Tuberculosis

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Jacksonville, Florida
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Learning Objectives

1. Provide empiric antibiotic therapy recommendations for patients with active tuberculosis (TB).
2. Differentiate between treating latent TB infection and active TB.
3. Determine the appropriate treatment options for a patient coinfected with HIV and TB.
4. Determine therapeutic options for the treatment of patients with multidrug-resistant TB.
5. Describe the common adverse effects and drug interactions of each first-line anti-TB agent.
6. Identify the importance of therapeutic drug monitoring in TB treatment.

Abbreviations in This Chapter

CNS  Central nervous system
GI   Gastrointestinal
LTBI  Latent tuberculosis infection
MDR-TB Multidrug-resistant tuberculosis
MTB  Mycobacterium tuberculosis
TB   Tuberculosis

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. R.L., a 28-year-old man (weight 98 kg), is given a diagnosis of active tuberculosis (TB). He has no relevant medical history and takes no prescribed medications, over-the-counter drugs, or herbal products. He has a drug allergy to codeine, and his calculated creatinine clearance (CrCl) is 94 mL/minute/1.73 m². His liver function tests are within normal limits. Which is the most appropriate treatment regimen for this patient?
   A. Isoniazid and rifampin, pyrazinamide, and ethambutol daily for 2 months, followed by isoniazid and rifampin daily for a 4-month continuation phase.
   B. Isoniazid, rifampin, pyrazinamide, and ethambutol daily for 4 months, followed by isoniazid and rifampin daily for a 2-month continuation phase.
   C. Isoniazid, rifampin, pyrazinamide, and ethambutol daily for 6 months.
   D. Isoniazid, rifampin, pyrazinamide, and ethambutol twice weekly for 9 months.

2. Which regimen is most appropriate during the continuation phase for treating a 75-kg patient coinfected with pulmonary TB and HIV? The patient is not taking any antiretrovirals for treatment of HIV.
   A. Rifampin 600 mg and isoniazid 900 mg twice weekly.
   B. Rifabutin 300 mg and isoniazid 900 twice weekly.
   C. Rifapentine 600 mg and isoniazid 900 mg once weekly.
   D. Rifampin 600 mg and isoniazid 300 mg daily.

Questions 3 and 4 pertain to the following case.

G.T. is a 33-year-old nurse with a positive tuberculin skin test of greater than 5 mm. A T-SPOT test confirms he has latent tuberculosis infection (LTBI). G.T. has high blood pressure and takes lisinopril 5 mg and ibuprofen for occasional muscle aches; otherwise, he is healthy and would like to begin treatment for LTBI.

3. Which regimen would be most appropriate for G.T.?
   A. Rifampin 600 mg for 9 months.
   B. Isoniazid 300 mg for 9 months.
   C. Rifampin 600 mg and pyrazinamide for 2 months.
   D. Rifapentine 600 mg and isoniazid 300 mg once weekly for 3 months.

4. G.T. returns 1 week later, stating that he had a bad reaction to isoniazid with a severe case of hives and refuses to take it again. Which regimen would be most appropriate for G.T.?
   A. Change to rifampin 600 mg daily for 4 months.
   B. Continue isoniazid 300 mg twice weekly for 9 months.
   C. Change to rifampin 600 mg and pyrazinamide for 2 months.
   D. Change to rifapentine 600 mg and isoniazid 300 mg once weekly for 3 months.
5. T.R. is a 26-year-old man being treated for multidrug-resistant tuberculosis (MDR-TB) for the past 2 months. His current medications include a daily regimen of pyrazinamide 2000 mg, moxifloxacin 400 mg, cycloserine 500 mg, para-aminosalicylic acid, and amikacin. T.R.’s most recent laboratory results show an increase in his serum creatinine (SCr) and a declining renal function (CrCl=55 ml/min). T.R. reports symptoms of feeling dizzy, lethargic, and unable to concentrate. Which of his TB medications most needs to be adjusted?

A. Moxifloxacin.
B. Pyrazinamide.
C. Cycloserine.
D. Para-amino salicylic acid.

6. A.W., a 29-year-old man who is HIV positive, presents to the clinic with a positive tuberculin skin test, negative chest radiography, and no clinical signs or symptoms. An interferon-γ release assay confirms LTBI. He is interested in taking the 12-dose regimen he has heard about (rifapentine/isoniazid). He is not receiving antiretroviral therapy at this time but wants to begin that as well. The patient takes no medications. All laboratory results are within normal limits. Which recommended HIV regimen would be best if the patient were to be treated with rifapentine/isoniazid for 12 weeks?

A. Dolutegravir once daily plus tenofovir/emtricitabine once daily.
B. Raltegravir twice daily plus tenofovir/emtricitabine once daily.
C. Elvitegravir/cobicistat/tenofovir/emtricitabine once daily.
D. Darunavir/ritonavir once daily plus tenofovir/emtricitabine once daily.

7. J.J. is a 28-year-old man with HIV and recently diagnosed pulmonary TB. The patient’s HIV is controlled on Tivicay (dolutegravir 50 mg) and Truvada (tenofovir 300 mg, emtricitabine 200 mg), all once daily. J.J.’s CD4 is 520 cells/mm³, and his viral load is undetectable. All laboratory results are within normal limits. Which regimen would be best for treating J.J.’s TB during the continuation phase of therapy?

A. Rifapentine 900 mg, isoniazid 900 mg once weekly.
B. Rifabutin 150 mg, isoniazid 300 mg twice weekly.
C. Rifabutin 450 mg, isoniazid 300 mg once daily.
D. Rifabutin 300 mg, isoniazid 300 mg once daily.

8. L.M, a 28-year-old man with HIV with a diagnosis of active TB. He currently takes a daily TB regimen of rifabutin 150 mg, isoniazid 300 mg, pyrazinamide 1500 mg, and ethambutol 800 mg, and an HIV regimen of raltegravir 400 mg twice daily plus emtricitabine 200/tenofovir 300 mg. He returns for a follow-up 1 month after beginning his TB treatment with complaints of blurred vision. Further testing shows he has lost the ability to detect the color green. Which medication is most likely responsible?

A. Isoniazid.
B. Rifabutin.
C. Pyrazinamide.
D. Ethambutol.
I. INTRODUCTION

A. Epidemiology (Global)
   1. In 2015, the World Health Organization (WHO) announced that TB was the leading cause of death from an infectious disease.
   2. Worldwide, TB is the most common opportunistic infection in patients with HIV.
   3. 1.8 million people died of TB in 2015.

B. Epidemiology (United States)
   1. In 2015, 9557 cases of TB were reported.
   2. About 500 people die each year of TB.
   3. Two-thirds of all reported TB cases are among foreign-born individuals.

C. Individuals Who Should Be Tested, According to the Centers for Disease Control and Prevention (Domain 1, Task 2)
   1. Health care workers caring for patients with active TB
   2. Individuals in continued contact with someone who has active TB (e.g., family member living in the same household)
   3. Individuals from a country where TB is common
   4. Individuals living or working in “high-risk” settings such as correctional facilities, long-term care facilities, and homeless shelters
   5. Young individuals (infants, children, adolescents) exposed to adults who are at increased risk of active TB or LTBI

D. Transmission
   1. *Mycobacterium tuberculosis* (MTB) is an airborne disease, spread in particles called droplet nuclei. These droplets may be passed by an infected person through coughing, sneezing, or shouting.
   2. The possibility of infection is related to the number of bacilli expelled.
   3. Frequent exposure to a person with infection

E. TB Infection Control (Centers for Disease Control and Prevention recommends a three-tiered approach to controlling TB) (Domain 4, Task 1)
   1. Administrative measures
      a. Control plan in place
      b. Educating/training health care personnel on TB
      c. Assigning specific personnel to be in charge of TB infection control
   2. Environmental controls: Physical containment of infection through proper ventilation/airflow
   3. Protective respiratory equipment

F. Diagnosis (Domain 1, Task 3)
   1. Proper history of patient to identify exposure to MTB
   2. Clinical signs
      a. Persistent cough
      b. Loss of appetite
      c. Chest pain
      d. Fatigue
      e. Night sweats
      f. Possible hemoptysis
      g. Other symptoms depend on the location of TB infection.
3. Presence of acid-fast bacilli from sputum microscopy: Many state/hospital laboratories use Gene-Xpert on smear-positive sputum specimens to identify MTB and rifampin resistance.

4. Positive culture for MTB. Note: A negative culture does not rule out disease; clinicians must use professional judgment.

G. Goals: The goals of TB treatment are to (1) cure the individual of TB and (2) reduce the transmission of TB to other individuals. The American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America guidelines give the three following objectives for anti-TB therapy:
1. Minimize death and disability of the individual patient (i.e., cure the patient)
2. Reduce the transmission of MTB to other individuals
3. Prevent MTB drug resistance while the patient is receiving therapy

H. Active TB Treatment: Typically divided into a 2-month “intensive phase” and a 4-month “continuation phase” (Domain 1, Task 4)
1. Treatment requires combination chemotherapy.
2. Most patients do not complete therapy within this 6-month period.
3. Treatment may be extended in certain situations:
   a. Pulmonary TB with a positive 2-month sputum culture
   b. Bone and joint involvement
   c. Central nervous system (CNS) involvement
   d. Patient with HIV not receiving antiretroviral therapy during TB treatment
4. Susceptibility testing is necessary to determine whether the patient is resistant to any of the first-line medications.

I. Preferred Treatment Regimens for Active TB: Intensive Phase
1. Daily dosing is preferred.
2. Thrice-weekly intermittent dosing may be considered if:
   a. Patient has a low risk of relapse
      i. MTB is drug-susceptible
      ii. Noncavitary TB and/or smear is negative at start of treatment
   b. Patient is HIV negative
3. Twice-weekly intermittent dosing may be considered if:
   a. Patient has completed the initial 2 weeks of daily therapy
   b. Patient has a low risk of relapse
      i. MTB is drug-susceptible
      ii. Noncavitary TB and/or smear is negative at start of treatment
   c. Patient is HIV negative
4. Medications used
   a. Isoniazid
   b. Rifampin
   c. Pyrazinamide
   d. Ethambutol

J. Preferred Treatment Regimens for Active TB: Continuation phase
1. Rifampin and isoniazid continued
2. Daily or thrice-weekly dosing is recommended.
3. Thrice-weekly dosing is preferred if intermittent dosing is necessary.
4. Isoniazid 900 mg/rifapentine 600 mg is seldom used and is generally not recommended. This regimen is typically considered only when directly observed therapy greater than once weekly cannot be achieved. Do not use unless the following criteria are met:
   a. Patient is HIV negative
   b. No cavitation detected on chest radiography
   c. Smear is negative at 8 weeks

Table 1. Medications Used in the Treatment of TB

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Recommended Dose in Adults</th>
<th>Adverse Reactions</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg</td>
<td>Hepatotoxicity; peripheral neuropathy</td>
<td>Administer with pyridoxine to prevent peripheral neuropathy</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10 mg/kg</td>
<td>Hepatotoxicity</td>
<td>Flu-like syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Orange discoloration of fluids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potent CYP inducer</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>15–30 mg/kg</td>
<td>Hepatotoxicity</td>
<td>Arthralgias</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15–25 mg/kg</td>
<td>Optic neuritis</td>
<td>Monitor color vision and visual acuity at baseline and then monthly</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>5 mg/kg</td>
<td>Uveitis, neutropenia</td>
<td>Orange discoloration of fluids</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>750–1000 mg</td>
<td>GI; QT prolongation; tendonitis</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>GI; QT prolongation; tendonitis</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>15–20 mg/kg</td>
<td>Otoxicity; Nephrotoxicity</td>
<td>Avoid in older adults, if possible, because of the increased risk of adverse effects</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10–20 mg/kg</td>
<td>CNS effects</td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; GI = gastrointestinal.

Patient Case

1. R.K. is a 34-year-old man (weight 62 kg) admitted to the hospital after 2 weeks of cough and night sweats. He reports “feeling bad” and a loss of appetite. Chest radiography reveals an infiltrate in the right lung with signs of cavitation. Vital signs include blood pressure 128/84 mm Hg, respiratory rate 20 breaths/minute, and heart rate 115 beats/minute. His HIV test is negative. His SCr is 1.7 mg/dL, and his white blood cell count is 9.2 x 10^3 cells/mm^3. His medical history includes depression. His medications include fluoxetine 20 mg daily. He is given a diagnosis of TB of right lung with cavitation. Which is the most appropriate treatment recommendation for this patient?
   A. Isoniazid 300 mg and rifampin 600 mg, pyrazinamide 2000 mg, ethambutol 1500 mg for 2 months, followed by isoniazid 300 mg and rifampin 600 mg for a 4-month continuation phase.
   B. Isoniazid 300 mg and rifampin 600 mg, pyrazinamide 2000 mg, ethambutol 1500 mg for 4 months, followed by isoniazid 300 mg and rifampin 600 mg for a 2-month continuation phase.
   C. Isoniazid 600 mg and rifampin 300 mg, pyrazinamide 2000 mg, ethambutol 1500 mg for 2 months, followed by isoniazid 300 mg and rifampin 600 mg for a 2-month continuation phase.
   D. Isoniazid 300 mg and rifampin 300 mg, pyrazinamide 2000 mg, ethambutol 1500 mg for 4 months, followed by isoniazid 300 mg and rifampin 600 mg for a 2-month continuation phase.
II. HIV/TUBERCULOSIS COINFECTION

A. Epidemiology (Global)
   1. TB is the leading opportunistic infection among patients with HIV.
   2. 1.1 million (12%) new TB cases were HIV positive in 2014.
   3. Most cases occur in developing countries (primarily sub-Saharan Africa).
   4. Risk of developing active TB is 26–31 times greater in individuals with HIV infection than in those without HIV infection.

B. Epidemiology (United States)
   1. 6% of U.S. patients with TB have HIV.
   2. Most coinfected cases occur in foreign-born individuals.
   3. U.S. cases have declined since the early 1990s.

C. Clinical Presentation (Domain 1, Task 3)
   1. Patients coinfected with HIV/TB may present differently from patients with TB who are HIV negative.
   2. Level of immunosuppression alters TB progression; patients with higher CD4 counts (e.g., greater than 350 cells/mm$^3$) typically present more like their HIV-negative counterparts.
   3. In patients with low CD4 cell counts, symptoms may be “subclinical.”
      a. Cavitation typically absent
      b. Extrapulmonary sites (e.g., lymph nodes) may be more involved.
      c. Lower lobe infiltrates are more common.

D. Treatment (Domain 1, Task 3)
   1. Treatment duration is 6 months.
   2. Treatment should begin as soon as possible. The START and TEMPRANO trials showed that earlier treatment resulted in reduced AIDS-defining illnesses and death.
   3. Immune reconstitution inflammatory syndrome (IRIS) is a concern of patients beginning antiretroviral therapy. IRIS presents as either a paradoxical worsening of infection (e.g., TB) or an unmasking of a new infection:
      a. Symptoms
         i. Fevers
         ii. Respiratory distress
         iii. Resumption of cough
         iv. Lymphadenopathy
      b. More common in patients with CD4 counts below 50 cells/mm$^3$
      c. Onset is typically within the first 4–8 weeks of initiating antiretroviral therapy.
      d. Both HIV and TB treatments are usually continued unless symptoms are severe.
   4. Unique to patients with HIV/TB coinfection is the use of several medications, resulting in:
      a. Overlapping drug toxicities
      b. Drug interactions, particularly with the rifamycins (see Table 2)
Table 2. Common Interactions Between Antiretrovirals and the Rifamycins

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Rifamycin</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>Rifampin</td>
<td>Decreases DTG significantly</td>
<td>DTG 50 mg twice daily</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Rifabutin</td>
<td>Decreases DTG minimally</td>
<td>Standard doses</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Rifampin</td>
<td>Likely decreases EVG</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Rifabutin</td>
<td>Decreases EVG AUC by 21% (RBN metabolite increases by 625%)</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Rifampin</td>
<td>Decreases RALT significantly</td>
<td>RALT 800 mg twice daily</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Rifabutin</td>
<td>Decreases RALT minimally</td>
<td>Standard doses</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Rifapentine</td>
<td>Increases RALT AUC by 71%</td>
<td>Standard doses</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>Rifampin</td>
<td>Decreases ATV significantly</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>Rifabutin</td>
<td>Increases RBN significantly</td>
<td>RBN 150 mg daily or RBN 300 mg thrice weekly</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>Rifampin</td>
<td>Decreases DRV significantly</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>Rifabutin</td>
<td>Increases RBN significantly</td>
<td>RBN 150 mg daily or RBN 300 mg thrice weekly</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>Rifampin</td>
<td>Decreases LPV significantly</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>Rifabutin</td>
<td>Increases RBN significantly</td>
<td>RBN 150 mg daily or RBN 300 mg thrice weekly</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rifampin</td>
<td>Decreases EFV significantly</td>
<td>EFV 600 mg daily (800 mg can be considered in patients weighing &gt; 60 kg)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rifabutin</td>
<td>Decreases RBN significantly</td>
<td>RBN 450 mg (or 600 mg) daily</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rifapentine</td>
<td>Decreases EFV minimally</td>
<td>Standard doses</td>
</tr>
</tbody>
</table>

*Rifapentine administered at 900 mg once weekly.

ATV = atazanavir; AUC = area under the curve; DTG = dolutegravir; EVF = efavirenz; LPV = lopinavir; RALT = raltegravir; RBN = rifabutin.

Patient Cases

2. D.Z. is a 42-year-old woman (weight 52 kg) who is HIV positive. She was recently given a diagnosis of pulmonary TB. Her HIV is controlled on efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg with a CD4 of 400 cells/mm$^3$ and an undetectable viral load. Which regimen would be best for treating D.Z.’s TB?
   A. Rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
   B. Rifabutin 150 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
   C. Rifampin 450 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
   D. Rifabutin 300 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.

3. L.M., a 28-year-old man who is HIV positive, has recently diagnosed pulmonary TB. The patient’s HIV is controlled on (darunavir 800 mg, ritonavir 100 mg, and tenofovir 300 mg, emtricitabine 200 mg), all once daily. L.M.’s CD4 is 280 cells/mm$^3$, and his viral load is undetectable. All laboratory values are within normal limits. Which regimen would be best for treating D.Z.’s TB?
   A. Rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
   B. Rifabutin 150 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
   C. Rifabutin 450 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
   D. Rifabutin 300 mg, isoniazid 300 mg, pyrazinamide 1500 mg, ethambutol 800 mg.
III. LATENT TUBERCULOSIS INFECTION

A. Epidemiology
   1. Some studies indicate that as much as one-third of the world’s population is infected with TB (i.e., latent TB).
   2. 10–15 million U.S. individuals are believed to have latent infection.
   3. 5%–10% of individuals with LTBI are at risk of progression to active TB. Those at high risk include the following:
      a. Patients with HIV (HIV is the greatest risk factor for progression)
      b. Older adults
      c. Infants and young children
      d. Immunocompromised individuals
      e. Injection drug users

B. Diagnostic Testing (Domain 1, Task 2)
   1. Tuberculin skin test
      a. Injection of 0.1 mL of tuberculin purified protein derivative into dermis
      b. Disadvantage: Bacille Calmette-Guérin vaccination can cause a false positive.
   2. Two interferon-γ release assays currently available:
      a. QuantiFERON-TB Gold In-Tube test
      b. T-SPOT test

C. Treatment Options (Domain 1, Task 6)
   1. Isoniazid 300 mg daily for 9 months is preferred treatment for:
      a. Patients with HIV
      b. Children 2–11 years of age (pediatric dose: 10–15 mg/kg/day)
      c. Pregnant women (with vitamin B6 and B12 supplementation) – May consider waiting until 2 months postpartum unless:
         i. Patient is HIV positive
         ii. Patient had a recent contact
      d. Breastfeeding is not a contraindication.
      e. Isoniazid 300 mg daily for 6 months is more cost-effective; however, it is less effective at preventing active disease than the 6-month option.
   2. Isoniazid 900 mg twice weekly for 9 months is preferred treatment for
      a. Pregnant women (with vitamin B6 and B12 supplementation)
      b. Directly observed therapy should be used.
      c. Isoniazid 900 mg twice weekly for 6 months is a more cost-effective option; however, it is less effective at preventing active disease than the 6-month option.
      d. Pediatric dose: 20–40 mg/kg twice weekly for 9 months
   3. Isoniazid 900 mg once weekly in combination with rifapentine 900 mg once weekly
      a. Treatment for individuals older than 12 years
      b. Currently, must be given directly observed therapy
      c. Not recommended for:
         iii. Individuals younger than 2 years
         iv. Patients with HIV/AIDS
         v. Women who are pregnant, or expecting to become pregnant during treatment
         vi. Individuals believed to be infected with isoniazid- or rifampin-resistant MTB
4. Rifampin 600 mg daily for 4 months
   a. Alternative for patients who cannot tolerate isoniazid
   b. Pediatric dose: 10–20 mg/kg/day for 6 months
5. Rifampin and pyrazinamide for 2 months is NOT recommended because of an increased risk of hepatotoxicity and death.

D. Note on Treatment: Active TB must be ruled out before LTBI can be treated.

Patient Case
Questions 4 and 5 pertain to the following case (question 5 can be found on the following page).
N.S. is a 25-year-old woman recently exposed to her boyfriend, who has active TB. A QUANTIFERON-TB Gold test confirms she has LTBI. N.S. is 3 months pregnant. She takes only a prenatal vitamin and is otherwise healthy. She is concerned about taking any medication that could harm her unborn child.

4. Which regimen is most appropriate for N.S.?
   A. Isoniazid 900 mg and rifapentine 900 mg once weekly for 3 months.
   B. Rifampin 600 mg daily for 4 months.
   C. Rifampin 600 mg daily and pyrazinamide 1500 mg daily for 2 months.
   D. Isoniazid 300 mg daily for 9 months.

IV. INDIVIDUAL MEDICATIONS FOR ACTIVE TUBERCULOSIS

A. Isoniazid
   1. Place in therapy: First-line agent; isoniazid and rifampin are the two most important agents in treating active TB
   2. Mechanism of action:
      a. Inhibits mycolic acid synthesis

Patient Case
5. N.S. has her 5-year-old child, T.S. (weight 20 kg [44 lb]), tested for TB at the clinician’s recommendation. Active TB is ruled out, but T.S. also has latent TB infection. Which regimen is most appropriate for T.S.?
   A. Isoniazid 200 mg and rifapentine 300 mg once weekly for 3 months.
   B. Isoniazid 200 mg daily for 9 months.
   C. Isoniazid 200 mg twice weekly for 9 months.
   D. Rifampin 200 mg daily and pyrazinamide 1000 mg daily for 2 months.

   b. Most effective during the first few days of treatment because of its potent early bactericidal activity (EBA). During this time, the largest proportion of MTB are rapidly dividing. EBA refers to a drug’s ability to rapidly reduce the number of bacteria. Typically, EBA refers to the first 2–5 days of treatment but can refer to a period of up to 2 weeks (extended EBA).
   c. Cmax is the pharmacokinetic parameter most associated with efficacy.
3. **Dose**
   a. Daily dose is 300 mg. Expected Cmax is 3–5 mcg/mL 2 hours post-dose.
   b. Intermittent dosing is 900 mg (two or three times weekly). Expected Cmax is 9–15 mcg/mL 2 hours post-dose.
   c. Higher doses (450–600 mg) may be needed in patients with low isoniazid concentrations, such as fast acetylators, or in patients with TB experiencing malabsorption.
   d. Food reduces the oral absorption of isoniazid, and the agent should be administered on an empty stomach.

4. **Adverse effects**
   a. Hepatotoxicity: Subclinical hepatitis occurs in as many as 10% of patients.
      i. Anorexia, weight loss, GI upset may occur
      ii. Aspartate aminotransferase and alanine aminotransferase should be monitored.
      iii. Slow acetylators may be at higher risk of hepatotoxicity.
   b. Peripheral neuropathy
      i. Administer 50 mg of pyridoxine.
      ii. Risk of peripheral neuropathy is higher in patients with diabetes, patients with HIV, pregnant women, and patients who consume large amounts of alcohol.

5. **Metabolism:** Acetylation by \(N\)-acetyltransferase
   a. Rapid acetylator half-life is 1–2 hours. May be at greater risk of treatment failure
   b. Slow acetylator half-life is 3–4 hours.

6. **Drug interactions**
   a. Isoniazid can inhibit CYP2E1, CYP2C19, and CYP3A.
   b. Isoniazid can induce CYP2E1.
   c. Examples of medications that may be affected: Warfarin, phenytoin, carbamazepine

B. **Rifampin**

1. **Mechanism of action:**
   a. Inhibits the beta-subunit of MTB’s RNA polymerase, preventing transcription
   b. Kills actively dividing bacilli as well as dormant bacilli
   c. Cmax and AUC both associated with efficacy. Cmax may be more associated with preventing resistance and AUC with bactericidal activity.

2. **Dose**
   a. Adult and pediatric: 10–20 mg/kg; up to a 600-mg oral dose is typical starting daily and intermittent dose
      i. Some argue that 600 mg is too low.
      ii. Administer 1 hour before or 2 hours after a meal.
   b. Expected Cmax is 8–24 mcg/mL 2 hours post-dose.

3. **Adverse effects**
   a. Hepatotoxicity
      i. Minor risk of hepatotoxicity, which is additive to isoniazid
      ii. Risk factors: Alcohol, advanced age, diabetes, concomitant hepatotoxic medications
   b. Flu-like syndrome
      i. Occurs with large (900–1800 mg) intermittent doses but seldom with daily doses
      ii. Usually occurs after months of treatment
   c. Orange fluid discoloration
      i. Not an “adverse effect” per se
      ii. Sweat, tears, and urine may be red/orange. Not harmful, but patients should be made aware
4. **Metabolism**
   a. Metabolized by intestinal and hepatic esterases
   b. Primary metabolite, 25-desacetyl rifampin, is partly active.

5. **Drug interactions**
   a. Many drug interactions
   b. Potent CYP3A4 inducer; inducer of other CYP and phase II enzymes and drug transporters
   c. See Table 3 for interactions with common HIV medications.

C. **Rifabutin**
   1. **Place in therapy:** Recommended as a substitute for rifampin because of rifampin’s potent enzyme induction. Rifabutin induces enzymes about 40% as much as rifampin.
   2. **Mechanism of action:** Inhibits the beta-subunit of MTB’s RNA polymerase
   3. **Dose**
      a. 300-mg dose is the typical starting daily and intermittent dose.
      b. 450-mg dose is recommended with CYP3A inducers.
      c. 150-mg dose is recommended with CYP3A inhibitors.
      d. Expected Cmax is 0.3–0.9 mcg/mL 3–4 hours post-dose.
      e. Food has little effect on absorption.
   4. **Adverse effects (concentration related)**
      a. Anterior uveitis
      b. Arthralgias
      c. Leucopenia
   5. **Metabolism**
      a. Extensive intestinal and hepatic metabolism
      b. CYP3A substrate
   6. **Drug interactions**
      a. Has most of the same drug interactions as rifampin, though not to the same extent (about 40% of that with rifampin)
      b. CYP3A4 substrate; thus, “bidirectional” interactions are possible and must be considered (see Table 3 for drug interactions with HIV antiretrovirals)

D. **Rifapentine**
   1. **Place in therapy**
      a. Rarely used in the continuation phase of active TB treatment
      b. May be used in the treatment of LTBI
   2. **Mechanism of action:** Inhibits the beta-subunit of MTB’s RNA polymerase
   3. **Dose**
      a. 600 mg once weekly for continuation phase
      b. 900 mg once weekly with 900 mg of isoniazid once weekly for 12 weeks for LTBI
      c. Food increases AUC by 30%–80%.
   4. **Adverse effects**
      a. Hepatotoxicity
      b. Flu-like syndrome
      c. Discoloration of bodily fluids
   5. **Metabolism:** Hydrolyzed by esterases to its less active metabolite, 25-desacetyl rifapentine
   6. **Drug interactions:** Similar to those of rifampin. Rifapentine’s induction capabilities are as potent (or almost as potent) as those of rifampin, so it offers no advantages over rifampin in avoiding drug interactions.
E. Pyrazinamide
1. Place in therapy
   a. First-line agent used during intensive phase
   b. Shortens the therapy duration from 9 months to 6 months
2. Mechanism of action:
   a. Not fully known
   b. Prodrug that is activated by the enzyme pyrazinamidase within MTB
3. Dose
   a. 25 mg/kg daily
   b. 50 mg/kg twice weekly
   c. 30–40 mg/kg daily for pediatric patients
   d. If CrCl is less than 30 mL/minute/1.73 m², consider a 25- to 35-mg/kg/dose thrice weekly.
4. Adverse effects
   a. Arthralgias
   b. GI upset
   c. Hepatotoxicity (increased risk with higher doses)
5. Metabolism: Oxidized to 5-OH-pyrazinoic acid; metabolized in liver, but metabolites can accumulate in patients with severe renal dysfunction
6. Drug interactions: No significant drug interactions

F. Ethambutol
1. Place in therapy: First-line agent used during intensive phase to protect rifampin from isoniazid resistance. Ethambutol may be discontinued once data return that MTB is susceptible to isoniazid.
2. Mechanism of action: Inhibits arabinogalactan (part of MTB's cell wall) synthesis
3. Dose
   a. 15–25 mg/kg daily
   b. 50 mg/kg twice weekly
   c. Pediatric dose: 25 mg/kg/dose daily
   d. Cmax is 2–6 mcg/mL at 2–3 hours
   e. Food does not affect absorption; however, antacids should be avoided within 2 hours of dosing.
4. Adverse effects: Optic neuritis
   a. Concentration-dependent toxicity
   b. Less common in patients with normal renal function
   c. Less common in patients taking doses lower than 30 mg/kg/day
   d. Routine testing for visual acuity using Snellen charts should be done.
   e. Routine testing for red/green color discrimination using Ishihara color plates should be done.
   f. If optic neuritis is recognized promptly, vision usually returns to baseline.
5. Metabolism
   a. Cleared renally and hepatically; up to 50% is excreted unchanged in the urine
   b. Dose adjustment is necessary in patients with renal dysfunction.
6. Drug interactions: As with pyrazinamide, no significant drug interactions

V. MULTIDRUG-RESISTANT TUBERCULOSIS

A. Definition: MTB that is resistant to isoniazid and rifampin. Primary cause is inadequate treatment of drug-susceptible TB.
B. Epidemiology (2015 global estimates)
   1. Around 480,000 individuals infected globally
   2. Accounts for 3.3% of new cases
   3. Around 250,000 people died of MDR-TB

C. Treatment (Domain 1, Task 4)
   1. At least FIVE effective medications should be used in treating MDR-TB (standard regimen).
      a. Pyrazinamide should be included, if isolate is susceptible.
      b. Intensive phase is recommended for 8 months.
      c. Continuation phase is 12 months of at least three or four effective medications.
      d. Treatment may be extended in either phase, depending on clinical response.
      e. Treatment can vary depending on factors such as extent of disease, patient tolerance, and patient comorbidities.
      f. A short-course regimen of 12 months or less is a treatment option recommended by the WHO in patients not previously treated with second-line TB medications whose MTB isolate is susceptible to the medications being used in the treatment regimen.
   2. According to the 2016 guidelines, the WHO groups them on the basis of evidence of efficacy and safety.
      a. Group A: A fluoroquinolone
         i. Levofloxacin
         ii. Moxifloxacin
      b. Group B: Aminoglycosides and capreomycin
         i. Amikacin
         ii. Capreomycin
         iii. Kanamycin
         iv. Streptomycin
      c. Group C: Other core second-line agents
         i. Ethionamide/prothionamide
         ii. Cycloserine/terizidone
         iii. Linezolid
         iv. Clofazimine
      d. Group D: Add-on agents
         i. D1: Pyrazinamide
         ii. D1: Ethambutol
         iii. D1: High-dose isoniazid
         iv. D2: Bedaquiline
         v. D2: Delamanid
         vi. D3: Para-aminosalicylic acid
         vii. D3: Imipenem/cilastin
         viii. D3: Meropenem
         ix. D3: Amoxicillin/clavulanate
   3. Patients should receive:
      a. Pyrazinamide
      b. One medication from group A
      c. One medication from group B
      d. Two medications from group C
   4. Note: Macrolides are no longer recommended in the treatment of MDR-TB.
   5. Note: Medications in groups A and C are grouped by order of preference.
6. Note: If patients cannot be treated with the minimum number of effective TB medications as listed earlier, an agent from group D2 and/or agents from group D3 may be added to make a total of FIVE effective medications.

D. Individual Medications Used for Treatment

1. Moxifloxacin
   a. Place in therapy
      i. One of the first medication selected for MDR-TB because of its desirable pharmacokinetic/pharmacodynamic properties
      ii. Moxifloxacin’s minimum inhibitory concentration against MTB is 0.125–0.5 mcg/mL.
   b. Mechanism of action: Inhibits DNA gyrase
   c. Dose: 400 mg is the typical starting dose.
   d. Metabolism
      i. Primarily metabolized by phase II enzymes
      ii. No renal dose adjustment necessary
   e. Drug interactions
      i. Rifampin decreases moxifloxacin’s AUC by 27%. A 600-mg moxifloxacin dose may be necessary to overcome this reduction.
      ii. Avoid with drugs containing di- or trivalent cations.

2. Levofloxacin
   a. Place in therapy
      i. One of the first-line medications selected for MDR-TB because of its desirable pharmacokinetic/pharmacodynamic properties
   b. Mechanism of action: Inhibits DNA gyrase
   c. Dose
      i. 750–1000 mg daily (about 10 mg/kg)
      ii. Food causes only a modest reduction in Cmax and no overall change in AUC.
   d. Metabolism: Eliminated renally, so dose adjustment is necessary in renal dysfunction
   e. Drug interactions: Avoid with drugs containing di- or trivalent cations.

3. Aminoglycosides (amikacin, kanamycin, streptomycin) and capreomycin
   a. Mechanism of action: Inhibits protein synthesis
   b. Dose
      i. 15–20 mg/kg
      ii. Cmax is 35–45 mcg/mL with daily dosing.
      iii. Cmax is 65–80 mcg/mL with thrice-weekly dosing.
   c. Adverse effects
      i. Nephrotoxicity
      ii. Ototoxicity
      iii. Peripheral neuropathy
      iv. Rash
   d. Metabolism: Eliminated by glomerular filtration
   e. Drug interactions: Interactions are mainly limited to medications that can reduce a patient’s renal function.

4. Clofazimine
   a. Mechanism of action: Not fully elucidated; may prevent replication by selectively binding mycobacterial DNA at the guanine base, or may be because of the production of reactive oxygen species
   b. Dose
      i. 50–200 mg once daily
      ii. Cmax is 0.5–2 mcg/mL (Tmax is variable: 2–12 hours post-dose).
c. Adverse effects
i. Skin discoloration is the most common adverse effect (a bronze discoloration of body tissues), which typically manifests within the first few weeks after initial treatment but may last months to more than a year after discontinuation. Dry skin is also common.
ii. GI intolerance
d. Metabolism: Primarily hepatic; not fully understood
e. Drug interactions: No significant drug interactions

5. Cycloserine
a. Mechanism of action: Disrupts the incorporation of d-alanine into peptidoglycan during cell wall synthesis
b. Dose
i. 10–20 mg/kg twice daily (typically 250–500 mg)
ii. Pediatric dose typically 10–20 mg/kg/day in two divided doses
iii. Cmax of 20–35 mcg/mL 1–2 hours post-dose
iv. Dosage adjustment necessary in patients with renal dysfunction, with target concentrations less than 30 mcg/mL (not recommended in patients with a CrCl of less than 50 mL/minute/1.73 m²)
c. Adverse effects:
   i. Most common CNS adverse effects: Anxiety, confusion, depression, dizziness, difficulty concentrating, drowsiness, lethargy, hyperexcitability, paresthesias, seizures, tremor, vertigo
   ii. CNS toxicity may be greater at higher concentrations (greater than 35 mcg/mL), and concentrations should be maintained below 30 mcg/mL to reduce the risk of adverse effects.
d. Metabolism: Primarily renal, minimal hepatic metabolism. Do not use if CrCl is 50 mL/minute/1.73 m².
e. Drug interactions: No significant drug interactions, though an increased risk of neurological symptoms may occur with isoniazid or the fluoroquinolones

6. Ethionamide
a. Mechanism of action
i. Inhibition of mycolic acid synthesis
ii. Cross-resistance with isoniazid possible
b. Dose
i. 250–500 mg twice daily is typical.
ii. Pediatric dose is 15–20 mg/kg/day divided twice daily.
iii. Cmax is 1.5–3.0 mcg/mL 2 hours post-dose.
c. Adverse effects
i. GI adverse effects (can be severe): Can reduce by splitting the dose initially, or starting with lower doses and increasing gradually
ii. Other, less common adverse effects
   (a) Hepatotoxicity
   (b) Visual disturbances
   (c) Goiter
d. Metabolism
   i. Sulfoxidation, desulfurization, and deamination, followed by methylation
   ii. 250–500 mg orally daily recommended in patients with a CrCl less than 30 mL/minute/1.73 m²
e. Drug interactions: No significant drug interactions

7. Linezolid
a. Mechanism of action: Binds to 23s rRNA, inhibiting protein synthesis
b. Dose: 600 mg daily
c. Adverse effects
   i. Diarrhea, nausea
   ii. Headache
   iii. Anemia
   iv. Thrombocytopenia
   v. Lactic acidosis
   vi. Peripheral neuropathy
   vii. Optic neuropathy

d. Metabolism: Primarily oxidation

e. Drug interactions: Contraindicated with monoamine oxidase inhibitors

8. Para-aminosalicylic acid
   a. Mechanism of action: Unknown; has activity against folic acid pathway
   b. Dose
      i. 4 g three times daily (twice daily has been used as an alternative)
      ii. Pediatric dose is 50 mg/kg three times daily, up to 12 g per day.
      iii. Granules best absorbed with food
      iv. Cmax is 15–20 mcg/mL 4–6 hours post-dose for sustained-release granules.
   c. Adverse effects
      i. GI upset most common; newer aminosalicylic acid (Paser) granules are better than older dosage forms. Diarrhea is still a common adverse effect, but this usually improves within the first 2 weeks of administration.
      ii. Hypothyroidism
      iii. Steatorrhea
   d. Metabolism: Metabolized in the GI tract and liver to inactive metabolites
   e. Drug interactions: No significant drug interactions
   f. Notes: Available as granules (empty granules may pass through system and appear in the patient’s stool)

9. Bedaquiline/delamanid
   a. Bedaquiline: According to the Centers for Disease Control and Prevention, bedaquiline may be used as part of combination therapy for pulmonary TB “when an effective treatment regimen cannot otherwise be provided.” Currently limited by cost and safety concerns
   b. Delamanid: Approved by European Medicines Agency but not in the United States at this time

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**Patient Case**

6. S.D. is a 27-year-old man (weight 70 kg) admitted to the hospital with complaints of hemoptysis the past 2 days. He admits having been given a diagnosis of TB 3 months ago, but he left treatment before completing therapy. The patient is given a diagnosis of TB resistant to rifampin and isoniazid (MDR-TB). All laboratory results are within normal limits. He is HIV negative. Which is the most appropriate initial regimen for S.D.?

A. Pyrazinamide 2000 mg once daily, levofloxacin 750 mg once daily, amikacin 1000 mg daily, cycloserine 250 mg once daily, ethionamide 250 mg twice daily.

B. Levofloxacin 750 mg once daily, amikacin 1000 mg daily, cycloserine 250 mg once daily, ethionamide 250 mg twice daily, clofazimine 100 mg once daily.

C. Pyrazinamide 2000 mg once daily, levofloxacin 750 mg once daily, amikacin 1000 mg daily, cycloserine 250 mg once daily.

D. Pyrazinamide 2000 mg once daily, levofloxacin 750 mg once daily, clofazimine 100 mg daily, cycloserine 250 mg once daily, ethionamide 250 mg twice daily.
E. Therapeutic Drug Monitoring *(Domain 1, Task 7)*

1. The measuring of serum drug concentrations to individualize drug therapy in conjunction with other relevant patient factors (e.g., clinical signs and symptoms, laboratory tests)
2. May be used to assess patient adherence, maximize efficacy, or minimize adverse events
3. For the first- and second-line TB drugs, two concentration time points can be measured to help individualize therapy: a 2-hour sample (3 hours for rifabutin) and a 6-hour sample. The 2-hour sample captures the Cmax (see Table 3).
4. A 6-hour sample is used to determine malabsorption or delayed absorption.
   a. Malabsorption: Both 2- and 6-hour concentrations are below the expected range (increased dose may be necessary)
   b. Delayed absorption: The 2-hour concentration is below the expected range, but the 6-hour concentration is within range (no dose adjustment necessary)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Adult Dose</th>
<th>Concentration Range (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (daily)</td>
<td>300 mg</td>
<td>3–5</td>
</tr>
<tr>
<td>Isoniazid (intermittent)</td>
<td>900 mg</td>
<td>9–15</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg</td>
<td>8–24</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2000 mg</td>
<td>20–60</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1500 mg</td>
<td>2–6</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300 mg</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1000 mg</td>
<td>8–12</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3–5</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>250–500 mg</td>
<td>20–35</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>50–200 mg</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>15–20 mg/kg</td>
<td>35–45 (once-daily dosing)</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>250–500 mg</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Para-amino salicylic acid</td>
<td>4 g</td>
<td>15–20</td>
</tr>
</tbody>
</table>

TDM = therapeutic drug monitoring.
Patient Case

Questions 7 and 8 pertain to the following case.

M.K. is a 24-year-old man with recently diagnosed pulmonary TB. His current medication regimen is as follows: isoniazid 900 mg thrice weekly, rifampin 600 mg thrice weekly, pyrazinamide 2000 mg thrice weekly, and ethambutol 1200 mg thrice weekly. His symptoms have improved since initial diagnosis 1 month ago, but he has not gained weight, and sputum remains smear positive. His physician is concerned that the medications are not fully effective and orders therapeutic drug monitoring.

Rifampin 2-hour concentration: 6 mcg/mL
Rifampin 6-hour concentration: 3 mcg/mL
Isoniazid 2-hour concentration: 4 mcg/mL
Isoniazid 6-hour concentration: 10 mcg/mL

7. Which best describes what is occurring with respect to isoniazid and rifampin?
   A. Isoniazid—malabsorption, rifampin—delayed absorption.
   B. Isoniazid—malabsorption, rifampin—malabsorption.
   C. Isoniazid—delayed absorption, rifampin—malabsorption.
   D. Isoniazid—delayed absorption, rifampin—delayed absorption.

8. Which dose adjustment would be best?
   A. Increasing isoniazid to 1200 mg and rifampin to 1200 mg.
   B. Increasing rifampin to 900 mg.
   C. Increasing isoniazid to 1200 mg.
   D. No dose adjustment necessary.
REFERENCES

Treatment Guidelines

Epidemiology

Diagnosis and Screening

Isoniazid
Rifamycins

Pyrazinamide/Ethambutol and Second-line Agents

HIV/TB Coinfection


Drug Interactions


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: A**

Treatment of active pulmonary TB consists of a 2-month intensive phase and a 4-month continuation phase, making Answers B and D incorrect. The intensive phase consists of a four-drug regimen: isoniazid, rifampin, pyrazinamide, and ethambutol. Answers A and C contain the correct number of months for the intensive and continuation phase; however, Answer C is incorrect because of dosing. Isoniazid is dosed at 5 mg/kg (300 mg is typical starting dose) and rifampin at 10 mg/kg (600 mg is typical starting dose) (Answer A is correct).

2. **Answer: A**

According to the information provided, the patient takes efavirenz 600 mg/emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg. Rifampin and rifabutin are known CYP enzyme inducers, with rifabutin less inducing (about 40% less) than rifampin. Both can lower efavirenz concentrations. Either agent can be given with efavirenz to properly manage the patient’s TB and HIV. However, rifabutin has a bidirectional interaction. Efavirenz can reduce rifabutin concentrations, making it difficult to optimize therapy. If used concurrently, a rifabutin dose of 450 mg is recommended. Rifabutin 150 mg (Answer B) is too low. Rifabutin 300 mg (Answer D) could be used but might need dose adjustment. A more manageable regimen would use rifampin, which is not a CYP substrate, and concentrations would be unaffected by efavirenz (Answer C is incorrect because this would be a lower-than-necessary dose). Efavirenz, when administered at the standard 600-mg dose, still produces trough concentrations well above the concentrations required to suppress HIV in vitro in most patients who are coadministered rifampin/efavirenz (Answer A is correct).

3. **Answer: B**

Rifampin is not recommended with most protease inhibitors because its inductive properties cause largely reduced concentrations of CYP substrates, such as the protease inhibitors. Darunavir is contraindicated with rifampin, making Answers A incorrect. Rifabutin, because of its less-potent inductive abilities, is recommended in place of rifampin. However, because rifabutin is a CYP3A substrate and the protease inhibitors can increase rifabutin concentrations, which can lead to toxicity (e.g., anterior uveitis or neutropenia), a reduction in dose is likely warranted from 300 mg (Answer D) to 150 mg (Answer B). 450-mg dose would increase the risk of rifabutin toxicity, making Answer C incorrect.

4. **Answer: D**

The safety of the isoniazid/rifapentine regimen has not been established in pregnant women, making Answer A incorrect. Rifampin and pyrazinamide have an increased risk of hepatotoxicity and should not be used to treat LTBI (Answer C). Isoniazid can increase the risk of hepatotoxicity in the first few months, and in the absence of risk factors, holding treatment until 2–3 months postpartum may be considered (Answer B). However, this patient has a risk factor because she was in recent contact with a person with active TB; therefore, she should be treated with isoniazid 300 mg daily for 9 months (https://www.cdc.gov/tb/publications/ltbi/treatment.htm), making Answer D correct.

5. **Answer: B**

Rifapentine is not recommended in children younger than 12 years because of a lack of studies, making Answer A incorrect. Answer D is incorrect because of the increased risk of hepatotoxicity with rifampin/pyrazinamide. The preferred regimen for children age 2–11 is 9 months of daily isoniazid at 10–15 mg/kg, or 20–40 mg/kg for intermittent therapy. This patient weighs 20 kg (44 lb). A daily isoniazid dose would be 200–300 mg (many clinicians will opt for the lower dose) (Answer B is correct). An intermittent dose would be 400–800 mg (Answer C is only 200 mg and is an insufficient dose).

6. **Answer: A**

According to the current guidelines, MDR-TB should be treated with at least five effective medications. Answer C contains four active medications, making it incorrect. Of the five effective medications, one should be pyrazinamide if the patient is not resistant, and this patient is not (the patient is only resistant to rifampin and isoniazid), making Answer B incorrect. Of the two remaining answers, Answer D may include five active medications but does not contain a medication from WHO group B (an injectable agent, e.g., an aminoglycoside or capreomycin), making Answer A correct.
7. **Answer: C**
With respect to therapeutic drug monitoring, malabsorption refers to lower-than-expected concentrations of a medication because of its inadequate absorption, which can occur as the result of several factors, including disease state (e.g., HIV, diabetes). Delayed absorption is, by definition, absorption of a drug later than what typically occurs (i.e., the Tmax is at a later time). This patient’s rifampin concentrations at 2 and 6 hours are below the expected range of 8–24 mcg/mL (malabsorption) but are not delayed, making Answers A and D incorrect. Isoniazid at a 900-mg dose produces concentrations at around 2 hours of 9–12 mcg/mL. The 6-hour value is within the expected range, whereas the 2-hour value is not (delayed absorption), making Answer B incorrect and Answer C correct.

8. **Answer B**
Although its absorption is delayed, isoniazid is producing the expected concentrations; therefore, a dose adjustment is not needed (Answers A and C are incorrect). Rifampin concentrations are well below the expected concentration range of 8–24 mcg/mL. If the patient’s symptoms were improving, a dose adjustment might not be needed (Answer D). However, because this is not the case, and the rifampin dose should be increased. Rifampin follows linear pharmacokinetics; thus, doubling the dose would double the concentrations. A dose increase to 1200 mg is warranted (Answer B).
1. **Answer: A**
The patient has no underlying reasons for not receiving the preferred treatment regimen of rifampin, isoniazid, pyrazinamide, and ethambutol for a 2-month intensive phase, followed by a 4-month continuation phase consisting of rifampin and isoniazid, making Answer A correct. Answer B is incorrect because it states a 4-month intensive phase and a 2-month continuation phase. Answer C is incorrect because it is all four medications for 6 months. Answer D is incorrect because it is using all four medications for 9 months, as well as being twice weekly.

2. **Answer: D**
Intermittent TB (once weekly, twice weekly or thrice weekly dosing) treatment may be considered in several cases, particularly if a patient is at low risk of relapse and HIV negative. Twice weekly therapy of rifampin and isoniazid is not recommended in co-infected patients due to an increase risk of rifamycin resistance making answer A incorrect. Rifabutin, while often substituted for rifampin in co-infected patients, is not recommended twice weekly either for the same reasons, making answer B incorrect. Rifapentine and isoniazid once weekly are not recommended in patients with HIV making answer C incorrect. Daily treatment with either rifampin or rifabutin and isoniazid is recommended to avoid recurrent disease and rifamycin resistance, making answer D the correct choice. *Note in the event a co-infected patient does not receive antiretroviral treatment for HIV, a continuation phase of 7 months is recommended over 4 months for drug-susceptible pulmonary TB.

3. **Answer: B**
The preferred treatment option for LTBI is isoniazid 300 mg daily for 9 months, making Answer B correct and Answer D incorrect. This patient has no factors that would warrant his trying another regimen such as rifampin, making Answers A and C incorrect. Rifampin and pyrazinamide is no longer recommended because of an increased risk of hepatotoxicity, making Answer C incorrect.

4. **Answer: A**
This patient had a reaction to isoniazid; therefore, a reasonable alternative would be treatment with rifampin for 4 months, making Answer A correct. Rifampin has several drug interactions, and the patient must be cautioned not to begin any new medications without first determining whether rifampin will interact. The patient only takes lisinopril (and occasionally ibuprofen), which is not an issue. Using an intermittent regimen containing isoniazid (Answers B and D) would not help with the reaction. In addition, the dosing is incorrect. Answer C is incorrect because of the increased risk of hepatotoxicity with rifampin and pyrazinamide.

5. **Answer: C**
Because the patient’s renal function is declining, any medications eliminated renally may need to be adjusted. Cycloserine concentrations should be monitored and dose adjusted, if necessary, to maintain serum concentrations below 30 mcg/mL. Moxifloxacin has been associated with CNS adverse effects; however, because of the timing of the adverse effects in conjunction with declining renal function, the adverse effects are more likely to be associated with cycloserine, making Answer C correct and Answers A incorrect. Para-aminosalicylic acid is metabolized in the liver and not renally adjusted (therefore answer D is incorrect). Pyrazinamide is metabolized in the liver; its metabolites can accumulate in renal insufficiency, however, dosage adjustment is not needed unless CrCl is less than 30 ml/min (making Answer B incorrect).

6. **Answer: B**
Drug interactions with rifapentine and many of the antiretrovirals have not been studied. Rifapentine is as potent an inducer, or almost as potent, as rifampin, however, and the potential effect on an antiretroviral used in conjunction with rifapentine is extrapolated. Rifampin reduces dolutegravir’s AUC by 54% and its Cmin by 72%. If used concurrently, dolutegravir should be administered twice daily rather than once daily, making Answer A incorrect. Elvitegravir, a CYP3A substrate, is expected to have its concentrations greatly reduced by rifampin and rifapentine and should not be coadministered, making Answer C incorrect. Although studies have not examined rifapentine’s impact on...
darunavir concentrations, darunavir’s concentrations are significantly decreased by rifampin, and it not recom-
mended (Answer D). Rifapentine once weekly actually increases raltegravir’s AUC by 71% (and decreasing its Cmin by 12%), but raltegravir’s safety profile is not expected to have a significant impact clinically, making Answer B correct.

7. Answer: D
Rifapentine and isoniazid once-weekly regimen is not recom-
mended in patients with HIV because of the increased risk of rifamycin resistance, making Answer A incorrect. Rifabutin (as well as rifampin) is an option for treatment. Rifabutin does decrease concentrations of dolutegravir but only to a small extent. Dolutegravir does not induce rifabutin concentrations, making a 450-mg dose unnecessary (Answer C); nor does dolutegravir inhibit rifabutin concentrations, making a 150-
mg rifabutin dose unnecessary (Answer B). An initial standard dose of 300 mg is therefore recommended (Answer D).

8. Answer: D
The most serious adverse effect associated with ethambutol is optic neuritis. Optic neuritis may affect one or both eyes, causing blurred vision and a decline in visual acuity, and can cause a patient to be unable to detect the colors red and green (Answer D is correct). Rifabutin can cause anterior uveitis, an inflammation of the middle layer in the eye that may also lead to blurred vision. However, the inability to detect green/red is not likely with rifabutin toxicity, making Answer B incorrect. Isoniazid and rifampin are not known to contribute to vision problems, making Answers A and C incorrect.