in HIV-positive patients with negative TSTs in certain situations:
  - Recent contact to an active case
  - History of prior untreated or inadequately treated TB
  - Fibrotic lesions consistent with TB on CXR in the setting of CD4 counts < 200 cells/mm³ and no prior history of TB treatment (once active TB is excluded)
- Because of HIV confers an increased risk for INH hepatotoxicity, HIV-positive patients should undergo pre-treatment LTFs and more frequent laboratory monitoring, particularly if additional risk factors for hepatotoxicity are present.

- DOT is suggested, if feasible, to monitor for side effects and to ensure treatment completion.

**LTFs rollover text:** Liver function tests include transaminases and bilirubin

**DOT rollover text:** Directly observed therapy
Now that you’ve learned about LTBI treatment in patients with HIV, try answering a few review questions.
Which of the following is not an indication for treatment of LTBI in patients with HIV, regardless of TST status?

a. Recent contact to an active case
b. History of prior untreated or inadequately treated TB
c. Fibrotic lesions consistent with TB on CXR in the setting of CD4 counts < 200 cells/mm3 and no prior history of TB treatment
d. CD4 count < 100 cells/mm3

Response a: The correct answer is d. CD4 count < 100 cells/mm3 alone is not an indication for empiric LTBI treatment, regardless of TST status.

Response b: The correct answer is d. CD4 count < 100 cells/mm3 alone is not an indication for empiric LTBI treatment, regardless of TST status.
Response c: The correct answer is d. CD4 count < 100 cells/mm³ alone is not an indication for empiric LTBI treatment, regardless of TST status.

Response d: You’re right. CD4 count < 100 cells/mm³ alone is not an indication for empiric LTBI treatment, regardless of TST status.
Which of the following procedures is not required prior to initiation of LTBI treatment in a patient with HIV?

- a. Exclusion of active TB by symptoms screen, chest x-ray as well as sputums and/or bronchoscopy, if indicated
- b. Screening for hepatitis B and C
- c. Baseline liver function testing
- d. Initiation of treatment with antiretrovirals
- e. Review of results of susceptibility testing of the index case, if the patient is a contact
- f. Education of the patient on symptoms and risk factors for active TB

Response a: The correct answer is D. Decisions regarding treatment of HIV with antiretrovirals should be made based on CD4 count and other facts.
Response b: The correct answer is D. Decisions regarding treatment of HIV with antiretrovirals should be made based on CD4 count and other facts.

Response c: The correct answer is D. Decisions regarding treatment of HIV with antiretrovirals should be made based on CD4 count and other facts.

Response d: Correct. Decisions regarding treatment of HIV with antiretrovirals should be made based on CD4 count and other facts.

Response e: The correct answer is D. Decisions regarding treatment of HIV with antiretrovirals should be made based on CD4 count and other facts.

Response f: The correct answer is D. Decisions regarding treatment of HIV with antiretrovirals should be made based on CD4 count and other facts.
Congratulations!

You have completed the LTBI Treatment in Patients with HIV module.

Click here to view the references for this module and a list of all HIV Review Points.

Click MENU to return to the main menu.
Infants and Children File
Case Presentation

Mr. C is hospitalized with smear-positive cavitary pulmonary TB. He started a four-drug regimen two days ago. A contact investigation identifies his wife and two children (ages 2 and 8 years) as household contacts. They are all asymptomatic.

Mrs. C’s TST is 10 mm induration. The two children have TSTs of 0 mm. All chest x-rays are normal. Mr. C is eager to leave the hospital.

TST rollover text: Tuberculin Skin Test
What should you do next? Select one of the options below.

a. Discharge Mr. C to home, as his family has already been exposed.

b. Discharge Mr. C to home and start the wife and children on rifampin.

c. Discharge Mr. C to home and start the children on INH, rifampin, pyrazinamide, and vitamin B6.

d. Plan for alternative living arrangements for Mr. C. until smears are negative, he is clinically improving, and he has been on TB drugs for at least 2 weeks.

e. Advise Mr. C to remain hospitalized for the duration of treatment.

Response a: Be careful. Although Mr. C’s family has already been exposed, close contacts should be evaluated and treated before he is discharged from the hospital. Because there are children under 5 in the household, you should exercise extra caution when planning for the Mr. C’s discharge. Try again.
Response b: Not quite. Ideally, you should confirm that Mr. C is no longer infectious prior to discharging him to his home where there is a child under age 5. However, if keeping Mr. C isolated is not feasible, most experts would consider returning Mr. C. to his home once his family is evaluated and treated appropriately. Rifampin is generally reserved for contacts to INH-resistant cases or for those with intolerance to INH. Try again.

Response c: Incorrect. Treating the children is not recommended in this case because there is no evidence of active TB in the children. Try again.

Response d: Correct. Immunosuppressed individuals and children under 5 are at greater risk for progression to active disease and disseminated forms of TB. Because Mr. C lives with a child under 5, you should consider alternative living arrangements for Mr. C until smears are negative, he is clinically improving, and has been on TB treatment for 2 weeks.

Disseminated forms of TB rollover text: TB involving at least 2 non-contiguous organs, blood or bone marrow.

Response E: Incorrect. There is no indication for long-term inpatient treatment of active TB in this case. Try again.
In clinical practice, alternative living arrangements often prove impossible or an undue burden on a family. Decisions regarding discharge must take into account many factors, including:

- Infectiousness of the case (which is likely significantly reduced after even a few days of TB treatment)
- Immune status of household contacts
- Likelihood of prior exposure
- Complex social and financial issues

Unless there is known or suspected resistance, INH would be the treatment of choice for the family. Rapid genetic susceptibility testing of the index case’s organism (for mutations conferring INH and rifampin resistance) can be invaluable in this setting. If testing suggests sensitivity to INH and rifampin, most experts would consider Mrs. C and their children reasonably well protected by treatment with INH even if Mr. C were returned home.
their children reasonably well protected by treatment with INH even if Mr. C were returned home.
You help Mr. C make alternative living arrangements until smears are negative and he has been on TB drugs for at least 2 weeks.
Now let’s focus on the family contacts. Mrs. C has a TST of 10mm induration and is asymptomatic. Her chest x-ray is normal. You recommend INH along with vitamin B6 for 9 months, as per CDC guidelines.

Prescription

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
Although the youngest child in this household is 2 years of age, you should ask if the child is still nursing. If so, reassure Mrs. C that it is safe to continue breastfeeding during treatment. A breast fed baby will normally ingest less than 15% of their mother’s dose of INH, a concentration that is neither sufficient to cause toxicity nor to protect the infant from progression from latent to active TB. Furthermore, it is likely that vitamin B6 supplementation given to the mother is adequate to protect the baby from potential toxicity.

Case Summary

+ Mrs. C

- Healthy asymptomatic woman
- contact to case
- TST 10mm
- normal CXR
Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
In situations where an exclusively breastfed infant is being treated with INH and the nursing mother is not receiving vitamin B6 supplementation, vitamin B6 supplementation may be given to the infant at 0.1-0.5 mg/kg/day. Vitamin B6 supplementation is also important in children and adolescents on milk- and meat-deficient diets, children who experience paresthesias while receiving isoniazid therapy, and those with HIV infection. Dosing for children is 1-2 mg/kg/day.

Case Summary

+ MRS. C
  - Healthy asymptomatic woman
  - contact to case
  - TST 10mm
  - normal CXR
Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
You’ve taken care of Mr. C and Mrs. C. Now you need to recommend treatment for their children. Both children have TSTs of 0 mm and their x-rays are normal.

How should you treat the 8-year-old?

Select one of the options below.

a. Treat with INH for 9 months,

b. Treat with INH for 8-12 weeks until TST is repeated. If repeat TST is 5 mm or greater, continue treatment for a total of 9 months.

c. Do not treat with INH at this time. Conduct follow up TST at 8 weeks after last exposure. If TST is 5 mm or greater, treat with INH for 9 months.

d. Do not treat with INH. Educate the child and parents about symptoms of TB disease and arrange clinical follow up every 6 months for 2 years.

e. Treat with rifampin for 2 months.
Case Summary

+ MRS. C
  - Healthy asymptomatic woman, contact to case, TST 10mm, normal CXR

+ 8 YEAR OLD
  - Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR

+ 2 YEAR OLD
  - Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR

Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.

Response a: Incorrect. A final decision to treat the 8-year-old with a TST of 0 mm with 9 months of INH cannot be made at this time, because repeat TST is indicated 8-12 weeks after last exposure to the active case. Try again.

Response b: Incorrect. The TST should be repeated 8-12 weeks after last contact to the case, as is recommended for all recent contacts with an initial negative TST. However, because the child is not immunosuppressed and not under age 5, window prophylaxis is not indicated. Try again.

Window prophylaxis rollover text: Empiric INH for these 8-12 weeks before the TST is repeated.

Response c: Correct. As is recommended for all recent contacts with an initial negative TST, the TST should be repeated 8-12 weeks after last contact to the case, because it may take this long for the delayed hypersensitivity response to tuberculin to occur.
Response d: Be careful. Even though window prophylaxis is not indicated, it is important to conduct repeat testing at 8-12 weeks after last contact to the case. Try again.

Window prophylaxis rollover text: Treatment with INH from initial negative TST until repeat TST 8-12 weeks after last contact with the active case.

Response e: Actually, most experts agree that rifampin should be reserved for contacts of INH-resistant cases and for those with intolerance to INH. If rifampin is necessary, a 6-month regimen is recommended in infants and children. A 4-month regimen is recommended in adults. Try again.
How should you treat the 2-year-old?

a. Treat with INH for 12 months.

b. Treat with INH for 9 months.

c. Treat with INH for 8-12 weeks until TST is repeated. If repeat TST is 5 mm or greater, continue INH to complete a 9-month course.

d. Do not treat with INH at this time. Conduct follow up TST at 8 weeks after last exposure. If TST is 5 mm or greater, treat with INH for 9 months.

e. Treat with rifampin, INH, PZA, and ethambutol for 4 months.

Case Summary

+ MRS. C
  - Healthy asymptomatic woman, contact to case, TST 10mm, normal CXR

+ 8 YEAR OLD
  - Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR
+ 2 YEAR OLD

- Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR

Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.

Response a: Incorrect. If the child is to be treated for LTBI, there is no additional benefit to a regimen beyond 9 months. A final decision to treat the 2-year-old with a TST of 0 mm with 9 months of INH cannot be made at this time, because repeat TST is indicated 8-12 weeks after last contact to the active case. Try again.

Response b: Not quite. Not quite. A final decision to treat the 2-year-old cannot be made at this time. A repeat TST is indicated 8-12 weeks after last contact to the active case. Try again.

Response c: Correct. Children under 5 years of age are considered to be relatively immunosuppressed because of their immature immune systems. Young children have a higher risk of rapid disease progression, and this progression can occur before the TST reaction is positive. As such, young children who are contacts to a case should be given window prophylaxis with INH until the presence of LTBI can be excluded.

Window prophylaxis rollover text: Window prophylaxis is treatment with INH from initial negative TST until repeat TST 8-12 weeks after last contact with the active case.

Response d: Be careful. Children under 5 are considered to be immunosuppressed because of their immature immune systems. Young children have a higher risk of rapid disease progression, and this progression can occur before the TST reaction is positive. As such, young children who are contacts to a case should be treated with INH until the presence of LTBI can be excluded. Try Again.
Response e: Incorrect. In the absence of symptoms or radiologic abnormalities, there is no indication for treatment for active TB in the child. Try again.
Infants with untreated LTBI have up to a 40% likelihood of developing TB and are more susceptible to disseminated forms of the disease. Furthermore, INH therapy for LTBI appears to be more effective (with risk reduction estimated at 70-90%) and less hepatotoxic in infants and children compared to adults. Clearly, the substantial benefit of LTBI treatment in children under 5 far outweighs the minimal risks.

Case Summary

+ MRS. C
- Healthy asymptomatic woman, contact to case, TST 10mm, normal CXR

+ 8 YEAR OLD
- Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR

+ 2 YEAR OLD
- Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR
Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text:  **INH refills should not be given because monthly follow up is needed.**

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
The children return for follow up TSTs twelve weeks after last exposure to their father. The 2-year-old (weight 13 kg) now has a TST of 7 mm induration, and the 8-year-old (weight 22 kg) has a TST of 10 mm induration. Because the TSTs are 5 mm or greater, you continue treatment for the 2-year-old and initiate treatment in the older child.

Case Summary

+ MRS. C
- Healthy asymptomatic woman, contact to case, TST 10mm, normal CXR

+ 8 YEAR OLD
- Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR, follow up TST 10mm, weight 22 kg
+ 2 YEAR OLD

- Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR, follow up TST 7 mm, weight 13 kg

Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
You proceed with treatment of the children via directly observed preventive therapy (DOPT).

What dosing would you provide for the 2-year old and 8-year old?

Select one of the options below.

Review the INH Dosing Chart for help calculating pediatric dosing of INH.

- a. 300 mg and 600 mg, respectively, dosed bi-weekly
- b. 300 mg and 600 mg respectively, dosed daily
- c. 150 mg and 300 mg, respectively, dosed bi-weekly
- d. 100 mg and 400 mg, respectively, bi-weekly

* Due to its high arbovit complex, INH suspension can cause severe diarrhea. Therefore, crushed tablets mixed with semi-soft food, milk, or formula is the preferred mode of administration in infants and children who are not able to swallow tablets.
Pediatric dosing chart:

<table>
<thead>
<tr>
<th>Child's Weight</th>
<th>Daily isoniazid dose (10-15mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milligram</td>
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<td>Pounds</td>
<td>Kilogram</td>
</tr>
<tr>
<td>6.6 - 11</td>
<td>3 - 5 Kg</td>
</tr>
<tr>
<td>11.1 - 16.4</td>
<td>5.1 - 7.5 Kg</td>
</tr>
<tr>
<td>16.5 - 22</td>
<td>7.6 - 10 Kg</td>
</tr>
<tr>
<td>22.1 - 33</td>
<td>10.1 - 15 Kg</td>
</tr>
<tr>
<td>33.1 - 44</td>
<td>15.1 - 20 Kg</td>
</tr>
<tr>
<td>Over 44</td>
<td>Over 20 Kg</td>
</tr>
</tbody>
</table>

Maximum Isoniazid Daily Dose is 300 mg

* Due to its high sorbitol content, INH suspension can cause severe diarrhea. Therefore, crushed tablets mixed with semisoft food, milk, or formula is the preferred mode of administration, even infants, as early as is feasible.

Case Summary

+ MRS. C
  - Healthy asymptomatic woman, contact to case, TST 10mm, normal CXR

+ 8 YEAR OLD
  - Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR, follow up TST 10mm, weight 22 kg

+ 2 YEAR OLD
  - Healthy, asymptomatic, contact to case, initial TST 0mm, normal CXR, follow up TST 7 mm, weight 13 kg

Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
Response a: Correct. Ideally, young children who are contacts to a case should be offered DOPT dosed 20-30 mg/kg biweekly (or 10-15 mg/kg daily if DOPT administer daily) to ensure treatment completion and monitor for side effects.

Response b: Incorrect. Daily dosing is 10-15 mg/kg. Try again.

Response c: Incorrect. Dosing is 20-30 mg/kg bi-weekly. Try again.

Response d: Incorrect. Dosing is 20-30 mg/kg bi-weekly. Try again.
After the first few months of treatment via DOPT, the children are doing well. However, funding for DOPT is no longer available. At this point, you treat the 2-year-old and 8-year-old as follows: Select one of the options below.

Review the INH Dosing Chart for help calculating pediatric dosing of INH.

- a. 300 mg and 600 mg, respectively, dosed bi-weekly
- b. 300 mg and 600 mg, respectively, dosed tri-weekly
- c. 300 mg and 600 mg, respectively, dosed daily
- d. 150 mg and 300 mg, respectively, dosed daily
Pediatric dosing chart:

<table>
<thead>
<tr>
<th>Child's Weight</th>
<th>Daily Isoniazid dose (10-15 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pounds</td>
</tr>
<tr>
<td>6.6 - 11</td>
<td>3 - 5 Kg</td>
</tr>
<tr>
<td>11.1 - 16.4</td>
<td>5.1 - 7.5 Kg</td>
</tr>
<tr>
<td>16.5 - 22</td>
<td>7.6 - 10 Kg</td>
</tr>
<tr>
<td>22.1 - 33</td>
<td>10.1 - 15 Kg</td>
</tr>
<tr>
<td>33.1 - 44</td>
<td>15.1 - 20 Kg</td>
</tr>
<tr>
<td>Over 44</td>
<td>Over 20 Kg</td>
</tr>
</tbody>
</table>

Maximum Isoniazid Daily Dose is 300 mg

* Due to its high sorbitol content, INH suspension can cause severe diarrhea. Therefore, crushed tablets mixed with semisoft food, milk, or formula is the preferred mode of administration, even infants, as early as is feasible.

Case Summary

+ MRS. C
- Healthy asymptomatic woman, contact to case, TST 10 mm, normal CXR

+ 8 YEAR OLD
- Healthy, asymptomatic, contact to case, initial TST 0 mm, normal CXR, follow up TST 10 mm, weight 22 kg

+ 2 YEAR OLD
- Healthy, asymptomatic, contact to case, initial TST 0 mm, normal CXR, follow up TST 7 mm, weight 13 kg

Prescription Tab

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.
Response a: Actually, treatment should be given on a daily schedule when not administered via DOPT. Try Again.

Response b: Actually, treatment should be given on a daily schedule when not administered via DOPT. Try Again.

Response c: Incorrect. Usual daily dosing is 10-15 mg/kg for children. Try Again.

Response d: That’s right. When not administered via DOPT, treatment should be given on a daily schedule. Usual daily dosing is 10-15 mg/kg for children.

Let’s review what you’ve learned about LTBI in pediatrics.
Review

- Do not allow patients with infectious active TB to return to a home setting shared by children under 5 or immunosuppressed persons.

- Untreated infants with LTBI have up to a 40% likelihood of developing TB, and children under 5 are more susceptible to disseminated forms of the disease.

- INH therapy for LTBI appears to be more effective (with risk reduction estimated at 70-90%) and less hepatotoxic in infants and children compared to adults.

- Once active TB is excluded, you should provide window prophylaxis for children under 5 and individuals who are immunosuppressed. If repeat TST at 8-12 weeks is 5 mm or greater, continue INH to complete a 9-month course.

Window prophylaxis rollover text:  Treatment with INH from initial negative until repeat TST 8-12 weeks after last contact with the active case.
• Utilize appropriate weight-based pediatric dosing of INH: 10-15 mg/kg for daily dosing, 20-30 mg/kg for biweekly dosing via DOPT.

• Because the high sorbitol content in the liquid formulation of INH causes cramping and diarrhea in more than half of children, it is recommended that INH be administered in the form of crushed tablets mixed with semisoft food, milk or formula in infants and children who are not able to swallow tablets.

• Do not defer LTBI treatment or discourage breastfeeding in nursing mothers who are contacts to a case of active TB.
Now that you’ve learned about LTBI treatment in infants and children, try to answer a few review questions.
Review questions:

Window prophylaxis is indicated in individuals with HIV as well as

a. Children under age 10

b. Infants and children under age 5

Response a: The correct answer is B. Once active TB is excluded, window prophylaxis is indicated in children under 5.

Response b: That’s right. Once active TB is excluded, window prophylaxis is indicated in children under 5.
The likelihood that an untreated infant with LTBI will develop active TB is:

- a. 5%
- b. 10%
- c. 20%
- d. 40%
- e. 80%

Response a: The correct answer is D. Given this high risk of progression to TB disease and the low risk of treatment with INH in the pediatric population, children who are contacts to an active TB case are considered high priority for treatment of LTBI.

Response b: The correct answer is D. Given this high risk of progression to TB disease and the low risk of treatment with INH in the pediatric population, children who are contacts to an active TB case are considered high priority for treatment of LTBI.
Response c: The correct answer is D. Given this high risk of progression to TB disease and the low risk of treatment with INH in the pediatric population, children who are contacts to an active TB case are considered high priority for treatment of LTBI.

Response d: Correct. Given this high risk of progression to TB disease and the low risk of treatment with INH in the pediatric population, children who are contacts to an active TB case are considered high priority for treatment of LTBI.

Response e: The correct answer is D. Given this high risk of progression to TB disease and the low risk of treatment with INH in the pediatric population, children who are contacts to an active TB case are considered high priority for treatment of LTBI.
Congratulations!

You have completed the LTBI Treatment in Infants and Children module.

Click here to view the references for this module and a list of all Infants and Children Review Points.

Click MENU to return to the main menu.
Pregnancy File
Mrs. P is a 25-year-old woman who presents to your office for evaluation. She is 3 months pregnant with her first child. Her husband was recently diagnosed with cavitary pulmonary tuberculosis. HIV testing is negative. **TST** is 12 mm.

**TST** rollover text: Tuberculin Skin Test
Should Mrs. P have had a TST placed during pregnancy?

Select one of the options below.

a. Yes
b. No

Response a: TSTs and IGRAs are safe in pregnancy and should be interpreted in the same way in the diagnosis of LTBI in pregnancy as in other situations.

Response b: Actually, TSTs and IGRAs are safe in pregnancy and should be interpreted in the same way in the diagnosis of LTBI in pregnancy as in other situations.

IGRAs rollover text: interferon-gamma release assays
In some settings serving large immigrant communities, prenatal visits may serve as opportunities to screen for LTBI in these populations. In Mrs. P’s case, she is a contact to an active TB case, so diagnosis and treatment of LTBI is essential.
As your first step, you:

Select one of the options below.

a. Screen for symptoms of active TB, and order a chest x-ray.

b. Screen for symptoms of active TB but do not order a chest x-ray, since x-rays are contraindicated in pregnancy.

c. Prescribe INH 300 mg daily along with vitamin B6 25 mg daily for 9 months.

d. Reassure Mrs. P and ask her to return 3 months postpartum to initiate treatment for latent TB infection.

e. Start Mrs. P on treatment as a TB suspect with weight-based doses of isoniazid, rifampin, pyrazinamide, and ethambutol, because there is a higher risk of reactivation in pregnant women.

Symptoms of active TB rollover text: TB symptoms include cough, fever, night sweats, and hemoptysis.
Response a: You’re right. The most important step in evaluating any patient identified through **targeted tuberculin testing** as having LTBI is to exclude active tuberculosis. A symptom screen and a chest x-ray are the first steps in this evaluation.

Let’s take a look inside Mrs. P’s chart.

**Targeted tuberculin testing rollover text:** Testing groups of people who are at risk for TB infection and identifying those who would benefit from treatment.

Response b: Not quite. In the pregnant patient, a chest x-ray should be performed with appropriate abdominal shielding. The most important step in evaluating any patient identified through targeted tuberculin testing as having LTBI is to exclude active tuberculosis. Try again.

Response c: Incorrect. Mrs. P should not be treated for LTBI until active tuberculosis has been excluded. Try again.

Response d: You must rule out active tuberculosis before making any treatment decisions. Try again.

Response e: There is no firm evidence that risk of new infection or reactivation of TB in pregnant women is different from matched controls. However, TB in pregnant women can present insidiously, since symptoms may be attributed to pregnancy rather than disease, and weight loss may be difficult to recognize. Try again.
You complete a baseline TB screening on Mrs. P. She reports only mild morning sickness for the past 3 months and no symptoms of active TB.

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No

Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
A chest x-ray, performed with appropriate abdominal shielding, is normal.

Do you initiate treatment of LTBI at this time?

Select one of the options below.

a. Yes  
b. No

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No  
Unintentional weight loss? No  
Night sweats for more than a week? No
Fever for more than a week? No 
Hoarseness for more than 3 weeks? No 
Hemoptysis (coughing up blood)? No 

Response a: Correct. Because Mrs. P is a close contact to an infectious TB case (a major risk factor for progression to active disease), she should be evaluated and treated during pregnancy.

Response b: Actually, because Mrs. P is a close contact to an infectious TB case (a major risk factor for progression to active disease), she should be evaluated and treated during pregnancy.

Major risk factor rollover text: Major risk factors include immunosuppression and recent contact to a case.
Pregnant women with major risk factors should be evaluated and treated for LTBI during pregnancy.

There is no increased risk of teratogenicity with INH (or rifampin). The risk of maternal active TB, maternal death, and mother-to-child transmission of TB in utero or soon after birth far outweighs the risk associated with treatment with INH.

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No
Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
On the other hand, because of the increased risk of hepatotoxicity during pregnancy and the early postpartum period, pregnant women without major risk factors who are at relatively lower risk of progressing to active disease should not be treated. Instead, they should be asked to return for re-evaluation (with symptom screen and chest x-ray to ensure active disease has not developed) and treatment 3 months postpartum.

Re-evaluation rollover text: Re-evaluation should include symptom screen and chest x-ray to ensure active disease has not developed.

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No
Unintentional weight loss? No

Night sweats for more than a week? No

Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
There is no contraindication to breastfeeding while on INH (or rifampin). It is important to note that the low levels of INH excreted in breast milk are not sufficient to protect an infant exposed to an active TB case. Also, vitamin B6 supplementation for the nursing infant may be considered in some cases (see Infants and Children module).

Let’s review what’s been covered so far.

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No
Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
Review

- **TST and IGRA**s are safe and effective in pregnancy.
- All patients identified as having LTBI should be evaluated to exclude active TB disease. The first step is a symptom screen and chest x-ray.
- A chest x-ray performed with abdominal shielding is appropriate in a pregnant woman to exclude active TB.
- There is no evidence that risk of new infection or reactivation is higher in pregnant women.
- Pregnant women without major risk factors for progression to active TB disease should return for re-evaluation and treatment 3 months postpartum.
- Pregnant women with major risk factors for progression to active TB disease (immunosuppression or recent contact to a case) should be treated for LTBI during pregnancy.
TST rollover text: Tuberculin Skin Test

IGRAs rollover text: Interferon-gamma release

Major risk factors rollover text: Major risk factors include immunosuppression or recent contact to a case.
Because Mrs. P is a close contact to an active case and has no evidence of active tuberculosis, you plan to initiate treatment of LTBI.

You ask Mrs. P about prior liver disease, and she denies any history of hepatitis, jaundice, right upper quadrant pain, or exposure to alcohol or other hepatotoxins.

Testing for hepatitis B, and C is negative.

Case Summary
25-yo healthy pregnant woman
Contact to case
HIV negative
No history of liver disease or hepatotoxins
TST 12 mm
Normal CXR
LFTs at time 0: normal

Symptoms
Screening for Symptoms of Active TB:
Have you had...
Cough for more than 2 weeks? No
Unintentional weight loss? No
Night sweats for more than a week? No
Fever for more than a week? No
Hoarseness for more than 3 weeks? No
Hemoptysis (coughing up blood)? No
At this point, you counsel Mrs. P on symptoms of hepatitis and avoidance of hepatotoxins. You emphasize the importance of discontinuing medications and returning to see you immediately if symptoms of hepatitis develop.

What else should you do?
Select an option below.

a. Initiate treatment with INH.

b. Draw baseline liver function tests (LFTs), initiate treatment with INH, and draw LFTs again if symptoms of hepatitis develop.

c. Draw baseline LFTs, initiate treatment with INH, and repeat LFTs monthly.

d. Draw baseline LFTs, initiate treatment with INH, and repeat LFTs weekly.

e. Draw baseline LFTs, initiate treatment with rifabutin, and repeat LFTs weekly.
Case Summary
25-yo healthy pregnant woman
Contact to case
HIV negative
No history of liver disease or hepatotoxins
TST 12 mm
Normal CXR
LFTs at time 0: normal

Symptoms
Screening for Symptoms of Active TB:
Have you had...
Cough for more than 2 weeks? No
Unintentional weight loss? No
Night sweats for more than a week? No
Fever for more than a week? No
Hoarseness for more than 3 weeks? No
Hemoptysis (coughing up blood)? No

Response a: Incorrect. Because pregnancy and the early postpartum period confer an increased risk for INH hepatotoxicity, pregnant women should undergo pre-treatment liver function tests. Try again.

Response b: Not quite. Because pregnancy and the early postpartum period confer an increased risk for INH hepatotoxicity, pregnant women should undergo both pre-treatment and follow up liver function tests. Try again.
Response c: That’s right. Because of the increased hepatotoxicity risk in pregnancy and the immediate postpartum period, the CDC recommends careful clinical and laboratory monitoring in pregnant women but does not specify frequency. Most experts recommend symptom review and LFTs at least monthly. Most important is counseling patients to discontinue medications and seek medical attention if symptoms of hepatitis develop.

Response d: Almost. Although pregnant women should undergo pre-treatment liver function tests and regular monitoring for liver toxicity, most experts would not recommend weekly laboratory monitoring. Try again.

Response e: Incorrect. Although pregnant women should undergo pre-treatment liver function tests and regular monitoring for liver toxicity, weekly laboratory monitoring is not recommended, and INH remains the treatment of choice. Try again.
In addition to clinical and laboratory monitoring at least monthly, pregnant women should undergo a general evaluation for chronic liver disease, alcohol use, and exposure to other hepatotoxins, testing for HIV and hepatitis B and C. It is crucial to remember that the increased hepatotoxicity risk extends through the first 3 months postpartum. INH is considered safe in pregnancy and is not considered a human teratogen.

Case Summary
25-yr healthy pregnant woman
Contact to case
HIV negative
No history of liver disease or hepatotoxins
TST 12 mm
Normal CXR
LFTs at time 0: normal
Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No

Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
Mrs. P’s baseline (LFTs) are within normal limits. You initiate treatment for latent TB infection with INH 300 mg daily along with vitamin B6 25 mg daily.

You schedule her for follow up symptom evaluation and exams at least monthly to ensure that her LFTs remain normal. If there is mild elevation of transaminases, you should monitor more frequently to confirm stability.

You provide Mrs. P clear instructions to avoid hepatotoxins and to discontinue treatment and contact her healthcare provider if symptoms of hepatitis develop.

Hepatotoxins rollover text: Hepatotoxins include alcohol and acetaminophen.

Let’s do another review.
Prescription

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.

Case Summary

25-yr healthy pregnant woman

Contact to case

HIV negative

No history of liver disease or hepatotoxins

TST 12 mm

Normal CXR

LFTs at time 0: normal

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No

Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
Review

- Although INH is considered safe in pregnancy, pregnancy and the early postpartum period confer an increased risk for INH hepatotoxicity.
- Women treated for LTBI during pregnancy should undergo a general evaluation for chronic liver disease, alcohol use, and exposure to other hepatotoxins, testing for HIV and hepatitis B and C, as well as pre-treatment LFTs.
- If LFTs are normal, INH can be started with follow up symptom evaluation and exams monthly at a minimum.
- If there is mild elevation of transaminases, more frequent monitoring is recommended.
- Patients should receive clear instructions to avoid hepatotoxins and be alert for signs and symptoms of hepatitis.
• Patients must be counseled to discontinue treatment and contact their healthcare provider immediately if symptoms of hepatitis develop.

• It is important to remember that the increased INH hepatotoxicity risk continues into the early postpartum period.

Hepatotoxins rollover text: Common hepatotoxins include alcohol and acetaminophen.

LFTs rollover text: Liver function tests include transaminases (AST and ALT) and bilirubin.

Hepatitis rollover text: Hepatitis symptoms include nausea, vomiting, abdominal pain (especially right upper quadrant), jaundice, fatigue, and dark urine.
Mrs. P returned for her first two monthly evaluations and exams, and her LFTs remained within normal limits.

Now Mrs. P calls 2 weeks after her last appointment complaining of right upper quadrant pain and vomiting. You instruct her to stop taking the INH and report to clinic immediately for evaluation. Her exam is normal. However, her liver function testing reveals an AST of 178 and an ALT of 200.

Mrs. P reports no alcohol use or ingestion of acetaminophen or other hepatotoxins, and an abdominal ultrasound is normal.

You tell Mrs. P to discontinue the INH and return for follow up in one week.
Case Summary

25-yo healthy pregnant woman

Contact to case

HIV negative

No history of liver disease or hepatotoxins

TST 12 mm

Normal CXR

LFTs at time 0: normal

Prescription

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No

Fever for more than a week? No

Hoarseness for more than 3 weeks? No

Hemoptysis (coughing up blood)? No
Mrs. P returns for her one week follow-up visit, and transaminases have normalized. What do you do?

Select one of the options below.

a. Restart INH at a dose of 100 mg daily to complete a total of 9 months of treatment.
b. Restart INH at a dose of 300 mg daily to complete a total of 4 months of treatment.
c. Start rifampin 600 mg daily to complete a total of 4 months of treatment.
d. Start rifampin 600 mg daily and pyrazinamide 1500 mg daily to complete a total of 2 months of treatment.
e. Do not resume treatment and reassure Mrs. P that she has reduced her risk of progression to active disease.

Prescription

INH 300 mg one tab orally daily, dispense 30, no refills.

**Rollover text:** INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.

Case Summary

25-yr healthy pregnant woman

Contact to case

HIV negative

No history of liver disease or hepatotoxins

TST 12 mm

Normal CXR

LFTs at time 0: normal

Symptoms

Screening for Symptoms of Active TB:

Have you had...

Cough for more than 2 weeks? No

Unintentional weight loss? No

Night sweats for more than a week? No

Fever for more than a week? No

Hoarseness for more than 3 weeks? No
Hemoptysis (coughing up blood)? No

Response a: Mrs. P has developed symptoms and elevated liver enzymes > 3x the upper limit of normal on INH. Given that she is pregnant and therefore at increased risk of hepatotoxicity, you should not restart INH. Furthermore, daily dosing of INH in adults is 5 mg/kg. Lower doses may not be effective. Try again.

Response b: Incorrect. Mrs. P has developed symptoms and elevated liver enzymes > 3x the upper limit of normal on INH. Given that she is pregnant and therefore at increased risk of hepatotoxicity, you should not restart INH. Furthermore, 4 months of INH treatment is an inadequate treatment duration to reduce the risk of progression to active TB disease. Try again.

Response c: Correct. Mrs. P requires treatment of LTBI during pregnancy because she was a contact to a case. Following usual thresholds for discontinuation of treatment, INH should be discontinued. Because Mrs. P is pregnant and at increased risk of hepatotoxicity, you should not restart INH, the drug on which she developed elevated liver enzymes. Rifampin 600 mg daily for 4 months is an alternative to INH 300 mg for 9 months for treatment of LTBI in contacts to INH-resistant cases and those intolerant of INH and is considered safe in pregnancy.

**Usual thresholds for discontinuation of treatment** rollover text: Usual thresholds are asymptomatic elevation of transaminases to greater than five times the upper limit of normal or greater than three times the upper limit of normal with symptoms.

Response d: Incorrect. Two months of Rifampin and PZA for LTBI treatment has shown an unacceptably high risk of hepatotoxicity. Try again.

Response e: Be careful. Mrs. P requires treatment of LTBI during pregnancy because she was a contact to a case and is therefore at high risk of progression to active disease. Try again.
Mrs. P continues her treatment of LTBI, returns for monthly evaluations, and incurs no further complications.

Let’s go over what you just learned.
Review

- INH 300 mg daily for 9 months is first-line treatment for LTBI. Rifampin 600 mg daily for 4 months is an alternative in patients who do not tolerate INH and is considered safe in pregnancy.

- A regimen of Rifampin and PZA daily for 2 months has unacceptably high risk of hepatotoxicity.

- When side effects occur, do not reduce TB drug doses below recommended levels, as lower doses may be not be effective.
Now that you’ve learned about LTBI treatment in pregnant women, try to answer a few review questions.
Which of the following pairs of pregnant women should be treated for LTBI during pregnancy?

Select one of the options below.

a. A recent arrival from Mexico and a woman with gestational diabetes  
b. A woman with gestational diabetes and a woman with HIV  
c. A woman with HIV and a recent contact to a case  
d. A recent contact to a case and a recent arrival from Mexico

Response a: The correct answer is C. HIV and recent contact to a case are major risk factors for progression to active TB. In the other situations, LTBI treatment may be deferred until 3 months postpartum. Try to answer another question.

Response b: The correct answer is C. HIV and recent contact to a case are major risk factors for progression to active TB. In the other situations, LTBI treatment may be deferred until 3 months postpartum. Try to answer another question.
Response c: Correct. HIV and recent contact to a case are major risk factors for progression to active TB. In the other situations, LTBI treatment may be deferred until 3 months postpartum.

Response d: The correct answer is C. HIV and recent contact to a case are major risk factors for progression to active TB. In the other situations, LTBI treatment may be deferred until 3 months postpartum. Try to answer another question.
Routine screening and monitoring for all patients treated for LTBI includes: a general evaluation for chronic liver disease, alcohol use, and exposure to other hepatotoxins, follow up symptom evaluation every month, and instructions to avoid hepatotoxins (alcohol, acetaminophen, etc.) and to discontinue treatment and contact their healthcare provider if symptoms of hepatitis (abdominal, especially right upper quadrant, pain, nausea, vomiting, jaundice) develop.

In pregnant women, all of the following are also recommended, except:

Select one of the options below.

- Testing for HIV
- Testing for hepatitis B and C
- pre-treatment liver function tests
- baseline liver ultrasound
- follow up LTBI monitoring during the first few months of treatment
e. follow up LFT monitoring during the first few months of treatment

Response a: The correct answer is D. A baseline liver ultrasound is not recommended. However, testing for HIV, hepatitis B and C, and baseline and follow-up LFTs are recommended, because of the increased risk of hepatotoxicity on INH during pregnancy. Try to answer another question.

Response b: The correct answer is D. A baseline liver ultrasound is not recommended. However, testing for HIV, hepatitis B and C, and baseline and follow-up LFTs are recommended, because of the increased risk of hepatotoxicity on INH during pregnancy. Try to answer another question.

Response c: The correct answer is D. A baseline liver ultrasound is not recommended. However, testing for HIV, hepatitis B and C, and baseline and follow-up LFTs are recommended, because of the increased risk of hepatotoxicity on INH during pregnancy. Try to answer another question.

Response d: That’s right. A baseline liver ultrasound is not recommended. However, testing for HIV, hepatitis B and C, and baseline and follow-up LFTs are recommended, because of the increased risk of hepatotoxicity on INH during pregnancy.

Response e: The correct answer is D. A baseline liver ultrasound is not recommended. However, testing for HIV, hepatitis B and C, and baseline and follow-up LFTs are recommended, because of the increased risk of hepatotoxicity on INH during pregnancy. Try to answer another question.
Indications to discontinue INH and consider treatment of LTBI with rifampin in a pregnant woman include the following:

Select one of the options below.

a. transaminases greater than five times the upper limit of normal
b. transaminases greater than three times the upper limit of normal with right upper quadrant pain and vomiting
c. self-limited GI upset after a dose of INH
d. patient preference for a 4-month regimen
e. a and b

Response a: Usual thresholds for discontinuation of INH should be used. These include transaminases greater than five times the upper limit of normal without symptoms OR
transaminases greater than three times the upper limit of normal with symptoms. The drug on which such side effects developed should not be restarted in a pregnant woman.

Response b: Usual thresholds for discontinuation of INH should be used. These include transaminases greater than five times the upper limit of normal without symptoms OR transaminases greater than three times the upper limit of normal with symptoms. The drug on which such side effects developed should not be restarted in a pregnant woman.

Response c: Usual thresholds for discontinuation of INH should be used. These include transaminases greater than five times the upper limit of normal without symptoms OR transaminases greater than three times the upper limit of normal with symptoms. The drug on which such side effects developed should not be restarted in a pregnant woman.

Response d: Usual thresholds for discontinuation of INH should be used. These include transaminases greater than five times the upper limit of normal without symptoms OR transaminases greater than three times the upper limit of normal with symptoms. The drug on which such side effects developed should not be restarted in a pregnant woman.

Response e: Correct. Usual thresholds for discontinuation of INH should be used. The drug on which such side effects developed should not be restarted in a pregnant woman.
Congratulations! You have completed the LTBI Treatment in Pregnancy module.

Click [here](#) to return to view the references for this module and a list of all Pregnancy Review Points.

Click MENU to return to the main menu.
Renal Failure File
Case Presentation

Mrs. M, a 75-year-old woman with end-stage renal disease (ESRD) and diabetes, presents for routine medical follow up. She has been on chronic hemodialysis for the past 3 years. She immigrated from Mexico 30 years ago.
Assuming the dialysis center has been screening patients appropriately for TB, when should Mrs. M have undergone a symptom screen and diagnostic testing for LTBI?

Select one of the options below.

a. At initial diagnosis of advanced chronic kidney disease or around the time of dialysis initiation, regardless of the presence of additional risk factors, and annually thereafter if no new TB exposures occur.

b. At initial diagnosis of advanced chronic kidney disease or around the time of dialysis initiation, if additional risk factors are present, and annually thereafter if no new TB exposures occur.

c. At initial diagnosis of advanced chronic kidney disease or around the time of dialysis initiation, regardless of the presence of additional risk factors and thereafter only if a new TB exposure occurs.
d. Only if there is known contact to a TB case or additional immunosuppressing conditions.

Response a: Correct. Advanced chronic kidney disease is an immunosuppressing condition in which impairment of cell-mediated immunity results in increased risk of TB. Therefore, even in the absence of any additional risk factors or known contact to a TB case, patients with advanced kidney disease should be screened for LTBI at initial diagnosis or around the time of dialysis initiation, and annually thereafter if no new TB exposures occur. The prevalence of LTBI in this patient population is high.

Response b: Be careful. Advanced chronic kidney disease itself is an immunosuppressing condition in which impairment of cell-mediated immunity results in increased risk of TB. Therefore, LTBI screening is warranted whether or not additional risk factors are present. Try again.

Response c: Careful. An even more aggressive approach to LTBI screening is warranted, given the fact that chronic kidney disease results in impairments in cell-mediated immunity. Try again.

Response d: Incorrect. A more aggressive approach to LTBI screening is warranted, given the fact that chronic kidney disease results in impairments in cell-mediated immunity. Try again.
Because of the high mortality and difficulties associated with treatment for active TB in this patient population, the risk of transmission to other patients within dialysis units, and the worsening impairment in cell-mediated immunity with advancing renal failure, patients with chronic kidney disease should be screened for LTBI as early as possible.
Due to impaired cellular immunity, patients with end-stage renal disease on chronic hemodialysis are approximately 10-25 times more likely to develop active TB compared to the general population.

Table 3. Relative risk* for developing active tuberculosis (TB), by selected clinical conditions

*Relative to control population; independent of tuberculin-test status.

Numbers in parentheses are reference numbers.

Clinical condition: Silicosis
Relative risk: 30 (37,38)

Clinical condition: Diabetes mellitus
Relative risk: 2.0 - 4.1 (42-44)
Clinical condition: Chronic renal failure/hemodialysis
Relative risk: 10.0 - 25.3 (39-41)

Clinical condition: Gastrectomy
Relative Risk: 2-5 (45-47)

Clinical condition: Jejunoileal bypass
Relative risk: 27-63 (48-49)

Clinical Condition: Solid organ transplantation-Renal
Relative risk: 37 (50)

Clinical Condition: Solid organ transplantation-Cardiac
Relative risk: 20-74 (51,52)

Clinical Condition: Carcinoma of head or neck
Relative risk: 16 (53)

Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR June 9, 2000, vol 49, no RR-6

Case Summary

75-yo woman
- originally from Mexico
- ESRD on HD x 3 years
- diabetes
Review

- Due to impaired cellular immunity, patients with end-stage renal disease on chronic hemodialysis are approximately 10-25 times more likely to develop active TB compared to the general population.
- There is a high prevalence of LTBI among patients with ESRD undergoing hemodialysis.

Case Summary

75-yo woman
- originally from Mexico
- ESRD on HD x 3 years
- diabetes
On two-step testing 3 years ago, Mrs. M. had a **TST** of 0 mm. Which of the following facts about two-step testing is false?

Select one of the options below.

a. It reduces the likelihood that a boosted reaction will be interpreted as new infection in patients who are periodically tested.

b. It is generally recommended when TSTs are used for initial screening for LTBI in chronic dialysis patients.

c. It is generally recommended when IGRA is used for initial screening for LTBI in chronic dialysis patients.

d. It is recommended when TSTs are used for initial screening for LTBI in healthcare workers.

e. It involves repeating testing 1-3 weeks after the initial test.
Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.

Case Summary

75-yr woman
- originally from Mexico
- ESRD on HD x 3 years
- diabetes

Response a: Actually, this statement is true. Two-step testing is employed for initial screening in individuals who are periodically tested to reduce the likelihood that a boosted reaction will be interpreted as new infection. Try again.

Response b: Actually, this statement is true. Two-step testing is recommended for initial screening for LTBI in this patient population. Alternatively, a single IGRA could be considered. Try again.

Response c: Correct. Currently, two-step testing is not generally recommended when IGRAs are used as the phenomenon of “boosting” has not been reported with IGRAs. In certain persons with LTBI, the delayed type hypersensitivity responsible for TST reactions wanes over time. The "booster phenomenon" occurs when an initial TST result is falsely negative, but a subsequent TST placed 1-3 weeks after the first is positive, because of “boosting” of the immune response to tuberculin rather than to recent infection with M. tuberculosis. Thus, two-step testing helps to establish a baseline TST status and is recommended for initial LTBI screening in any situation in which periodic screening for LTBI is anticipated (e.g. healthcare workers, chronic dialysis patients,
individuals living in high-risk congregate settings, individuals with HIV and ongoing TB exposure risk, etc.).

Response d: Actually, this statement is true. Two-step testing is recommended for initial TST screening of healthcare workers, who, like patients with chronic renal disease, should be screened for LTBI annually. Alternatively, a single IGRA could be considered. Try again.

Response e: Actually, this statement is true. Two-step testing does involve repeat testing 1-3 weeks after the initial test. Try again.
Review

- Two-step testing involves repeating the TST 1-3 weeks after the initial test.

- Two-step testing is recommended in individuals who are periodically tested (e.g. healthcare workers, patients with chronic renal failure on dialysis, individuals living in high-risk congregate settings, individuals with HIV and ongoing TB exposure risk) to reduce the likelihood that a boosted reaction will be interpreted as new infection.

- Two-step testing is generally thought to be unnecessary when IGRA tests are used, as “boosting” has not been reported with IGRA tests. Some experts recommend a single IGRA in situations where two-step testing would otherwise be used.
TST text rollover– Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.

IGRA text rollover - interferon-gamma release assays

Case Summary

75-yr woman

- originally from Mexico

- ESRD on HD x 3 years

- diabetes
Mrs. M initially reports no complaints but then admits to “feeling a little run down” from dialysis. She is glad that she has lost some weight, about 10 lbs in the past 3 months, although she has not changed her diet and has not been exercising. She smokes a pack of cigarettes a day, and has had a “smoker’s cough” for 4 months. She is 5’2” and weighs 90 lbs. Hemoglobin is 10.0 g/dL, albumin in 2.9 g/dL. TST was 0 mm at annual screening at her dialysis center 2 weeks ago.

Case Summary

75- yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 pack a day smoker
- smoker’s cough
- 12% weight loss (last current wt 90 lbs, in 5’2”)
- Hemoglobin 10.0 g/dL, albumin 2.9
- TST 0 mm
- 1 ppd smoker

- “smoker’s cough”

- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)

- Hgb 10, albumin 2.9

- TST 0 mm
At this point, you:

Select one of the options below.

a. Reassure Mrs. M that these symptoms are normal for someone on dialysis.

b. Perform a complete physical examination and order a chest x-ray and sputums for smear, NAA, and culture.

c. Repeat the TST now.

d. Call the dialysis center immediately, as Mrs. M likely has active TB that she likely acquired through nosocomial transmission from a healthcare worker at the facility, since she has no risk factors.
Case Summary

75-yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm

Response a: While fatigue and weight loss can occur in patients on chronic hemodialysis, often due to uremia, such an attribution would be a diagnosis of exclusion. Alternative explanations for Mrs. M’s symptoms need to be considered. Try again.

Response b: Correct. It is crucial that physicians caring for patients with ESRD on chronic hemodialysis remain alert for subtle symptoms and signs of active TB. Due to impaired cellular immunity, extrapulmonary forms of TB are more common in these patients, and non-specific symptoms such as weight loss, malaise, and fatigue due to disseminated TB may be misinterpreted as symptoms of uremia. Furthermore, the recent TST of 0 mm should not reassure you: a negative TST never excludes active TB, and the prevalence of cutaneous anergy to TST is significantly higher in the ESRD patients compared to the general population (44% versus 16% in one study).

Let’s review what you’ve learned.

Response c: Incorrect. Two-step testing is often employed in patients with ESRD on chronic hemodialysis in an effort to increase the sensitivity of TST by boosting the immune response to PPD. However, the rate of anergy remains high in this population.
even with repeated testing. Furthermore, repeating the TST now would be of little clinical value in the diagnosis of active TB, which should be the focus of your evaluation at this time.

Response d: Not exactly. While nosocomial transmission of TB in dialysis centers has been reported, it is far more likely that if Mrs. M has active TB, it developed as a result of reactivation of LTBI that she acquired in her country of origin. As a patient with ESRD on chronic hemodialysis, she has impaired cellular immunity, increasing her risk of reactivation. Try again.
Review

- Additional risk factors for active TB in hemodialysis patients include: age, smoking, reduced body mass index, low serum albumin, ischemic heart disease, and anemia.

- The mortality rate of TB in dialysis patients is high.

- Extrapulmonary forms of the disease are more common in ESRD patients, and nonspecific symptoms such as malaise and weight loss may be interpreted as signs of uremia.

- Nosocomial transmission of TB has been documented in US hemodialysis centers.
• Even when two-step testing is used, the prevalence of anergy to TST in the ESRD population is significantly higher than in the general population (44% versus 16%).
On examination, Mrs. M has cervical and axillary lymphadenopathy. You order a chest x-ray.

Case Summary

75-yr woman

- immigrated from Mexico 30 yrs ago

- ESRD on HD x 3 yrs

- diabetes

- 1 ppd smoker

- “smoker’s cough”

- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)

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- Hgb 10, albumin 2.9

- TST 0 mm
The chest x-ray shows a right upper lobe infiltrate with cavitation. She also tells you that her fingersticks have been in the 300s almost every day for the past few weeks. Sputum smears and nucleic acid amplification return as positive for M. tuberculosis complex.

Case Summary

75-yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)

Published by Articulate® Storyline       www.articulate.com
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
Because of her uncontrolled diabetes and the need for respiratory isolation, you admit Mrs. M to the hospital to initiate treatment for active TB. A contact investigation reveals evidence of transmission to 5 out of 6 household contacts, and testing at the dialysis center is ongoing. Based on review of schedules at the dialysis center, the health department identifies 50 patients and 6 non-immunocompromised healthcare workers as contacts to Mrs. M.

Case Summary

75-yo woman

- immigrated from Mexico 30 yrs ago

- ESRD on HD x 3 yrs

- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
Which of the following is an appropriate approach to the contact investigation?

Select one of the options below.

a. Do not perform TSTs or IGRA and treat all 50 patients and 6 healthcare workers for LTBI, given the high risk of transmission from this very infectious case.

b. Perform TSTs in the healthcare workers but not in the patients, and treat the patients empirically with a full course of treatment for LTBI because of the high risk of progression to TB disease.

c. Perform TSTs in all patients and healthcare workers not previously treated for LTBI, and treat all the healthcare workers regardless of TST result because of the high risk of nosocomial transmission of TB to the dialysis patients.
d. Perform IGRAs or TSTs in all patients and healthcare workers not previously treated for LTBI.

Case Summary

75-yr woman

- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2’’)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB

Response a: Not exactly. All contacts should undergo a symptom screen and those without a history of LTBI (both patients and healthcare workers) should also undergo TST or IGRA for evaluation. While the case is quite infectious, documentation of transmission among contacts should be documented. Try again.

Response b: Be careful. All contacts should undergo a symptom screen and those without a history of LTBI (both patients and healthcare workers) should also undergo TST or IGRA for evaluation. Try again.
Response c: Not quite. All contacts should undergo a symptom screen and those without a history of LTBI (both patients and healthcare workers) should also undergo TST or IGRA for evaluation. Try again.

Response d: Correct. All contacts should undergo a symptom screen and those without a history of LTBI (both patients and healthcare workers) should also undergo TST or IGRA for evaluation. Some studies suggest that IGRAs may be preferable in patients with ESRD on dialysis given the high rates of cutaneous anergy.

Let’s review.
Review

- All contacts not previously treated for LTBI (both patients and healthcare workers) should undergo a TB symptom screen and TST or IGRA for evaluation.

- IGRAs may be more accurate than TST in chronic dialysis patients.

Case Summary

75-yo woman

- immigrated from Mexico 30 yrs ago

- ESRD on HD x 3 yrs

- diabetes

- 1 ppd smoker
- “smoker’s cough”

- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)

- Hgb 10, albumin 2.9

- TST 0 mm

- cervical and axillary lymphadenopathy

- CXR with RUL infiltrate with cavitation

- sputum smear and NAA + for MTB
The contact investigation yields the following:

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs
Case Summary

75-yo woman

- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2’’)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
You feel confident that active TB has been excluded by symptom screen and chest x-ray in the 2 healthcare workers and 15 patients with previously untreated LTBI or newly positive IGRAs. You have received a report indicating that Mrs. M’s TB is sensitive to all first-line drugs.

### CI Results

**Healthcare workers:**
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

**Patients:**
- 10 newly positive IGRAs
- 5 previously positive and untreated
- 5 previously positive but never treated
- 21 negative IGRAs
Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Case Summary

75-<wbr/>yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
What LTBI treatment do you offer these 17 individuals?

Select one of the options below.

a. Rifampin 600 mg daily for 4 months
b. INH 900 mg and rifapentine 900 mg weekly for 8 weeks via DOT
c. INH 900 mg (biweekly for the healthcare workers, triweekly dosed after dialysis for the patients) for 9 months via DOT
d. Daily INH (renally dosed for the patients on dialysis) for 9 months
e. Rifabutin 300 mg daily

CI Results

Healthcare workers:
- 1 newly positive IGRA
1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Case Summary
75-ya woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
Response a: Actually, rifampin is generally reserved for those with intolerance to INH or exposure to an INH-resistant case. Try again.

Response b: Incorrect. The new short-course regimen of INH and rifapentine weekly via DOT is a 12-week regimen. This regimen has not yet been studied in a population with chronic kidney disease or in dialysis patients, although it might be considered in select patients with close monitoring for side effects. Try again.

Response c: Correct. INH remains the treatment of choice for patients with chronic kidney disease or those on dialysis. TB drugs should be dosed after dialysis. If resources are available, DOT is recommended; priority for DOT should be given to IGRA/TST converters. Rifampin is generally reserved for those with intolerance to INH and for contacts of INH-resistant cases. Rifabutin is felt to be an acceptable alternative to rifampin when hepatotoxicity is a treatment-limiting factor.

Response d: Not quite. There is no need for dose alteration of INH in patients with chronic kidney disease or in those on dialysis. Try again.

Response e: Incorrect. Rifabutin is not a first-line regimen for LTBI treatment. It is felt by experts to be a reasonable alternative to rifampin when hepatotoxicity becomes a treatment-limiting factor. Try again.
No dose adjustment for renal failure is necessary. The 2 drugs most commonly used for the treatment of LTBI (INH and rifampin) do not require dose adjustment even in the setting of advanced chronic kidney disease or ESRD on hemodialysis. Data regarding clearance of anti-tuberculosis drugs are best documented for patients with creatinine clearance less than 30 mL/min, or for those undergoing hemodialysis.

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRA

Patients:
- 35 newly positive IGRA
- 35 previously positive but never treated
- 100 negative IGRA

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Patients:

- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Case Summary

75-yo woman

- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
For individuals with mild renal failure or undergoing peritoneal dialysis, data are less available. In addition to the effects on drug clearance, the diseases that cause renal failure and concomitant treatments can also impact drug levels (by altering absorption or drug interactions). Moxifloxacin does not require dose adjustment; levofloxacin, ethambutol, and pyrazinamide do require dose adjustment for renal insufficiency.

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRA

Patients:
- 10 newly positive IGRA
- 15 previously positive and untreated
- 20 previously positive but never treated
- 20 negative IGRA

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Case Summary

75-yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2’’)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
Vitamin B6 supplementation is important, especially in the setting of uremia. Additionally, you should take into account the increased incidence of chronic hepatitis B and C infection as well as increased use of hepatotoxic medications. Also consider baseline LFTs and more frequent laboratory monitoring for hepatotoxicity in this population.

Hepatotoxic medications text rollover: These include HMG-CoA reductase inhibitors.

LFT text rollover – Liver function tests (LFTs) include transaminases and bilirubin.

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated

- 11 newly positive IGRA
- 14 previously positive and never treated
- 10 previously positive but never treated
- 20 negative IGRA
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Case Summary

75-yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB
You also need to decide how to manage the healthcare workers (all immunocompetent) and patients with negative IGRAs. At this point, you:

Select one of the options below.

a. Start the patients on empiric treatment with INH pending repeat IGRA at 8-12 weeks after last contact with the case (window prophylaxis). Offer INH only to those healthcare workers with positive IGRAs on repeat testing 8-12 weeks after last contact with the case.

b. Repeat IGRA at 8-12 weeks after last contact with the case and offer rifampin to the patients and healthcare workers with positive IGRAs.

c. Perform TSTs at 8-12 weeks after last contact with the case and offer INH to the patients and healthcare workers with TSTs of 5 mm or greater.
Perform TSTs at 8-12 weeks after last contact with the case and offer INH to the patients and healthcare workers with TSTs of 10 mm or greater.

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Case Summary

75- yo woman
- immigrated from Mexico 30 yrs ago
- ESRD on HD x 3 yrs
- diabetes
- 1 ppd smoker
- “smoker’s cough”
- 10-lb weight loss, (current wt 90 lbs, ht 5’2”)
- Hgb 10, albumin 2.9
- TST 0 mm
- cervical and axillary lymphadenopathy
- CXR with RUL infiltrate with cavitation
- sputum smear and NAA + for MTB

Response a: Correct. Although CDC guidelines recommend window prophylaxis in individuals with HIV and in children under age 5, it could also be a reasonable approach for the dialysis patients, given the high level of infectiousness of the TB case. First, these patients are significantly immunocompromised. Also, from a public health perspective, the dialysis center represents a congregate setting of susceptible individuals. Failure to prevent TB in a single patient could result in ongoing transmission, with potentially disastrous results. For the immunocompetent healthcare workers, the IGRA should be repeated 8-12 weeks after last contact with the case, and those with positive IGRA should be treated for LTBI with standard therapy.

Response b: Not quite. While window prophylaxis might be considered in this scenario, another option would be to repeat IGRA in both the patients and healthcare workers 8-12 weeks after last contact with the case. Those with positive IGRA would then be treated for LTBI. However, rifampin would not be the drug of choice, given that the index case is known to have a pansensitive organism. Rifampin is generally reserved for contacts of INH-resistant cases or for those with intolerance to INH. Try again.

Response c: Incorrect. Because you chose to screen for LTBI using an IGRA as the initial test, repeat testing should use the same modality. However, if TSTs had been used as the initial test, a repeat TST of 5 mm or greater would be considered positive. Try again.

Response d: Be careful. Because you chose to screen for LTBI using an IGRA as the initial test, repeat testing should use the same modality. If TSTs had been used as the initial test, TSTs would be repeated at 8-12 weeks after last contact with the case. In patients with end-stage renal disease on chronic hemodialysis, a positive TST is defined as
induration of 10 mm or greater, if there has been no known contact to a TB case. However, in this case, the patients are contacts to a TB case and in this situation, a positive TST is defined as induration of 5 mm or greater. Try again.
Of the 4 healthcare workers and 20 patients with initial negative IGRAs, 1 healthcare worker and 5 patients have positive IGRAs on repeat testing. You start these 6 individuals on treatment with INH. Mr. C, one of the patients with known hepatitis B and C, develops anaphylaxis to INH; on rifampin, he develops nausea and vomiting and AST of 300.

Case Summary:

- dialysis patient with hepatitis B and C
- contact to pansensitive TB case
- TST converter
- anaphylaxis to INH
- nausea, vomiting, AST 300 on rifampin
CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs
At this point, you hold the rifampin until liver enzymes return to baseline and then initiate:

Select one of the options below.

a. INH at a lower dose.

b. Rifampin at a lower dose.

c. No medications for LTBI at this time as the risks of treatment outweigh the benefits in this case.

d. Rifampin and PZA.

e. Rifabutin.

Case Summary:

- dialysis patient with hepatitis B and C
- contact to pansensitive TB case
- TST converter
- anaphylaxis to INH
- nausea, vomiting, AST 300 on rifampin

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Response a: No! Mr. C has developed anaphylaxis on INH, and this medication should never be given to the patient again, at any dose. Try again.

Response b: Be careful. There is no need for dose adjustment of rifampin for chronic kidney disease or dialysis patients. When side effects occur, administering the same drug at a lower dose is not recommended, as side effects are likely to recur regardless of dose and lower doses of medications may not be effective for treatment of LTBI. Try again.

Response c: Incorrect. Mr. C is at high risk of progression to active TB. He is a patient with significantly impaired cell mediated immunity due to advanced chronic kidney
disease and is also a documented IGRA converter after a recent contact to a TB case. Treatment of LTBI is crucial in this case. Try again.

Response d: Actually, the regimen of rifampin and PZA for 2 months is no longer recommended in any patient due to the high risk of hepatotoxicity associated with it. Mr. C has already manifested significant hepatotoxicity on rifampin alone. Try again.

Response e: That’s right. Given the importance of treating LTBI in Mr. C, who is at high risk of progression to TB disease, most experts recommend a trial of rifabutin in this case, because of the lower risk of hepatotoxicity associated with this medication. Some experts recommend dose adjustment of rifabutin in patients with creatinine clearance < 30 with monitoring of drug levels of rifabutin as well as the active metabolite in order to ensure that dosing is adequate and to avoid toxicity.
**Review**

- For patients with advanced chronic kidney disease, a positive TST is defined as induration of 10 mm or greater.
- INH remains the treatment of choice in patients with advanced chronic kidney disease. Dose adjustment is not necessary, and INH should be dosed after dialysis.
- Dose adjustment and monitoring of drug levels may be considered with rifabutin but is not necessary when rifampin is used in the setting of renal insufficiency.

**Case Summary:**

- dialysis patient with hepatitis B and C
- contact to pansensitive TB case
- TST converter
- anaphylaxis to INH
- nausea, vomiting, AST 300 on rifampin

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs
Mr. C tolerates the rifabutin, and you successfully treat all of the patients and healthcare workers for LTBI.

Case Summary:
- dialysis patient with hepatitis B and C
- contact to pansensitive TB case
- TST converter
- anaphylaxis to INH
- nausea, vomiting, AST 300 on rifampin

CI Results
Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs
Today, a new patient presents to your office with complaints of dysuria and intermittent fevers. Mr. D is a 40-year-old man with mild chronic renal insufficiency and no known risk factors for renal disease. He has a history of prior pulmonary TB treated in China 5 years ago. He comes with a report of a urinalysis showing hematuria, pyuria, a urine culture positive for E. coli, and an intravenous pyelogram showing blunting of the calices, a ureteral stricture, and calcifications within the vas deferens and prostate.

Case Summary:

40-yo man
- mild chronic renal insufficiency
- active pulmonary TB treated in China 5 yrs ago
- hematuria, pyuria
- urine culture + E. coli

- intravenous pyelogram: blunted calyces, ureteral stricture, calcifications in vas deferens and prostate

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs
At this point, you:

Select one of the options below.

a. Request a chest x-ray and 3 first morning midstream urine specimens for AFB smear and culture.

b. Request 3 first morning midstream urine specimens for AFB smear and culture.

c. Admit Mr. D for a renal biopsy.

d. Initiate treatment for bacterial pyelonephritis.

Case Summary:

40-yo man

- mild chronic renal insufficiency

- active pulmonary TB treated in China 5 yrs ago
hematuria, pyuria

urine culture + E. coli

intravenous pyelogram: blunted calyces, ureteral stricture, calcifications in vas deferens and prostate

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs

Response a: Correct. The clinical presentation is highly suggestive of genitourinary TB. Patients with genitourinary TB frequently present with dysuria and hematuria. The urine is classically sterile by routine culture, but because some patients have concurrent bacteriuria, a positive culture does not exclude the presence of urinary TB. Although often normal in early disease, IVP findings may be unilateral or bilateral and may resemble findings of chronic pyelonephritis.

IVP findings text rollover: findings of genitourinary TB on IVP (intravenous pyelogram) include lower tract findings (erosion of the tips of the calyces, blunting of the calyces or
overt papillary necrosis, and parenchymal scarring and calcification) and upper tract findings (ureteral strictures, a contracted bladder, calcifications in the vas deferens, seminal vesicles, or prostate).

Response b: Not quite. You are right to suspect genitourinary TB in this case. However, given the history of pulmonary TB, you need to screen for active pulmonary TB as well. In addition to documenting sites of disease, it is important to determine whether this case is transmissible to others. Try again.

Response c: Try again. A renal biopsy would not be the next step in the workup. Less invasive tests are likely to yield a diagnosis in this case.

Response d: Careful. Although the urine culture positive for E. coli suggests the possibility of concurrent bacterial infection, the clinical presentation and IVP findings are more consistent with another diagnosis in this case. Try again.
Although nonpathogenic mycobacteria may occasionally cause false positive urine smear results, urine culture is the gold standard for diagnosis. Three to six first morning midstream specimens should be sent to maximize sensitivity, since bacilli are shed into the urine intermittently, with only 30 to 40 percent of single specimens returning as positive in patients with active disease. Given the history of pulmonary TB, chest x-ray screening for active pulmonary TB is essential, even in the absence of symptoms.

Case Summary:

40-yeo man
- mild chronic renal insufficiency
- active pulmonary TB treated in China 5 yrs ago
- hematuria, pyuria
- urine culture + E. coli

- intravenous pyelogram: blunted calyces, ureteral stricture, calcifications in vas deferens and prostate

CI Results

Healthcare workers:
- 1 newly positive IGRA
- 1 previously positive but never treated
- 4 negative IGRAs

Patients:
- 10 newly positive IGRAs
- 15 previously positive and treated
- 5 previously positive but never treated
- 20 negative IGRAs
The diagnosis of genitourinary TB is suggested by a history of prior TB, sterile pyuria, and typical findings on IVP.

IVP findings text rollover: findings of genitourinary TB on IVP (intravenous pyelogram) include lower tract findings (erosion of the tips of the calyces, blunting of the calyces or overt papillary necrosis, and parenchymal scarring and calcification) and upper tract findings (ureteral strictures, a contracted bladder, calcifications in the vas deferens, seminal vesicles, or prostate).
Review questions:

Which of the following drugs requires dose adjustment in renal failure?

Select one of the options below.

a. INH
b. Rifampin
c. Ethambutol
d. Moxifloxacin

Response a: The correct answer is C. Ethambutol, but not INH, rifampin, or moxifloxacin, requires dose adjustment in renal failure.
Response b: The correct answer is C. Ethambutol, but not INH, rifampin, or moxifloxacin, requires dose adjustment in renal failure.

Response c: Ethambutol, but not INH, rifampin, or moxifloxacin, requires dose adjustment in renal failure.

Response d: The correct answer is C. Ethambutol, but not INH, rifampin, or moxifloxacin, requires dose adjustment in renal failure.
Review questions:

Patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often, because:

Select one of the options below.

a. drug treatment of active TB is challenging in the setting of advanced chronic kidney disease.

b. cell-mediated immunity is thought to worsen with advancing renal failure.

c. the mortality of active TB in this population is high.

d. the prevalence of LTBI in this population is high.

e. there is a high risk of transmission of active TB within dialysis units
f. all of the above

Response a: The correct answer is F. In the setting of advanced renal failure, cell-mediated immunity is impaired, the prevalence of LTBI is high, there is a high death rate associated with active TB, drug treatment of active TB is challenging, and there is a high risk of transmission of active TB within dialysis units. Therefore, patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often.

Response b: The correct answer is F. In the setting of advanced renal failure, cell-mediated immunity is impaired, the prevalence of LTBI is high, there is a high death rate associated with active TB, drug treatment of active TB is challenging, and there is a high risk of transmission of active TB within dialysis units. Therefore, patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often.

Response c: The correct answer is F. In the setting of advanced renal failure, cell-mediated immunity is impaired, the prevalence of LTBI is high, there is a high death rate associated with active TB, drug treatment of active TB is challenging, and there is a high risk of transmission of active TB within dialysis units. Therefore, patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often.

Response d: The correct answer is F. In the setting of advanced renal failure, cell-mediated immunity is impaired, the prevalence of LTBI is high, there is a high death rate associated with active TB, drug treatment of active TB is challenging, and there is a high risk of transmission of active TB within dialysis units. Therefore, patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often.

Response e: The correct answer is F. In the setting of advanced renal failure, cell-mediated immunity is impaired, the prevalence of LTBI is high, there is a high death rate
associated with active TB, drug treatment of active TB is challenging, and there is a high risk of transmission of active TB within dialysis units. Therefore, patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often.

Response f: In the setting of advanced renal failure, cell-mediated immunity is impaired, the prevalence of LTBI is high, there is a high death rate associated with active TB, drug treatment of active TB is challenging, and there is a high risk of transmission of active TB within dialysis units. Therefore, patients with advanced chronic kidney disease or ESRD on chronic hemodialysis should be screened for TB early and often.
Congratulations!

You have completed the LTBI Treatment in Patients With Renal Failure module.

Click MENU to return to the main menu where you can select another module or exit the course.
TNF Antagonists File
Mrs. E is a 56 year old woman who has severe rheumatoid arthritis and has been referred by her rheumatologist for evaluation of latent TB infection prior to starting treatment with etanercept a TNF-α inhibitor. She was born in Guatemala and has been in the United States for seven years. She denies ever having had a TB skin test. There is no known exposure to an active TB case. There are no signs or symptoms of TB disease. 

**TNF-α inhibitor rollover text:** TNF-α is a cytokine that plays an important role in the recruitment of macrophages and lymphocytes which are pivotal in granuloma formation and the host defense against mycobacterial infections. 

**TNF-α inhibitors refer to a group of agents used to treat a variety of inflammatory illnesses such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease.**
At this point, what should you do?

Select one of the options below.

a. Reassure Mrs. E that she has no risk factors for TB infection since she has been in the US for over five years.

b. Place a TST on Mrs. E and initiate treatment with INH if the induration is 5 mm and/or her chest x-ray is normal.

TST rollover text: Tuberculin skin test. Note that interferon-gamma release assays (IGRAS) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAS, refer to the IGRA reference book.

c. Perform an IGRA on Mrs. E and if it is negative, start etanercept for her RA.

IGRA rollover text: interferon-gamma release assay
d. Initiate empiric treatment with INH regardless of the TST or IGRA result because the risk of progression to active TB is exceedingly high in patients treated with TNF antagonists.

Response a: Be careful. All patients prescribed a TNF-α inhibitor must undergo screening for latent TB infection prior to initiating treatment even if no other risk factors are present. This is because there is a high risk of progression to active TB disease with this type of immunosuppressant. Try again.

Response b: Correct. The United States Centers for Disease Control and Prevention (CDC) recommends treatment of LTBI prior to starting a TNF-α inhibitor in all patients who have a TST result of ≥ 5mm induration or a positive IGRA. A chest x-ray is also an essential part of the evaluation. Patients with a negative TST (<5 mm) or a negative IGRA should still be treated for LTBI if there is evidence of remote TB disease on the CXR or an epidemiologic link to prior TB exposure.

Response c: Not quite. The United States Centers for Disease Control and Prevention (CDC) recommends that even if the IGRA result is negative, patients should be treated for LTBI if there is evidence of remote TB disease on the CXR or an epidemiologic link to prior TB exposure. In this case Mrs. E’s history of residence in Guatemala is considered an epidemiologic link to prior TB exposure regardless of her IGRA result. Try again.

Remote TB disease on the CXR rollover text: An example of remote TB disease on the CXR is regional fibrosis with or without hilar lymphadenopathy. As always, it is crucial that active pulmonary disease be excluded prior to initiation of LTBI treatment.

Epidemiologic link to prior TB exposure rollover text: Epidemiologic links to prior TB exposure include history of contact to an active case or residence in a high prevalence country.
Response d: Incorrect. Treatment for LTBI should only be initiated after active TB infection has been sufficiently ruled out by an absence of signs and symptoms of disease as well as a normal chest x-ray.
You have another patient, Mr. I, who is due to start treatment with infliximab for inflammatory bowel disease. He is also from Guatemala. Both he and Mrs. E have TSTs of 10 mm induration. Neither has a history of known contact to a TB case.

Which patient is at greater risk of developing active TB related to the arthritis treatment?

a. Mr. I  
b. Mrs. E

Response a: That’s right. Although all anti-TNF agents are associated with a substantial risk of progression to active TB disease, studies suggest that treatment with infliximab is associated with a higher risk of development of active TB than treatment with etanercpt.
Response b: Incorrect. Several studies suggest that treatment with infliximab, a monoclonal anti-TNF antibody, is associated with a higher risk of development of active TB than treatment with etanercept, a soluble TNF receptor. Other monoclonal anti-TNF antibodies include adalimumab, golimumab, and certolizumab.
You have recommended treatment for LTBI for Mrs. E. However, because of her disabling joint pain, she does not want her LTBI treatment to delay initiation of treatment with etanercept.

Case Summary

+ 58-year-old woman from Guatemala
+ immigrated 7 years ago
+ rheumatoid arthritis
+ TST 10 mm
Given Mrs. E’s strong desire to start her treatment with etanercept, what should you do?

a. Advise against treatment with etanercept.
b. Treat Mrs. E with rifampin daily for 6 months and then start etanercept.
c. Treat Mrs. E with rifampin, INH, PZA, and ethambutol daily for 2 months and then start etanercept.
d. Treat Mrs. E with INH and vitamin B6 daily and recommend that etanercept be started ideally after at least one month of initiating LTBI treatment.
e. Start etanercept now, and monitor Mrs. E monthly for signs and symptoms of TB disease.

Response a: Actually, treatment with etanercept is not contraindicated because of Mrs. E’s TB risk. However, appropriate measures to minimize that risk are indicated. Try again.
Response b: Incorrect. INH for nine months is still considered to be the standard of care for the treatment of LTBI in patients with planned treatment with TNF-α inhibitors. Some experts suggest that because four months of rifampin appears to be safe and is cost effective, that this may represent a reasonable alternate regimen in this patient population. Further studies are warranted to evaluate its efficacy in reducing risk to progression of active TB disease. At this time most clinicians reserve this option for patients with intolerance of INH and contacts to INH resistant cases. Try again.

Response c: Incorrect. INH remains the treatment of choice for LTBI in patients with planned treatment with TNF-α antagonists. Occasionally, a patient may be on rifampin, INH, PZA, and ethambutol (RIPE) as treatment for suspected active TB when workup subsequently reveals an alternative diagnosis. If the patient has been on RIPE for at least two months, this may be considered adequate treatment. However, this regimen is not a recommended treatment for LTBI. Try again.

Response d: Correct. There has been considerable debate over the management of patients with LTBI and planned treatment with TNF antagonists. Some have advocated full treatment of LTBI prior to initiation of TNF antagonists. Although completion of 9 months of treatment with INH remains the safest approach, most experts agree that at least one month of LTBI treatment should be given before starting anti-TNF alpha therapy. In some cases, concurrent treatment may be acceptable.

Full treatment of LTBI prior to initiation of TNF antagonists rollover text: Why? Because studies from the 1970s document decreasing effectiveness of INH in preventing active disease based on the duration of treatment: 75% for a 52-week regimen, 65% for a 24-week regimen, and 21% for a 12-week regimen.

At least one month of LTBI treatment should be given before starting anti-TNF alpha therapy rollover text: Why? Studies of INH prophylaxis in HIV patients in the pre-antiretroviral era suggest that INH is effective in preventing progression to active TB, even in the setting of severe immunocompromise.
Response e: Be careful. Therapy for LTBI is warranted prior to initiating etanercept. Try again.

Case Summary

+ 58-year-old woman from Guatemala
+ immigrated 7 years ago
+ rheumatoid arthritis
+ TST 10 mm
Mrs. E begins treatment with INH, and treatment with etanercept is initiated 1 month later. After 3 months, she develops malaise and weight loss. She has no cough or respiratory symptoms.

Chest x-ray is normal. You initiate a workup to exclude the presence of:

Click the Prescription tab to view the prescription.

- a. Side effects related to INH
- b. Side effects related to infliximab
- c. Extrapulmonary TB
- d. Lymphoma
Prescription

INH 300 mg one tab orally daily, dispense 30, no refills.

Rollover text: INH refills should not be given because monthly follow up is needed.

Vitamin B6 25 mg one tablet orally daily, dispense 30, 3 refills.

Case Summary

+ 58-year-old woman from Guatemala
+ immigrated 7 years ago
+ rheumatoid arthritis
+ TST 10 mm

Response a: Not exactly. Malaise and weight loss would be unusual side effects of INH. Try again.

Response b: Not exactly. Malaise and weight loss would be unusual side effects of infliximab. Try again.

Response c: Correct. Vigilance for constitutional symptoms during treatment with TNF-α antagonists is crucial, as patients on TNF α inhibitors who progress to active tuberculosis are more likely to develop disseminated or extrapulmonary forms of the disease.

Let’s review what you’ve learned in this module.

Response d: Incorrect. While malaise and weight loss are symptoms of lymphoma, lymphoma would not be high on the list of diagnostic possibilities. Try again.
Review

- Among patients in whom treatment with TNF α-antagonists is planned, testing and treatment for LTBI is recommended.
- The risk of progression to active TB is higher among patients treated with infliximab (a monoclonal TNF antibody) than among those treated with etanercept (a soluble TNF receptor).
- The United States CDC recommends treatment of LTBI prior to starting a TNF-α inhibitor in all patients who have a TST result of ≥ 5 mm induration or a positive IGRA.
- The standard therapy for LTBI is INH for 9 months.
- While the duration of LTBI therapy prior to starting a TNF-α inhibitor has not been established, most experts suggest that patients receive at least one month of LTBI treatment prior to starting the immunosuppressive.
- Patients on TNF-α inhibitors who progress to active tuberculosis are more likely to develop disseminated or extrapulmonary TB than patients with no prior history of exposure to these agents. Clinicians and patients should be advised to monitor for signs of disease such as fever, malaise, weight loss and lymphadenopathy.
TNF-α inhibitor rollover text: TNF-α inhibitors refer to a group of agents used to treat a variety of inflammatory illnesses such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease.

- IGRA rollover text: interferon gamma release assays

- Patients with a negative TST (<5 mm) or a negative IGRA should also be treated for LTBI if there is evidence of remote TB disease on the CXR or an epidemiologic link to prior TB exposure.

- TST rollover text: Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.

- The standard therapy for LTBI is isoniazid for 9 months.

- While the duration of LTBI therapy prior to starting a TNF α inhibitor has not been established, most experts suggest that patients receive at least one month of LTBI treatment prior to starting the immunosuppressive.

- Patients on TNF-α inhibitors who progress to active tuberculosis are more likely to develop disseminated or extrapulmonary TB than patients with no prior history of exposure to these agents. Clinicians and patients should be advised to monitor for signs of disease such as fever, malaise, weight loss and lymphadenopathy.
Now that you’ve learned about LTBI and TNF antagonists, try to answer a few review questions.
Review questions:

Once active TB is excluded, which of the following patients should not be offered LTBI treatment prior to initiating treatment with a TNF antagonist?

a. A 25-year-old woman with a TST of 7 mm and no known risk factors for TB exposure
b. A 30-year-old man with a TST of 4 mm and no known risk factors for TB exposure
c. A 50-year-old man with a TST of 0 mm who immigrated from Mexico 10 years ago
d. A 75-year-old woman with a TST of 4 mm and right upper lobe scarring, stable on radiographs for 10 years.
e. A 45-year-old man with a negative IGRA who was a contact to a TB case 2 years ago

Response a: The correct answer is b. Individuals with a TST of 5 mm or greater or a positive IGRA should be offered treatment regardless of risk factors. Individuals with a
negative IGRA or TST under 5 mm should be offered treatment if there is evidence of regional fibrosis on the chest radiograph or if there is a history of contact to a case or residence in a high prevalence country.

Response b: You’re right. Individuals with a TST of 5 mm or greater or a positive IGRA should be offered treatment regardless of risk factors. Individuals with a negative IGRA or TST under 5 mm should be offered treatment if there is evidence of regional fibrosis on the chest radiograph or if there is a history of contact to a case or residence in a high prevalence country.

Response c: The correct answer is b. Individuals with a TST of 5 mm or greater or a positive IGRA should be offered treatment regardless of risk factors. Individuals with a negative IGRA or TST under 5 mm should be offered treatment if there is evidence of regional fibrosis on the chest radiograph or if there is a history of contact to a case or residence in a high prevalence country.

Response d: The correct answer is b. Individuals with a TST of 5 mm or greater or a positive IGRA should be offered treatment regardless of risk factors. Individuals with a negative IGRA or TST under 5 mm should be offered treatment if there is evidence of regional fibrosis on the chest radiograph or if there is a history of contact to a case or residence in a high prevalence country.

Response e: The correct answer is b. Individuals with a TST of 5 mm or greater or a positive IGRA should be offered treatment regardless of risk factors. Individuals with a negative IGRA or TST under 5 mm should be offered treatment if there is evidence of regional fibrosis on the chest radiograph or if there is a history of contact to a case or residence in a high prevalence country.
Treatment with a TNF antagonist increases the risk of:

a. Progression to active TB
b. Disseminated TB
c. Extrapulmonary TB
d. All of the above

Response a: The correct answer is d. Treatment with TNF antagonists increases the risk of progression to active TB and when progression occurs, the likelihood of disseminated or extrapulmonary forms of the disease is higher.

Response b: The correct answer is d. Treatment with TNF antagonists increases the risk of progression to active TB and when progression occurs, the likelihood of disseminated or extrapulmonary forms of the disease is higher.
Response c: The correct answer is d. Treatment with TNF antagonists increases the risk of progression to active TB and when progression occurs, the likelihood of disseminated or extrapulmonary forms of the disease is higher.

Response d: That’s correct. Treatment with TNF antagonists increases the risk of progression to active TB and when progression occurs, the likelihood of disseminated or extrapulmonary forms of the disease is higher.
Congratulations!

You have completed the LTBI and TNF Antagonist module.

Click here to view the references for this module and a list of all TNF Antagonists Review Points.

Click MENU to return to the main menu.
Transplantation File
Case Presentation

Mr. W is a 56-year-old man who was recently referred for liver transplantation because of end-stage liver disease due to chronic hepatitis B infection. He was born in the United States and works as a university professor. He does not recall ever having a PPD in the past and he denies having any symptoms associated with active TB disease. There is a remote history of IV drug use, and he denies all other risk factors for TB exposure.
You are asked to assess his pre-transplant TB risk. At this time, you:

Select one of the options below.

a. Place a TST and if it is negative perform an IGRA and consider placing a second TST in 1-3 weeks.

TST rollover text: Tuberculin skin test.

IGRA rollover text: interferon-gamma release assays. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
b. Recommend testing only with an IGRA since TST is not used in transplant patients because of the high likelihood that they will be anergic.

c. Recommend no additional work-up for latent or unrecognized active TB since he has no risk factors for MTB exposure, and he is asymptomatic.

d. Defer LTBI testing to the post-transplant phase, since he would not be able to tolerate LTBI treatment at this time due to his severe underlying liver disease.

Response a: Correct. All transplant candidates should be evaluated for latent TB infection (by TST, IGRA or both). The incidence of active MTB infection in solid organ transplant recipients is 20-75 times higher than in the general population, and most cases are thought to be due to reactivation in the recipient. As always, risk varies based on epidemiologic factors, and many experts recommend treatment for LTBI even in the absence of a positive test if there is a clear epidemiologic link to TB. Among transplant recipients, lung transplant patients have the highest risk of progression to active disease.

Epidemiologic factors rollover text: origin from or residence in a country with moderate to high prevalence of TB, history of homelessness, incarceration, and/or substance abuse, etc.

Response b: Try again. In general, both the TST and the IGRA are considered acceptable. However, the IGRA may have certain advantages in this population. Try again.

Response c: Careful. There is a high incidence of active MTB infection in solid organ transplant recipients, and most cases are thought to be due to reactivation of latent disease in the recipient. Therefore, all transplant candidates should undergo a thorough history for TB exposure as well as testing with a TST, IGRA, or both. Try again.

Response d: Incorrect. Delaying testing until the post-transplant period is not recommended since patients undergo significant immunosuppression in this phase, which can further impair the sensitivity of the tests for LTBI. Transplant candidates diagnosed with latent TB who are unable to complete treatment pre-transplant due to
severe underlying liver disease or the emergent need for transplantation can be monitored closely and begin treatment early post-transplant. Try again.
Although LTBI may be difficult to treat in the pre-transplant period, delaying testing to the post-transplant period is not recommended, since post-transplant immunosuppression can impair the sensitivity of tests for LTBI. Interestingly, despite all the data supporting screening, it is estimated that fewer than 50% of transplant candidates actually undergo pre-transplant MTB testing.

Case Summary

56-yr man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
Which test to use?

Deciding which test to use is still a point of controversy in the literature.

In general, both the TST and the IGRA are considered acceptable. Some experts advise that if the TST is administered, it should be done using the 2-step testing process in order to identify an amnestic reaction.

IGRAs have the advantage of having a higher specificity for LTBI in patients with a history of BCG vaccination, and there is some data to suggest that they confer greater sensitivity in the immunocompromised host compared to the TST.
Case Summary

56-yo man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
Unfortunately, because of the concerns regarding anergy in this population, responding to a negative result poses a clinical challenge. While the CDC does not advocate the routine use of both tests, they suggest that employing both tests may be helpful in individuals with a high risk of progression to disease and/or in whom the risk of a poor outcome is high, when the initial test (whichever test was used first) is negative.

However, because transplant candidates represent such a high-risk population, many experts would recommend treating the patient for LTBI if there is a clear epidemiologic link to TB exposure even in the absence of a positive test.
Case Summary

56-yo man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
Mr. W’s second step TST result is 7 mm. He is asymptomatic and his CXR shows a 2 mm calcified nodule in the left upper lung zone. The transplant surgeon has indicated to you that she is concerned about Mr. W’s deteriorating liver function.

Case Summary

56- yo man
- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function
At this time, you recommend:

Select one of the options below.

a. No further treatment since the cut-off TST for this population is 10 mm or greater.

b. Treatment for LTBI in the post-transplant period.

c. Treatment for LTBI with PZA/RIF for 2 months to be certain that he completes therapy before his transplant.

d. Additional work-up with sputum x 3 for smear, MTD, and culture, because the abnormalities on the CXR are worrisome for active TB disease.

Case Summary

56-yo man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function

Response a: Incorrect. Induration of 5 mm or more reflects a positive result for solid organ transplant candidates. Additionally, it is important to note that solid organ transplant candidates are considered immunosuppressed, and despite the use of the 2-step method and the more recent use of IGRAs, LTBI will go undiagnosed in a certain proportion of patients because of an impaired delayed-type hypersensitivity response. Try again.

Response b: Correct. This is an acceptable approach to a challenging situation. Once active disease is excluded, pre-transplant treatment of LTBI is recommended for patients with a TST of 5 mm or greater or a positive IGRA as well as for those with a negative TST or IGRA but a strong epidemiologic link to TB (e.g., history of exposure to an individual with active TB), receipt of an organ from a donor with LTBI, or radiographic changes suggestive of previously healed TB (e.g., apical fibronodular changes).

Response c: Incorrect. Because of the unacceptably high risk of hepatitis, the CDC does not recommend the routine use of the PZA/RIF regimen. This would be of particular concern in pre-transplant patients with underlying liver disease. Try again.

Response d: Incorrect. The report of a single calcified nodule on the chest x-ray is a non-specific finding that may be associated with healed TB and granuloma formation. Since the patient has no symptoms or signs of active TB, no additional work-up is indicated. However, whenever other radiologic abnormalities are present (e.g. infiltrates, cavities, fibronodular changes), the possibility of active pulmonary TB needs to be considered and evaluated. Try again.
However, exceptions to the rule of pre-transplant treatment occur in cases of liver transplant candidates in whom there may be an unacceptably high risk of hepatotoxicity with isoniazid. Most experts suggest that patients with end-stage liver cirrhosis defer treatment until after transplantation. In rare instances, some can be successfully treated with close supervision by an experienced transplant ID specialist, but the decision should be made on a case-by-case basis weighing the individual risks and benefits.

Case Summary

56-yy man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function
The diagnosis of untreated active TB disease in either a recipient or donor is usually a contraindication to transplantation in the acute phase due to the high risk of dissemination and associated mortality. Once the patient is considered cured of active TB disease, transplant can be considered although the optimal timing for transplant remains controversial.

Case Summary

56-yo man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function
After making the decision to defer treatment of LTBI to the post-transplant period, you recommend:

Select one of the options below.

a. Rifampin 600 mg daily for 4 months  
b. Rifabutin 300 mg daily for 4 months  
c. INH 300 mg daily for 9 months  
d. INH 900 mg and rifapentine 900 mg weekly for 12 weeks

Case Summary

56-yr-old man
- US-born professor
- End-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function

Response a: Incorrect. The rifamycins should be avoided post-transplant due to the interaction with the calcineurin inhibitors. Try again.

Calcineurin inhibitors rollover text: tacrolimus, cyclosporine

Response b: Incorrect. Because rifabutin appears to be less hepatotoxic than rifampin, many experts would consider using this regimen in selected patients in the pre-transplant period. However, the rifamycins should be avoided post-transplant due to the interaction with the calcineurin inhibitors. Try again.

Calcineurin inhibitors rollover text: tacrolimus, cyclosporine

Response c: Correct. INH remains the treatment of choice in the post-transplant period. In the pre-transplant period INH or rifampin is acceptable. Because rifabutin appears to be less hepatotoxic than rifampin, many experts would consider using this regimen in selected patients in the pre-transplant period. However, the rifamycins should be avoided post-transplant due to the interaction with the calcineurin inhibitors. The combination of rifamycins with this class of drugs reduces the serum concentrations of the immunosuppressants and can lead to the development of rejection unless careful therapeutic drug monitoring is performed.

Calcineurin inhibitors rollover text: tacrolimus, cyclosporine

Response d: Incorrect. First, the 12-week regimen of INH 900 mg and rifapentine 900 mg weekly for 12 weeks has not been studied in the setting of transplant. Furthermore, the rifamycins should be avoided post-transplant due to the interaction with the
calcineurin inhibitors. The combination of rifamycins with this class of drugs reduces the serum concentrations of the immunosuppressants and can lead to the development of rejection unless careful therapeutic drug monitoring is performed. Try again.

Calcineurin inhibitors rollover text: tacrolimus, cyclosporine
Review

- The incidence of active TB infection in solid organ transplant recipients is 20-75 x higher than the general population.
- The TST or IGRA can be used as a screening test.
- Some experts recommend that patients undergo the 2-step testing process if the TST is used in order to identify the booster effect.
- Induration of 5 mm or more is considered a positive result for solid organ transplant candidates.
- Most experts recommend treatment of LTBI in solid organ transplant patients, once active disease is excluded, in any one of the following instances:
  1. PPD 5 mm or greater or a positive IGRA
  2. History of contact to an individual with active TB
  3. History of untreated LTBI in the past
4. Radiographic findings suggestive of prior healed TB (e.g., apical fibronodular changes)
Review

- Most experts suggest that patients with end-stage liver cirrhosis defer treatment until after transplantation, but the decision should be made on a case-by-case basis weighing the individual risks and benefits.

- The diagnosis of untreated active TB disease in either a recipient or donor is usually a contraindication to transplantation. Once the patient is cured of active TB disease, transplant can be reconsidered.

- In the pre-transplant period, either INH or a rifamycin may be used for treatment of LTBI.

- In the post-transplant period, rifamycins should be avoided due to drug interactions with post-transplant immunosuppressive medications.
If a solid organ transplant candidate has a well-documented history of prior treatment for latent TB infection, he/she will never need to be retreated again.

Select one of the options below.

a. True
b. False

Case Summary

56-yr man
- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function

Response a: Actually, this statement is false. If a solid organ transplant candidate with prior treated LTBI has a recent new exposure to an active TB case, re-treatment would be recommended. Some experts would also consider re-treatment in a recipient of an organ from a donor with untreated latent TB infection, although there is no clear consensus in the literature on this issue. Try again.

Response b: Correct. This statement is false. If a solid organ transplant candidate with prior treated LTBI has a recent new exposure to an active TB case, re-treatment would be recommended. Some experts would also consider re-treatment in a recipient of an organ from a donor with untreated latent TB infection, although there is no clear consensus in the literature on this issue.
The only solid organ transplant donors that need to be screened for LTBI prior to transplant are lung donors since MTB infections generally are not transmitted through other transplant grafts such as kidneys or livers.

Select one of the options below.

a. True  
b. False

Case Summary

56-yo man  
- US-born professor  
- end-stage liver disease due to hepatitis B  
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function

Response a: Actually, this statement is false. Overall, donor transmission of MTB infection accounts for about 4% of reported post-transplant MTB cases. Transmission occurs with the highest frequency in the setting of lung transplantation; however, transmission can occur through other types of grafts as well (e.g., kidney and liver.) Therefore, all living donors should be evaluated for active TB disease and LTBI. The clinical work-up should include a TST and/or IGRA testing, and active TB disease must be ruled out. If feasible, living donors should be treated for LTBI prior to transplantation, however additional studies are needed to assess the benefits of this recommendation. Deceased donors present an especially challenging situation since there is often an absence of historical data, making it difficult to assess for latent or active MTB infection.

Try again.

Response b: Correct. This statement is false. Overall, donor transmission of MTB infection accounts for about 4% of reported post-transplant MTB cases. Transmission occurs with the highest frequency in the setting of lung transplantation; however, transmission can occur through other types of grafts as well (e.g., kidney and liver.) Therefore, all living donors should be evaluated for active TB disease and LTBI. The clinical work-up should include a TST and/or IGRA testing, and active TB disease must be ruled out. If feasible, living donors should be treated for LTBI prior to transplantation, however additional studies are needed to assess the benefits of this recommendation. Deceased donors present an especially challenging situation since there is often an absence of historical data, making it difficult to assess for latent or active MTB infection.
A matched organ becomes available for Mr. W prior to his being treated for LTBI. The deceased donor is a 48-year-old man who was born in Cuba. A medical history is obtained from his relatives who report that he was not taking any medications and was not known to have any co-morbid illnesses. He was considered to be in good health prior to his motor vehicle accident. He arrived in the United States four years ago and was noted to have a positive TST at that time. His wife indicates that he did not take the recommended treatment for LTBI. A chest x-ray and CT of the lungs are normal.

Case Summary

56-yo man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2\textsuperscript{nd} step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function
What do you do now?

Select one of the options below.

a. You are concerned about the risk of transmission of MTB infection via a transplanted organ, and suggest delaying the transplant until a biopsy of the lung has been performed and cultures confirm that he does not harbor active MTB.

b. You recommend cancellation of the transplant because the risk of dissemination in the immunosuppressed recipient is unacceptably high when the donor has LTBI that was untreated.

c. You recommend proceeding with the transplant and suggest that Mr. W be considered for treatment with INH for 9 months after transplant.

d. You recommend proceeding with the transplant and suggest that Mr. B receive treatment with Rifampin for 4 months after transplant.
Case Summary

56-yo man

- US-born professor
- end-stage liver disease due to hepatitis B
- remote IV drug use
- asymptomatic
- 2nd step TST 7 mm
- CXR with 3 mm calcified nodule in RUL
- deteriorating liver function

Response a: Incorrect. There is nothing in this scenario to suggest that the donor has active TB disease, and there is no indication to delay the transplant on this basis. Furthermore, it is not feasible to delay transplantation until culture results have been reported. Try again.

Response b: Incorrect. LTBI in the donor is not a contraindication for transplantation. Transplantation may proceed once active TB disease has been excluded. Because the incidence of LTBI in certain regions of the world can be as high as 30-40%, most experts, especially in areas where TB is endemic, agree that the recipient should be considered for treatment of LTBI infection after transplantation. Try again.

Response c: Correct. As long as active TB has been excluded, LTBI in the donor is not a contraindication for transplantation. Presently there is no clear consensus in the literature regarding the necessity of treating LTBI in the recipient of an organ from a donor with LTBI. However, because the incidence of LTBI in certain regions of the world can be as high as 30-40%, most experts, especially in areas where TB is endemic, recommend post-transplant treatment for LTBI in this situation. Let’s review what you have learned.
Response d: Incorrect. LTBI in the donor is not a contraindication to transplantation. However, the rifamycins should be avoided post transplant due to the interaction with the calcineurin inhibitors. The combination of rifamycins with this class of drugs reduces serum concentrations of the immunosuppressants and can lead to the development of rejection unless careful therapeutic drug monitoring is performed. Try again.

Calcineurin inhibitors rollover text: tacrolimus, cyclosporine
Review

- Re-treatment of LTBI in a solid organ transplant recipient may be considered in the setting of a new exposure to an active TB case or in a recipient of an organ from a donor with untreated LTBI.

- Donor transmission of MTB infection accounts for about 4% of reported post-transplant MTB cases.

- Donor transmission occurs with the highest frequency in the setting of lung transplantation; however, transmission can occur through other types of grafts as well.

- All living donors should be evaluated for active TB disease and LTBI.

- LTBI in the donor is not a contraindication for transplantation.

- Although there is no clear consensus in the literature on the issue of post-transplant treatment for LTBI in recipients of organs from donors with untreated
LTBI, most experts, especially in areas where TB is endemic, recommend post-transplant treatment for LTBI with INH in this situation.
Review questions

Which of the following individuals does NOT require treatment of LTBI?

Select one of the options below.

a. a kidney transplant recipient with a history of treated LTBI 10 years ago and a new contact to a TB case 2 weeks ago

b. a liver transplant recipient with apical fibronodular changes on chest x-ray in whom active TB disease has been excluded

c. a lung transplant recipient whose donor immigrated from Haiti 2 years ago and has a positive IGRA

d. a US-born heart transplant candidate with no known risk factors for TB exposure, no symptoms, a TST of 3 mm, and a normal chest x-ray.
Response a: Incorrect. A patient with no TB risk factors, no symptoms, negative screening tests for LTBI, and a normal chest x-ray would be presumed not to have LTBI and should not be treated. All the other patients should be treated for LTBI once active disease is excluded.

Response b: Incorrect. A patient with no TB risk factors, no symptoms, negative screening tests for LTBI, and a normal chest x-ray would be presumed not to have LTBI and should not be treated. All the other patients should be treated for LTBI once active disease is excluded.

Response c: Incorrect. A patient with no TB risk factors, no symptoms, negative screening tests for LTBI, and a normal chest x-ray would be presumed not to have LTBI and should not be treated. All the other patients should be treated for LTBI once active disease is excluded.

Response d: Correct. A patient with no TB risk factors, no symptoms, negative screening tests for LTBI, and a normal chest x-ray would be presumed not to have LTBI and should not be treated. All the other patients should be treated for LTBI once active disease is excluded.
Review questions

INH is the treatment of choice for post-transplant treatment of LTBI.

Select one of the options below.

a. True
b. False

Response a: Yes, the statement is true. INH is the treatment of choice for post-transplant treatment of LTBI. Rifamycins should be avoided in the post-transplant period due to problematic drug interactions with immunosuppressive medications.

Response b: Actually, the statement is true. INH is the treatment of choice for post-transplant treatment of LTBI. Rifamycins should be avoided in the post-transplant period due to problematic drug interactions with immunosuppressive medications.
Congratulations!

You have completed the LTBI Treatment in Transplant Patients module.

Click MENU to return to the main menu where you can select another module or exit the course.
Course Review and References Book
# TABLE OF CONTENTS

**Course Review**
- Contact to Drug-Resistant Case
- Hepatitis
- HIV/AIDS
- Infants & Children
- Pregnancy
- Renal Failure
- TNF Antagonists
- Transplantation

**References**
- Contact to Drug-Resistant Case
- Hepatitis
- HIV/AIDS
- Infants & Children
- Pregnancy
- Renal Failure
- TNF Antagonists
- Transplantation
References (RON: THIS IS STILL TO COME)

- Contact to Drug-Resistant Case
- Hepatitis
- HIV/AIDS
- Infants & Children
- Pregnancy
- Renal Failure
- TNF Antagonists
- Transplantation
Contact to Drug-Resistant Case

- Given the high morbidity and mortality associated with TB disease in close contacts, treatment of LTBI should be considered.

- As in LTBI with a pansensitive isolate, TB disease must be excluded prior to starting an LTBI regimen to minimize the potential for development of further resistance.

- Although there is limited data to support any single approach, CDC/ATS guidelines advocate treatment of MDR-LTBI with two drugs to which the index case’s isolate is susceptible; however, many experts advocate treatment with a fluoroquinolone alone if the index case isolate is susceptible to a fluoroquinolone.

- The regimen should be tailored for each individual based on the susceptibility results of the source case isolate.

- The regimen should be tailored for each individual based on the susceptibility results of the source case isolate.
Most experts recommend treatment for a duration of 6-12 months.

Transmission of MDR-TB is well documented, and therefore full evaluation of all contacts should be pursued. If the option of no drug treatment is selected, close and active clinical monitoring is essential.

Expert consultation to assist in treatment choices for contacts to MDR cases is recommended.

Window prophylaxis should be considered in very high-risk contacts who are TST-negative when exposure is intimate and prolonged, and transmission to other contacts has been documented.

Immunosuppressed contacts should be treated with a multi-drug MDR-LTBI regimen rather than monotherapy.

Every contact to a drug-resistant case should be followed clinically for two years at a minimum and should be educated about the signs and symptoms of TB disease.

Given the limited data and experience in treating LTBI due to contact to an XDR case, drug therapy is frequently not recommended, depending on the risk/benefit ratio in a given patient. In these cases, close clinical observation is essential, and expert consultation is recommended.

CDC/ATS text rollover: Centers for Disease Control and Prevention/ American Thoracic Society

MDR-TB text rollover: TB resistant to at least INH and rifampin.

Clinical monitoring text rollover: symptom screen every 3 months for a minimum of 2 years, along with chest x-ray and/or sputum analysis, if clinically indicated.
Expert Consultation text rollover: Each of the five TB Regional Training and Medical Consultation Centers (RTMCC) is available to assist in the treatment of challenging cases. Contact information for each center is listed in the LTBI Resources reference book.

TST text rollover—Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
Hepatitis

- Presence of hepatitis C alone is not a contraindication to LTBI treatment.

- Even in the absence of signs and symptoms, baseline and follow-up liver function tests are recommended for patients with a possible liver disorder, those with a history of chronic liver disease, and those who use alcohol regularly.

- Patient education and monitoring is the mainstay of prevention of drug-related hepatotoxicity. Patients should be educated on the signs and symptoms of hepatitis with strict instructions to avoid alcohol and hepatotoxic medications and to discontinue treatment and seek medical attention should signs and symptoms of hepatitis develop.

- In the setting of known viral hepatitis, it is not recommended to rechallenge with a drug on which a treatment-limiting adverse event was observed.

- Rifampin or rifabutin for 6 months may be considered when treatment-limiting thresholds are reached on NASH.

- When treatment-limiting thresholds are reached on rifampin, decisions regarding treatment of LTBI depend on a careful assessment of risks and benefits.

- Active, but not quiescent, hepatitis B increases the risk of INH-related hepatotoxicity.

- Treatment with a rifamycin is preferred in individuals who are HIV-positive with elevated ALT.

- Decisions to treat LTBI in the setting of hepatitis should be made based on an individualized assessment of risk of progression to TB disease and risk of drug-related hepatotoxicity.

- When the risk of progression to TB disease is high and LTBI treatment is felt to be important, consultation with a hepatologist and consideration of pretreatment of viral hepatitis are advised.
• INH remains the treatment of choice in asymptomatic patients with hepatitis C and normal or minimally elevated liver function.

• While INH hepatotoxicity usually occurs in a hepatocellular pattern, the pattern with the rifamycins is often cholestatic, although a mixed pattern can also be seen, especially in the setting of viral hepatitis.

• When the AST/ALT ratio is greater than 2, alcohol use should be suspected, and the patient should be re-educated regarding the importance of avoidance of alcohol and any other hepatotoxins.

• In the setting of known viral hepatitis, it is not recommended to rechallenge with a drug on which a treatment-limiting threshold was reached.

• Rifampin or rifabutin for 4 months may be considered when treatment-limiting thresholds are reached on INH.

• When treatment-limiting thresholds are reached on a rifamycin, decisions regarding treatment of LTBI depend on a careful assessment of risks and benefits.

• Active, but not quiescent, hepatitis B increases the risk of INH-related hepatotoxicity.

• Treatment with a rifamycin is preferred in individuals who are HBeAg seropositive with elevated ALT.

• Decisions to treat LTBI in the setting of hepatitis should be made based on an individualized assessment of risk of progression to TB disease and risk of drug-related hepatotoxicity.

• When the risk of progression to TB disease is high and LTBI treatment is felt to be important, consultation with a hepatologist and consideration of pre-treatment of viral hepatitis are advised.
Liver function tests text rollover: Liver function tests should include serum transaminases and bilirubin

Chronic liver disease text rollover: Examples include chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis.
HIV/AIDS

- Patients infected with HIV are at high risk of developing active disease after infection with \textit{M. TB}. HIV-infected patients who are \textit{TST} positive have a 7-10\% yearly risk of progression to active TB. Non-HIV-infected patients have a 10\% lifetime risk.

- As soon as HIV is diagnosed and regardless of CD4 count, patients should receive a \textit{TST} unless they are already known to be reactive.

- Because patients with CD4 counts under 200 cells/mm$^3$ have up to a 20\% incidence of normal chest radiographs during active TB, sputum should be collected if any symptoms or additional risk factors are present.

- Routine \textit{anergy testing} is no longer recommended.

- Routine \textit{anergy testing} is no longer recommended.

- Routine \textit{anergy testing} is no longer recommended.
- A TST is considered positive in an HIV-infected individual if the induration is 5 mm or greater.

- Two-step testing helps to establish a baseline TST status and is recommended for initial LTBI screening any time periodic screening for LTBI is anticipated (e.g. in health care workers, chronic dialysis patients, people living in high-risk congregate settings, people with HIV, and those at risk of ongoing TB exposure).

- Some experts recommend a single IGRA as an alternative to two-step testing.

- HIV-positive individuals with negative diagnostic tests for LTBI, CD4 counts < 200 cells/mm$^3$, and without indication for empiric LTBI treatment should be retested for LTBI once they show a response to antiretroviral therapy.

- If CD4 counts are > 200 cells/mm$^3$ and no other risk factors develop in the interim, patients with HIV should be screened for LTBI annually.

- INH is first-line therapy for LTBI in patients with HIV.

- A short-course regimen of rifampin and PZA is not recommended due to unacceptably high risk of hepatotoxicity.

- Rifampin should be reserved for contacts to INH-resistant cases or with intolerance to INH.

- Because of loss of TST sensitivity (anergy), LTBI therapy is recommended in HIV-positive patients with negative TSTs in certain situations:
  - Recent contact to an active case
  - History of prior untreated or inadequately treated TB
  - Fibrotic lesions consistent with TB on CXR in the setting of CD4 counts < 200 cells/mm$^3$ and no prior history of TB treatment (once active TB is excluded)
• Because HIV confers an increased risk for INH hepatotoxicity, HIV-positive patients should undergo pre-treatment liver function tests and more frequent laboratory monitoring, particularly if additional risk factors for hepatotoxicity are present.

• DOT is suggested, if feasible, to monitor for side effects and to ensure treatment completion.

M. TB text rollover – Mycobacterium tuberculosis

TST text rollover– Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.

Liver function tests text rollover: Liver function tests should include serum transaminases and bilirubin

DOT text rollover– Directly Observed Therapy

Anergy testing text rollover – Testing for delayed type hypersensitivity reactions to certain common antigens.
Infants and Children

- Do not allow patients with infectious active TB to return to a home setting shared by children under 5 or immunosuppressed persons.

- Untreated infants with LTBI have up to a 40% likelihood of developing TB, and children under 5 are more susceptible to disseminated forms of the disease.

- INH therapy for LTBI appears to be more effective (with risk reduction estimated at 70-90%) and less hepatotoxic in infants and children compared to adults.

- Once active TB is excluded, you should provide window prophylaxis for children under 5 and immunosuppressed persons. If repeat TST at 8-12 weeks is 5 mm or greater, continue INH to complete a 9-month course.

- Do not offer LTBI treatment or discourage breastfeeding in nursing mothers who are contacts to a case of active TB.
- Utilize appropriate weight-based pediatric dosing of INH: 10-15 mg/kg for daily dosing, 20-30 mg/kg for biweekly dosing via DOPT.

- Because the high sorbitol content in the liquid formulation of INH causes cramping and diarrhea in more than half of children, we recommend using INH in the form of crushed tablets mixed with semisoft food, milk, or formula as soon as is feasible.

- Do not defer LTBI treatment or discourage breastfeeding in nursing mothers who are contacts to a case of active TB.

**Window prophylaxis** text rollover: Window prophylaxis: empiric INH for these 8-12 weeks before the TST is repeated.

**TST** text rollover—Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
Pregnancy

- Tuberculin skin testing and interferon-gamma-release assays (IGRAs) are safe and effective in pregnancy.

- All patients identified as having LTBI should be evaluated to exclude active TB disease. The first step is a symptom screen and chest x-ray.

- A chest x-ray performed with abdominal shielding is appropriate in a pregnant woman to exclude active TB.

- There is no evidence that risk of new infection or reactivation is higher in pregnant women.

- Pregnant women without major risk factors for progression to active TB disease should return for re-evaluation and treatment 3 months postpartum.

- Pregnant women with major risk factors for progression to active TB disease (immunosuppression or recent contact to a case) should be treated for LTBI during pregnancy.

- Although INH is considered safe in pregnancy, pregnancy and the early postpartum period confer an increased risk for INH hepatotoxicity.

- Women treated for LTBI during pregnancy should undergo a general evaluation for chronic liver disease, alcohol use, and exposure to other hepatotoxins, testing for HIV and hepatitis B and C as well as pre-treatment liver function tests.

- If liver function is normal, INH can be started with follow up symptom evaluation and exams monthly as a minimum.

- If there is mild elevation of transaminases, more frequent monitoring is recommended.

- Patients should receive clear instructions to avoid hepatotoxins and be alert for signs and symptoms of hepatitis.

- Patients must be counseled to discontinue treatment and contact their healthcare provider immediately if symptoms of hepatitis develop.

- It is important to remember that the increased INH hepatotoxicity risk continues into the early postpartum period.

- INH 300 mg daily for 9 months is first-line treatment for LTBI.

- Rifampin 600 mg daily for 4 months is an alternative in patients who do not tolerate INH and is considered safe in pregnancy.

- A regimen of Rifampin and PZA daily for 2 months has a relatively high risk of hepatotoxicity.

- When side effects occur, do not reduce TB drug doses below recommended levels, as low doses may be not be effective.
• Pregnant women with major risk factors for progression to active TB disease (immunosuppression or recent contact to a case) should be treated for LTBI during pregnancy.

• Although INH is considered safe in pregnancy, pregnancy and the early post-partum period confer an increased risk for INH hepatotoxicity.

• Women treated for LTBI during pregnancy should undergo a general evaluation for chronic liver disease, alcohol use, and exposure to other hepatotoxins, testing for HIV and hepatitis B and C, as well as pre-treatment liver function tests.

• If liver function is normal, INH can be started with follow up symptom evaluation and exams monthly at a minimum.

• If there is mild elevation of transaminases, more frequent monitoring is recommended.

• Patients should receive clear instructions to avoid hepatotoxins and be alert for signs and symptoms of hepatitis.

• Patients must be counseled to discontinue treatment and contact their healthcare provider immediately if symptoms of hepatitis develop.

• It is important to remember that the increased INH hepatotoxicity risk continues into the early post-partum period.

• INH 300 mg daily for 9 months is first-line treatment for LTBI. Rifampin 600 mg daily for 4 months is an alternative in patients who do not tolerate INH and is considered safe in pregnancy.

• A regimen of Rifampin and PZA daily for 2 months has unacceptably high risk of hepatotoxicity.
• When side effects occur, do not reduce TB drug doses below recommended levels, as lower doses may be not be effective.
Renal Failure

- Due to impaired cellular immunity, patients with end-stage renal disease on chronic hemodialysis are approximately 10-25 times more likely to develop active TB compared to the general population.

- There is a high prevalence of LTBI among patients with ESRD undergoing hemodialysis.

- Additional risk factors for active TB in hemodialysis patients include: age, smoking, reduced body mass index, low serum albumin, ischemic heart disease, and anemia.

- The mortality rate of TB in dialysis patients is high.

- IGRA may be more accurate than TST in chronic dialysis patients.

- For patients with advanced chronic kidney disease, a positive TST is defined as 1 hour of 10 mm or greater.

- INH remains the treatment of choice in patients with active chronic kidney disease. Dose adjustment is not necessary, and INH should be dosed after dialysis.

- Drug adjustment and monitoring of drug levels may be considered with rifampin but is not necessary when rifampin is used in the setting of renal insufficiency.

- The diagnosis of genitourinary TB is suggested by a history of prior TB, sterile pyuria, and typical findings.

- There is no routine preventive chemotherapy program at this time.
• Extrapulmonary forms of the disease are more common in ESRD patients, and nonspecific symptoms such as malaise and weight loss may be interpreted as signs of uremia.

• Nosocomial transmission of TB has been documented in US hemodialysis centers.

• Even when two-step testing is used, the prevalence of anergy to TST in the ESRD population is significantly higher than in the general population (44% versus 16%).

• All contacts not previously treated for LTBI (both patients and healthcare workers) should undergo a TB symptom screen and TST or IGRA for evaluation.

• IGRAs may be more accurate than TST in chronic dialysis patients.

• For patients with advanced chronic kidney disease, a positive TST is defined as induration of 10 mm or greater.

• INH remains the treatment of choice in patients with advanced chronic kidney disease. Dose adjustment is not necessary, and INH should be dosed after dialysis.

• Dose adjustment and monitoring of drug levels may be considered with rifabutin but is not necessary when rifampin is used in the setting of renal insufficiency.

• The diagnosis of genitourinary TB is suggested by a history of prior TB, sterile pyuria, and typical intravenous pyelogram findings.

Intravenous pyelogram (IVP) findings text rollover: findings of genitourinary TB on IVP include lower tract findings (erosion of the tips of the calyces, blunting of the calyces or overt papillary necrosis, and parenchymal scarring and calcification) and upper tract findings (ureteral strictures, a contracted bladder, calcifications in the vas deferens, seminal vesicles, or prostate).
TST text rollover– Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
TNF Antagonist

- Among patients in whom treatment with TNF α-antagonists is planned, testing and treatment for LTBI is recommended.

- The risk of progression to active TB is higher among patients treated with infliximab (a monoclonal TNF antibody) than among those treated with etanercept (a soluble TNF receptor).

- The United States CDC recommends treatment of LTBI prior to starting a TNF α inhibitor to all patients who have a TST result of ≥ 5 mm induration or a positive interferon gamma release assay.

- Patients with a negative TST (≤ 5 mm) or a negative IGRA should also be treated for LTBI if there is evidence of recent TB disease on the CXR, or an epidemiologic link to prior TB exposure.

- The standard therapy for LTBI is isoniazid for 9 months.

- While the duration of LTBI therapy prior to starting a TNF α inhibitor has not been established, most experts suggest that patients receive at least one month of LTBI treatment prior to starting the immunosuppressive.

- Patients on TNF α inhibitors who progress to active tuberculosis are more likely to develop disseminated or extrapulmonary TB than patients with no prior history of exposure to these agents. Clinicians and patients should be advised to monitor for signs of disease such as fever, malaise, weight loss, and lymphadenopathy.
• Patients with a negative TST (<5 mm) or a negative IGRA should also be treated for LTBI if there is evidence of remote TB disease on the CXR or an epidemiologic link to prior TB exposure.

• The standard therapy for LTBI is isoniazid for 9 months.

• While the duration of LTBI therapy prior to starting a TNF α inhibitor has not been established, most experts suggest that patients receive at least one month of LTBI treatment prior to starting the immunosuppressive.

• Patients on TNF α inhibitors who progress to active tuberculosis are more likely to develop disseminated or extrapulmonary TB than patients with no prior history of exposure to these agents. Clinicians and patients should be advised to monitor for signs of disease such as fever, malaise, weight loss and lymphadenopathy.

TST text rollover—Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
Transplantation

- The incidence of active TB infection in solid organ transplant recipients is 20-75 x higher than the general population.
- The TST or IGRA can be used as a screening test.
- Some experts recommend that patients undergo the 2-step testing process if the TST is used in order to identify the booster effect.
- Induration of 5 mm or more is considered a positive result for solid organ transplant candidates.
- Most experts recommend treatment of LTBI in solid organ transplant patients, once active disease is excluded, in any one of the following instances:
  1. PPD 5 mm or greater or a positive IGRA
  2. History of contact to an individual with active TB
  3. History of untreated LTBI in the past
  4. Radiographic findings suggestive of prior healed TB (e.g., calcifications, bronchiectasis)
- Most experts suggest that patients with end-stage liver cirrhosis defer treatment until after transplantation, but the decision can be made on a case-by-case basis weighing the individual risks and benefits.
- The diagnosis of untreated active TB disease in either the recipient or donor is usually a contraindication to transplantation. Once the patient is cured of active TB disease, transplant can be reconsidered.

- In the pretransplant period, either INH or rifampin may be used for treatment of LTBI.
- In the post-transplant period, rifampin should be avoided due to drug interactions with posttransplant immunosuppressive medications.
- Relapse of LTBI in a solid organ transplant recipient may be considered in the setting of a new exposure to an active TB case or in a recipient of an organ from a donor with untreated LTBI.
- Donor transmission of M. tuberculosis infection accounts for about 4% of reported post-transplant TB cases.
- Donor transmission occurs with the highest frequency in the setting of lung transplantation; however, transmission can occur through other types of grafts as well.
- All living donors should be evaluated for active TB disease and LTBI.
- LTBI in the donor is not a contraindication for transplantation.
- Although there is no clear consensus in the literature on the issue of post-transplant treatment for LTBI in recipients of organs from donors with untreated LTBI, most experts, especially in areas where TB is endemic, recommend post-transplant treatment for LTBI in this situation.
4. Radiographic findings suggestive of prior healed TB (e.g., apical fibronodular changes)

- Most experts suggest that patients with end-stage liver cirrhosis defer treatment until after transplantation, but the decision can be made on a case-by-case basis weighing the individual risks and benefits.
- The diagnosis of untreated active TB disease in either a recipient or donor is usually a contraindication to transplantation. Once the patient is cured of active TB disease, transplant can be reconsidered.
- In the pre-transplant period, either INH or a rifamycin may be used for treatment of LTBI.
- In the post-transplant period, rifamycins should be avoided due to drug interactions with post-transplant immunosuppressive medications.
- Re-treatment of LTBI in a solid organ transplant recipient may be considered in the setting of a new exposure to an active TB case or in a recipient of an organ from a donor with untreated LTBI.
- Donor transmission of MTB infection accounts for about 4% of reported post-transplant MTB cases.
- Donor transmission occurs with the highest frequency in the setting of lung transplantation; however, transmission can occur through other types of grafts as well.
- All living donors should be evaluated for active TB disease and LTBI.
- LTBI in the donor is not a contraindication for transplantation.
- Although there is no clear consensus in the literature on the issue of post-transplant treatment for LTBI in recipients of organs from donors with untreated LTBI, most experts, especially in areas where TB is endemic, recommend post-transplant treatment for LTBI with INH in this situation.
TST text rollover– Tuberculin skin test. Note that interferon-gamma release assays (IGRAs) can be used in the diagnosis of LTBI in any situation where a TST would be considered. For more information on IGRAs, refer to the IGRA reference book.
Contact to Drug-Resistant Case


Hepatitis


28. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med 2000; 161:S221.


31. Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-


4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.


Infants & Children


Pregnancy


Renal Failure


TNF Antagonists


13. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor

Transplantation


Managing Common Adverse Effects Book
Adverse Effects Associated with Drugs Used for the Treatment of Latent Tuberculosis Infection

Recent estimates indicate that over 80% of cases of active Mycobacterium tuberculosis (MTB) infection in the US are the result of reactivation. This is why the treatment of LTBI has been identified by the CDC as pivotal to achieving the goal of TB elimination. Since only a minority of individuals with LTBI will actually go on to develop active MTB disease and because the drug regimens are associated with some degree of risk due to adverse events, it is essential that treatment strategies focus on high-risk patient populations who are most likely to receive the greatest benefit from treatment. In addition, it is critical that clinicians have the ability to weigh the long-term benefits of treatment in their individual patients versus the risk of experiencing an adverse effect from the drug.

On the following pages, you will find a listing of possible adverse effects associated with drugs commonly used for the treatment of LTBI.
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**Isoniazid**

- Hepatotoxicity
- Neurotoxicity
- Lupus-like syndrome
- Hypersensitivity reactions
- Monoamine poisoning
- Common drug interactions

**Rifampin**

- Skin/dermatologic
- Gastrointestinal
- Flulike syndrome
- Hepatotoxicity
- Immunologic reactions
- Common drug interactions

**Rifabutin**

- Skin/dermatologic
- Hematologic
- Uveitis
- Polyarthralgias

**References**
Isoniazid

Hepatotoxicity

Subclinical Hepatitis

- Transient elevation in liver enzymes can occur in as many as 10-20% of patients.
- Patients are generally asymptomatic and the LFTs are generally less than 100 IU/L.
- Usually self-limited and not an indication to discontinue INH treatment unless LFTs rise more than three times the upper limit of normal in a symptomatic patient or five times the upper limit of normal in an asymptomatic patient.

Clinical Hepatitis

- fulminant hepatitis is the most feared adverse effect of isoniazid therapy and has an incidence of less than 1%.
- Usually occurs in the first three months of therapy.
- Risk is highest in older patients >65, individuals with pre-existing liver disease, pregnancy, and the immediate postpartum period, HIV ser users and the concurrent use of hepatotoxic drugs such as phenytoin, phenobarbital, rifampin, and a clopidogrel.
- Symptoms include jaundice, malaise, anorexia, vomiting, jaundice, right upper quadrant pain with weight loss of hepatomegaly.
- Isoxazole and any other hepatotoxins should be discontinued. The case fatality rate is about 10% in patients who develop a clinically significant hepatitis.
- Isoxazole for the treatment of LTH should not be restarted again if cases, since the risk is unacceptable.

Neurotoxicity

- INH competes with pyridoxine (vitamin B6) in its action as a cofactor in the synthesis of norepinephrine and dopamine.
- Neurotoxic side effects include peripheral neuropathy, seizures, psychosis, and anemia.
- Peripheral neuropathy usually occurs in a stocking glove distribution with tingling or burning sensation in the fingers and toes.
- High doses of pyridoxine can be used to reverse the symptoms of INH effects (i.e., 500-1000 mg daily while the patient is receiving INH). However, high doses of pyridoxine should be avoided in individuals with renal insufficiency. There are reports of neuropathy attributed to pyridoxine in doses of 500 mg or greater.

Adverse effects of isoniazid include:

- Up to 1% of patients on INH develop anti-nuclear antibody (ANA), Less than 1% develop the clinical manifestations of lupus erythematosus. INH should be discontinued in patients who develop these symptoms.
- Fever, rash, Stevens-Johnson syndrome, hemolytic anemia, vasculitis and neuropathy are rare and INH for TB should be discontinued in these instances.

Clinical Hepatitis
Fulminant hepatitis is the most feared adverse effect of isoniazid therapy and has an incidence of less than 1%

- Usually occurs in the first three months of therapy.
- Risk is highest in older patients > 65, individuals with pre-existing liver disease, pregnancy and the immediate postpartum period, IV drug users and the concurrent use of hepatotoxic drugs such as phenytoin, phenobarbatol, rifampin and alcohol.
- Symptoms of anorexia, malaise, nausea, vomiting, jaundice, right upper quadrant warrant a work up of hepatitis.
- Isoniazid and any other hepatotoxin should be discontinued. The case fatality rate is about 10% in patients who develop clinically significant hepatitis.
- Isoniazid for the treatment of LTBI should not be restarted again in these cases since the risk is unacceptable.

**Neurotoxicity**

-INH competes with pyridoxine (vitamin B6) in its action as a cofactor in the synthesis of synaptic neurotransmitters. Neurotoxic, dose-related side effects include peripheral neuropathy, seizures, psychosis and ataxia.

-Peripheral neuropathy usually occurs in a stocking glove distribution with tingling or burning sensation of the fingers and/or toes. High doses of pyridoxine can be used to reverse the neurotoxic side effects i.e. 100-200 mg orally daily while the patient is receiving INH. However, high doses of pyridoxine should be avoided in individuals with renal insufficiency. There are rare reports of neuropathy attributed to pyridoxine in doses of 200 mg or greater.
- Prophylactic doses of pyridoxine are 10-25 mg/day are suggested for those at risk (pregnant women, malnourished patients, diabetics, alcoholics, HIV, renal failure)

**Lupus-like syndrome**

- Up to 20% of patients on INH develop anti-nuclear antibodies. Less than 1% develop the clinical manifestations of lupus erythematos. INH should be discontinued in patients who report new

**Hypersensitivity reactions**

- Fever, rash, Steven-Johnsons syndrome, hemolytic anemia, vasculitis and neutropenia are rare and INH for LTBI should be discontinued in these instances
Isoniazid (continued)

**Monoamine (histamine/tyramine) poisoning**

- Infrequently, some patients may experience flushing after ingestion of certain foods containing a high concentration of tyramines or histamines such as cheeses, fish, wine and chocolate. Reaction usually resolves within 2 hours.

- Patients should be counseled to avoid culprit foods while receiving INH.
Rifampin

Skin/Dermatologic

- Discoloration of bodily fluids (sputum, urine, seat, tears): Occurs in all patients. Patients should be warned that soft contact lenses and clothing may be permanently stained.
- Pruritus: May occur with or without a rash in around 6% of patients. Often not a true hypersensitivity reaction and is generally self-limited even with continued treatment.
- Flushing: Usually mild and may be associated with pruritus. Usually resolves spontaneously. Patients can be treated with antihistamine to prevent the reaction.

Gastrointestinal

- Nausea, anorexia, abdominal pain, diarrhea is variable during treatment and patients can be counseled to take a small amount of food before medication. Rarely requires discontinuation of treatment.

Flu-like Syndrome

- Occurs in 0.4-0.7% patients and more likely to occur with intermittent dosing.

Hepatotoxicity

- Transient asymptomatic hyperbilirubinemia in up to 0.6% of patients. Clinical hepatitis is extremely rare when rifampin is given as a monotherapy as it usually a cholestatic pattern often associated with phospholipid and hyperbilirubinemia.

Immunologic Reactions

- Severe rash, thrombocytopenia, hemolytic anemia, a cutaneous failure are rare but considered to be part of a spectrum of immunologic reactions warranting discontinuation of the drug.

Common Drug Interactions

- Oral contraceptives: Patients should be warned that rifampin can decrease effective serum concentrations of oral contraceptives making them ineffective.
- Warfarin: Rifampin decreases serum concentration of warfarin.
- Metabolism: Rifampin decreases serum concentration of methadone.
- Antiheroin rash: Bidirectional interactions with rifampin and methadone are rare but requiring reference to CDC website www.cdc.gov/ncidod/dvdr/ for up-to-date information.
- Immunosuppressives: tacrolimus, cyclosporine, corticosteroids: May reduce concentrations of immunosuppressives requiring dose adjustment and monitoring.
Gastrointestinal

-Nausea, anorexia, abdominal pain. Incidence is variable during treatment and patients can be counseled to take a small amount of food before medication. Rarely requires discontinuation of treatment

Flulike Syndrome

- Occurs in 0.4-0.7% patients and more likely to occur with intermittent dosing.

Hepatotoxicity

- Transient asymptomatic hyperbilirubinemia in up to 0.6% of patients. Clinical hepatitis is extremely rare when rifampin is given as a monotherapy as is usually a cholestatic pattern (increased alkaline phosphatase and hyperbilirubinemia)

Immunologic reactions

- Severe rash, thrombocytopenia, hemolytic anemia, acute renal failure are rare but considered to be part of a spectrum of immunologic reaction warranting discontinuation of the drug.
Common Drug Interactions

- Oral contraceptives: patients should be warned that rifampin can decrease serum concentrations of oral contraceptives making them less effective.

- Warfarin: rifampin decreases serum concentration of warfarin.

- Methadone: rifampin decreases serum concentration of methadone.

- Antiretrovirals: bidirectional interactions with rifampin and many antiretrovirals requiring reference to CDC website: www.cdc.gov/nchstp/tb for up-to-date information.

- Immunosuppressives: tacrolimus, cyclosporin, corticosteroids: May reduce concentrations of immunosuppressives requiring dose adjustment and monitoring.
Rifabutin

Used in patients with intolerance to rifampin or who have drug interactions with rifampin.

Skin/Dermatologic

- Discoloration of bodily fluids (sputum, urine, seat, tears): Occurs in all patients. Patients should be warned that soft contact lenses and clothing may be permanently stained.
- Pseud jaundice (skin discoloration with normal bilirubin) Usually self-limited and resolves with discontinuation of the drug.

Hematologic

- Hematologic disturbances may be more frequent when compared to rifampin.
- Neutropenia is reported in as many as 2% of patients with AIDS and occurs more frequently in daily dosing. Thrombocytopenia, anemia, and leukopenia have also been described.
- Atrioventricular (AV) block (0.01%) except when rifabutin is combined with drugs that reduce its clearance such as macrolides or certain anthracyclines.
- Patients should be counseled to report eye pain, redness and loss of vision.
- Neutropenia reported in as many as 2% of patients with AIDS and occurs more frequently in daily dosing. Thrombocytopenia, anemia and leucopenia have also been described.

**Uveitis**

- A rare complication (<0.01%) except when rifabutin is combined with drugs that reduce its clearance such as macrolides or certain antiretrovirals.
- Patients should be counseled to report eye pain, redness and loss of vision.

**Polyarthralgias**

- 1-2% of patients and may be treated with over-the-counter anti-inflammatory agents.

**Hepatotoxicity**

- Asymptomatic elevation of liver enzymes in a frequency similar to rifampin.
- Clinical hepatitis is rare.
References


LTBI Treatment Options (Includes short course therapy) Book
LTBI Treatment Options ¹,²,³

INH
- Daily
- Biweekly

Rifampin
- Daily
- Biweekly

Rifapentine/INH
- Weekly

Notes/References

Print Version
INH

Interval: Daily
Duration: 9 months
Dosing:
- Adult: 5 mg/kg (max 300 mg)
- Peds: 10-20 mg/kg (max 300 mg)
Administration: Self-administered or DOT

Interval: Biweekly
Duration: 9 months
Dosing:
- Adult: 15 mg/kg (max 800 mg)
- Peds: 20-40 mg/kg (max 900 mg)
Administration: DOT

Monitoring:
- Clinical monitoring monthly
- Baseline and monthly liver function monitoring indicated only in special situations (e.g. pregnancy, HIV, hepatitis)

See reference book on Adverse Effects for common side effects and drug interactions.

Comments:
- Hepatitis risk increases with age, alcohol consumption.
- Concurrent administration of pyridoxine (vit B6) 10-25 mg daily may prevent peripheral and central nervous system effects.
Dosing:

- Adult: 15 mg/kg (max 900 mg)
- Peds: 20 - 40 mg/kg (max 900 mg)

Administration: DOT

Monitoring:

- Clinical monitoring monthly
- Baseline and monthly liver function monitoring indicated only in special situations (e.g. pregnancy, HIV, hepatitis)
- See reference book on Adverse Effects for common side effects and drug interactions.

Comments:

- Hepatitis risk increases with age, alcohol consumption.
- Concurrent administration of pyridoxine (vit b6) 10 - 25 mg daily may prevent peripheral and central nervous system effects.
Rifampin

Interval: Daily
Duration: 4 months for adults, 6 months for peds

Dosing:
- Adult: 10 mg/kg (max 600 mg)
- Peds: 10-20 mg/kg (max 600 mg)

Administration: Self-administered or DOT

Interval: Biweekly
Duration: 4 months

Dosing:
- Adult: 10 mg/kg (max 600 mg)
- Peds: -

Administration: DOT

Monitoring:
- Clinical monitoring monthly
- Baseline and monthly CBC with platelets, AST and ALT may be considered in special situations (e.g. pregnancy, HIV, hepatitis).
- See reference book on Adverse Effects for common side effects and drug interactions.

Comments:
- Rifampin should generally be reserved for contacts to an INH-resistant case or to those who do not tolerate INH.
- Exercise caution in HIV-infected patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs).
Dosing:

- Adult: 10 mg/kg (max 600 mg)
- Peds: -

Administration DOT

Monitoring:

- Clinical monitoring monthly
- Baseline and monthly CBC with platelets, AST and ALT may be considered in special situations (e.g. pregnancy, HIV, hepatitis).
- See reference book on Adverse Effects for common side effects and drug interactions.

Comments:

- Rifampin should generally be reserved for contacts to an ING-resistant case or to those who do not tolerate INH.
- Exercise caution in HIV-infected patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs).
Rifapentine/INH

Interval: Weekly

Duration: 12 weeks

Dosing:
- Adult 900 mg of each drug
- Peds: -

Administration: DOT

Monitoring:
- Protocols under development.
- Consider clinical monitoring weekly (monthly at a minimum).
- Consider CBC with platelets, AST and ALT at baseline and at 2, 4, and 8 weeks.

Comments:
- Because of limited data in special populations, the new short-course regimen is recommended in individuals unlikely to complete a traditional 9-month regimen of INH who are 11 years of age or older, HIV-negative, unlikely to be infected with a resistant organism, not pregnant, and not taking hormonal birth control.
Comments:

- Because of limited data in special populations, the new short-course regimen is recommended in individuals unlikely to complete a traditional 9-month regimen of INH who are 11 years of age or older, HIV-negative, unlikely to be infected with a resistant organism, not pregnant, and not taking hormonal birth control.
Notes

- In certain situations in which INH and rifampin are contraindicated or not tolerated, rifabutin given 5 mg/kg (max 300 mg) daily (or biweekly via DOT) may be considered as an alternative.

- Additionally, extrapolating from data on rifampin and PZA (a regimen which was shown to be effective but prohibitively hepatotoxic), when an individual suspected of having active tuberculosis is started on 4 drugs (rifampin, INH, PZA and ethambutol) and subsequent diagnostic workup excludes the disease, 2 months of a 4-drug regimen may be considered adequate treatment for LTBI.

References


3 Jereb J, Goldberg SV, Powell K et al. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR 2011; 60: 1650–1652
Interferon Gamma Release Assays (IGRAs)
Interferon Gamma Release Assays (IGRAs)

IGRAs are in-vitro blood assays that measure T cell release of interferon-gamma (INF-gamma) following stimulation by Mycobacterium Tuberculosis antigens.

Similar to the TST, IGRAs cannot distinguish between latent and active TB infection and may be falsely negative in anergic patients.

A significant advantage over TST is that IGRA results are not affected by Bacille Calmette-Guerin (BCG) vaccination history or prior non-tuberculous infections which can cause falsely positive TST reactions.

Similar to the TST, IGRAs cannot distinguish between latent and active TB infection and may be falsely negative in anergic patients.

A significant advantage over TST is that IGRA results are not affected by Bacille Calmette-Guerin (BCG) vaccination history or prior non-tuberculous infections which can cause falsely positive TST reactions.
Results are available 24-48 hours after the blood draw and do not require a follow-up visit.

Two IGRAs are available in the US: Quantiferon-TB Gold In-Tube (QTF-GIT) assay and the T-Spot TB assay.

IGRAs have a specificity of >95% for the diagnosis of latent TB infection.

T-Spot has higher sensitivity (90%) than QTF-GIT (80%), which may be important when using the test in immunosuppressed patients.

**US CDC 2010 Guidelines**

General Recommendations:

IGRAs can be used in place of TST in all situations in which the CDC recommends TST as an aid in diagnosing TB infection.

Situations in which IGRA is preferred (although TST is acceptable):

For individuals that have historically low rates of returning to have TSTs read (homeless, drug users) or persons who have received BCG (as vaccine or cancer treatment) in order to increase the diagnostic specificity and improve acceptance of treatment for LTBI

Situations in which TST is preferred (although IGRA is acceptable):
Children < 5 years (although some recommend also using an IGRA to confirm the TST result in this group)

Situations in which TST or IGRA may be used without preference:

- Recent contacts (a repeat test after 8-10 weeks from time of last contact still required for IGRA)

- Periodic screening of persons who might have occupational or other exposure to MTB
Situations in which testing with both IGRA and TST may be considered:

- When the initial test (whichever test was used first) is negative and the risk for infection, progression to disease and/or poor outcome is high (e.g., HIV infected individuals or children under 5 years of age who are exposed to a person with infectious TB).

- When the initial test is positive and additional evidence of infection would be helpful to encourage adherence to LTBI treatment (e.g., foreign-born health care workers who believe that the TST is positive because prior BCG vaccine) or persons with low risk of infection and progression from infection to TB disease. A positive result from the second test increases the likelihood that the test reflects infection. An alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results.

Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate.

positive or that the risk for disease does not warrant additional evaluation or
treatment, regardless of test results.

- Repeating an IGRA or performing a TST might be useful when the initial IGRA result
  is indeterminate.

for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis
infection - United States, 2010.
LTBI Resources
LTBI Resources

- Expert Consultation
- Resources
  - Case Management
  - Contact Investigation
  - Diagnosis
  - General/Comprehensive TB
  - Pediatrics
  - Screening
  - Special Populations
  - Treatment
Expert Consultation

Contact the Regional Training and Medical Consultation Center in your region to speak with a medical expert regarding LTBI.

<table>
<thead>
<tr>
<th>Region</th>
<th>Center</th>
<th>Region Name</th>
<th>Phone</th>
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<tbody>
<tr>
<td>Southeast</td>
<td>Southeastern National TB Center</td>
<td>Phone 800-4TB-INFO (24-hour hotline) Online at: <a href="https://sntc.medicine.ufl.edu/ConsultRequest.aspx">https://sntc.medicine.ufl.edu/ConsultRequest.aspx</a></td>
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<tr>
<td>West</td>
<td>Curry International TB Center</td>
<td>Phone 877-390-6682 (M-F, 8:00 am – 4:30 pm PT)</td>
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<tr>
<td>Northeast</td>
<td>Global Tuberculosis Institute – New Jersey</td>
<td>Phone 800-4 TB DOCS (M-F, 9:00 am – 5:00 pm ET) Online at: <a href="http://www.umdnj.edu/globaltb/emailform.htm">http://www.umdnj.edu/globaltb/emailform.htm</a></td>
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<tr>
<td>Central</td>
<td>Heartland National TB Center</td>
<td>Phone 800-TEX-LUNG (M-F, 8:00 am – 5:00 pm CT)</td>
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<tr>
<td>North Central</td>
<td>Mayo Clinic Center for Tuberculosis</td>
<td>Phone 855-360-1466 (M-F, 8:00 am – 5:00 pm ET) Online at: <a href="http://www.mayo.edu/pmts/mc7900-mc7999/mc7915.pdf">http://www.mayo.edu/pmts/mc7900-mc7999/mc7915.pdf</a></td>
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Resources

Case Management

Case Studies in Tuberculosis: Nurse case management training tools for patient success - a collection of nurse case studies and accompanying tools. The cases are based on real-life experiences of TB nurse case managers in the Heartland Region and are designed to illustrate key concepts in TB control and prevention. Case Study #11 includes new LTBI 12-dose (3HP) regimen.


Treating Latent Tuberculosis Infection in High-Risk Populations- tool is used to improve secondary prevention of TB in groups at highest risk for TB disease. This includes sample protocols, forms, and job descriptions.

Contact Investigation

Medical Treatment for Contacts with LTBI- slide set provides information for contact investigations, including the decisions to initiate contact, investigating the site of transmission, diagnostic and public health evaluations, and medical treatment options for contacts with LTBI.


Targeted Testing and Treatment of Latent TB Infection- slide presentation that provides information for the rationale for TB screening, the meaning of targeted testing, risk factors for TB, priority candidates for testing, and current tools for detection.

http://www.currytbcenter.ucsf.edu/products/product_details.cfm?productID=ONL-08

Diagnosis

Guidelines for the Diagnosis of Latent Tuberculosis Infection in the 21st Century: Online Learning Resource- online tool that provides information about targeted skin testing for latent TB infection as strategic component of TB control.

http://www.umdnj.edu/globaltb/products/guideltbiweb.html

Pediatric Tuberculosis: An Online Presentation- slide presentation that provides information on enhancing diagnostic skills of clinicians working with children who have LTBI or active TB. http://www.currytbcenter.ucsf.edu/pediatric_tb/

Targeted Testing and Treatment of Latent TB Infection: An Online Presentation- slide presentation with audio that provides information on effectively testing for TB and treating LTBI. http://www.currytbcenter.ucsf.edu/testing_ltbi/
TB Core Reference Set for Clinicians CD – provides documents and resources with the latest information on tuberculosis. These resources will assist the clinician in making the appropriate diagnosis and treatment plan for adults and children based on guidelines from the Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics, American Thoracic Society, Francis J. Curry National TB Center and Infectious Diseases Society of America (IDSA). The section on Latent Tuberculosis Infection includes new LTBI 12-dose (3HP) regimen. http://www.heartlandntbc.org/products/orderform.pdf (refer to the letter “S”)

General/Comprehensive TB

Tuberculosis at a Glance: A reference for practitioners on basic tuberculosis information – Provides basic information on the diagnosis, treatment, and management of latent tuberculosis infection and tuberculosis disease, based on recommendations from the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society, and the American Thoracic Society. The chapter on Treatment of LTBI includes new LTBI 12-dose (3HP) regimen. http://www.heartlandntbc.org/products/ct_at_a_glance.pdf

You Can Prevent Tuberculosis Video: Patient educational video and supporting materials designed to enhance understanding of the relationship between latent TB infection (LTBI) and active disease and improve adherence to LTBI treatment. English and Spanish. https://ontomedicine.ufl.edu/Products.aspx

Pediatrics


PediatricTB for the Private Provider CD - Learn proper management and care of pediatric TB in the private sector, including screening and appropriate testing children who may have latent TB, diagnosing, and treating children with latent TB. CD includes four recorded presentations, CDA exam, and resource materials. CD may be ordered at http://ontomedicine.ufl.edu/Products.aspx or you may view each of the 4 presentations online at http://www/unm.edu/global/products/nmgmtb4.htm (search for Pediatric)
from the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society, and the American Thoracic Society. The chapter on Treatment of LTBI includes new LTBI 12-dose (3HP) regimen.

http://www.heartlandntbc.org/products/tb_at_a_glance.pdf

You Can Prevent Tuberculosis Video: Patient educational video and supporting handout designed to enhance understanding of the relationship between latent TB infection (LTBI) and active disease and improve adherence to LTBI treatment. English and Spanish. https://sntc.medicine.ufl.edu/Products.aspx

Pediatrics

Management for Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider- resource for primary care providers that provides information on targeted testing, risk assessment, and treatment for children and adolescents with LTBI. http://www.umdnj.edu/globaltb/products/mgmtltbi.htm

Pediatric TB for the Private Provider CD – Learn proper management and care of pediatric TB in the private sector, including screening and appropriately testing children who may have latent TB, diagnosing, and treating children with latent TB. CD includes four recorded presentations, Q&A sessions, and resource materials. CD may be ordered at http://sntc.medicine.ufl.edu/Products.aspx or you may view each of the 4 presentations online at http://sntc.medicine.ufl.edu/Webinars.aspx (search for Pediatric)

Pediatric Tuberculosis: An Online Presentation- slide presentation that provides information on enhancing diagnostic skills of clinicians working with children who have LTBI or active TB. http://www.currytbcenter.ucsf.edu/pediatric_tb/
Screening


Model Tuberculosis Prevention Program for College Campuses December 2010 Edition – a how-to manual that can be used by individuals on college campuses who are responsible for the practical development and implementation of a tuberculosis
screening and testing policy. It explains the basics about tuberculosis, who is most at risk? and what screening and testing policies can be put into place to lower the chances of tuberculosis spreading on campus. The chapter on Latent Tuberculosis Infection Treatment includes new LTBI 12-dose (3HP) regimen.


Special Populations

Assessing and Managing the Risk of Liver Disease in the Treatment of LTBI - can be used as a consultation for healthcare providers that are treating LTBI patients who are at risk for liver disease.


Limiting Liver Toxicity in the HIV Positive Patient with LTBI - pamphlet provides information about limiting liver toxicity in HIV infected patients with LTBI. It includes screening guidelines, strategies for limiting toxicity, and patient education.

http://www.heartlandntbc.org/products/limiting_liver_toxicity_in_the_HIV_positive_patient_with_ltbi.pdf


http://www.heartlandntbc.org/products.asp
LTBI Program Implementation in a Substance Abuse Treatment Facility: A Case Study-case study that discusses a detailed needs assessment, revised TB follow-up evaluation and treatment procedures, and an evaluation plan.

http://www.umdnj.edu/globaltb/products/substanceabuse.htm

Management for Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider- resource for primary care providers that provides information on targeted testing, risk assessment, and treatment for children and adolescents with LTBI.

http://www.umdnj.edu/globaltb/products/mgmtltbi.htm

Pediatric TB for the Private Provider CD – Learn proper management and care of pediatric TB in the private sector, including screening and appropriately testing children who may have latent TB, diagnosing, and treating children with latent TB. CD includes

Pediatric Tuberculosis: An Online Presentation – slide presentation that provides information on enhancing diagnostic skills of clinicians working with children who have LTBI or active TB.

http://www.umdnj.edu/globaltb/products/pediatric_tb.htm

Pediatric Tuberculosis: An Online Presentation – slide presentation that provides information on enhancing diagnostic skills of clinicians working with children who have LTBI or active TB.

http://www.umdnj.edu/globaltb/products/pediatric_tb.htm
four recorded presentations, Q&A sessions, and resource materials.
CD may be ordered at https://sntc.medicine.ufl.edu/Products.aspx or you may view each of the 4 presentations online at https://sntc.medicine.ufl.edu/Webinars.aspx (search for Pediatric)

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Treating Latent Tuberculosis Infection in High-Risk Populations - tool is used to improve secondary prevention of TB in groups at highest risk for TB disease. This includes sample protocols, forms, and job descriptions. http://www.currytbcenter.ucsf.edu/products/product_details.cfm?productID=WPT-06%20B

Treatment

Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection- document explains the new regimens used to treat LTBI. The new 12-dose regiment is considered to be one of the largest breakthroughs in LTBI treatment since the 1960s. The document explores all the implications associated with this novel treatment plan. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
Diagnosis and Treatment of Latent Tuberculosis Infection - drug treatment card for clinicians that provides information on diagnosis of LTBI, therapy options, and recommendations for treatment of infected patients.

http://www.umdnj.edu/globaltb/products/ltbidrugcard.html

LTBI: A Case Study for Instructors - case study for clinicians regarding LTBI. It focuses on testing for TB, treatment options for LTBI, and monitoring patients with LTBI.

http://www.currytbcenter.ucsf.edu/products/product_details.cfm?productID=ONL-05

LTBI Card: Patient's TB Testing and Treatment Record - wallet-sized card administered to LTBI patients to keep permanent record of their tuberculin skin test, chest x-rays, and treatment status.

http://www.umdnj.edu/globaltb/products/ltbicard.htm

http://www.currytbcenter.ucsf.edu/drtb/docs/10ManageCon.pdf

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection - document provides new recommendations for targeted tuberculin infection testing and treatment regimens for persons with LTBI.

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm

TB Elimination: Treatment Options for Latent TB Infection - document that explores the different options for LTBI. It describes in detail the pretreatment evaluation, choosing the most effective regimen, adverse drug reactions, and monitoring methods used during treatment.


http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

Update: Fatal and Severe Liver Injuries Associated With Rifampin and Pyrazinamide for Latent Tuberculosis Infection, and Revisions in American Thoracic Society/CDC Recommendations --- United States, 2001 -

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5034a1.htm