HIV/Infectious Diseases

Curtis L. Smith, Pharm.D., BCPS, FCCP

Ferris State University
Lansing, Michigan
HIV/Infectious Diseases

Curtis L. Smith, Pharm.D., BCPS, FCCP

Ferris State University
Lansing, Michigan
Learning Objectives

1. Formulate an appropriate regimen to prevent or treat HIV infections, including initiating and monitoring therapy.
2. Discuss appropriate treatment of the various acquired immunodeficiency syndrome opportunistic infections, including primary and secondary prophylaxis.
3. Describe appropriate treatment and preventive therapy for tuberculosis, including infections with drug-resistant organisms.
4. Design appropriate therapeutic regimens for treating systemic and superficial fungal infections and classify the various antifungal agents.

Self-Assessment Questions

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

1. K.E. is a 29-year-old asymptomatic patient who is HIV positive. She recently found out she is pregnant and is estimated to be early in her first trimester. Her most recent CD4 count was 170 cells/mm³, and her viral load was 100,000 copies/mL by reverse transcriptase polymerase chain reaction. Which is the best therapy for K.E. to prevent HIV transmission to her child?
   A. No drug therapy is needed; the risks to the fetus outweigh any benefits.
   B. Administer zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and consequently to the infant for 6 weeks.
   C. No drug therapy is needed now, but administer a single dose of nevirapine at the onset of labor.
   D. Administer a potent combination antiretroviral therapy (ART) regimen.

2. R.E. is a 33-year-old man who recently tested HIV positive. He is initiated on tenofovir alafenamide, emtricitabine, and dolutegravir. Which is the best counseling for R.E.?
   A. Watch for trouble sleeping because dolutegravir can cause insomnia.
   B. If you think you are having a drug-related adverse effect, cut the dose of all of your drugs in half.
   C. Talk to your pharmacist about drug interactions because both dolutegravir and tenofovir inhibit cytochrome P450 (CYP) 3A4.
   D. Tenofovir and emtricitabine cause additive peripheral neuropathy, so let your pharmacist know if you have tingling in your extremities.

3. P.P., a 43-year-old man who is HIV positive, presents to the clinic with a headache that has gradually worsened during the past 2 weeks. He does not feel very sick and has not experienced any focal seizures. His most recent CD4 count was 35 cells/mm³. His laboratory values are as follows: Gram stain negative, white blood cell count 2 cells/mm³, protein 35 mg/dL, glucose 75 mg/dL (peripheral 110 mg/dL), India ink positive, and cryptococcal antigen 1:1024. He is given a diagnosis of cryptococcal meningitis and successfully treated. Which is the best follow-up therapy for P.P.?
   A. No maintenance treatment is necessary.
   B. Administer fluconazole 200 mg/day orally.
   C. Administer amphotericin B 1 mg/kg/week intravenously.
   D. He is protected as long as he is also receiving Pneumocystis jiroveci (formerly carinii) pneumonia (PCP, PJP) prophylaxis.

4. A study compares the incidence of active tuberculosis (TB) infection in patients receiving isoniazid versus rifampin for latent TB infection. After completing therapy (6 months for isoniazid and 4 months for rifampin), 0.3% in the isoniazid group and 0.8% in the rifampin group progress to active disease. Which best represents how many patients would need to be treated with isoniazid over rifampin to prevent one progression to active disease?
   A. 5.
   B. 50.
   C. 200.
   D. Insufficient information to calculate this number.
5. G.T. is a 34-year-old woman positive for HIV who is brought to the emergency department by her boyfriend after experiencing headaches, a change in mental status, and loss of feeling on her right side. A computed tomographic scan shows two large ring-enhancing lesions in her brain indicating toxoplasmic encephalitis. Her most recent CD4 count was 85 cells/mm³, but that was 4 months ago. She currently takes no antiretroviral agents but does take dapsone for PCP prophylaxis. Which is the best therapy for G.T.?
   A. Atovaquone for 4–6 weeks.
   B. High-dose trimethoprim/sulfamethoxazole plus clindamycin for 6 weeks.
   C. Pyrimethamine plus sulfadiazine for 6 weeks.
   D. Pyrimethamine plus clindamycin and leucovorin for 6 weeks.

6. H.Y., a 49-year-old man with acute myeloid leukemia, is given a diagnosis of TB and initiated on empiric therapy with rifampin, isoniazid, ethambutol, and pyrazinamide. Three months into his TB therapy, he is hospitalized and given a diagnosis of aspergillosis; treatment is needed in addition to his TB treatment. Which is the best antifungal to use in H.Y.?
   A. Fluconazole.
   B. Voriconazole.
   C. Isavuconazonium.
   D. Amphotericin lipid formulation.

7. P.I. is a 35-year-old woman who presents to the clinic with a 2-week history of night sweats, fatigue, weight loss, and a persistent cough. A tuberculin skin test (TST) is placed, and a sputum sample is taken; then, P.I. is sent home with a prescription for levofloxacin 750 mg/day orally. Two days later, her TST is measured at 20-mm induration, and her sputum sample is positive for acid-fast bacilli. P.I., who has no pertinent medical history, has never been outside the United States. She lives in an area with an extremely low incidence of multidrug-resistant TB. Which regimen is the best therapy for P.I.?
   A. Isoniazid for 6 months.
   B. Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 more months.

8. A prospective, double-blind study compared the effects of two therapies—a potent combination ART with a ritonavir-boosted protease inhibitor (PI) and a potent combination ART with dolutegravir—in 350 patients with HIV. Which is the best statistical test to use to compare end points such as the mean change in viral load or mean change in CD4 counts?
   A. Analysis of variance.
   B. Chi-square test.
   C. Student t-test.
   D. Wilcoxon rank sum test.

9. J.Z. is a 42-year-old HIV-positive man with a diagnosis of cytomegalovirus (CMV) retinitis 9 months ago. Since then, he has been treated with valganciclovir. When he received a diagnosis of CMV retinitis, his CD4 count was 17 cells/mm³, and he was initiated on combination ART. Three months ago, his CD4 count was 175 cells/mm³. Today, his CD4 count is 312 cells/mm³. Which is the best recommendation for valganciclovir therapy in J.Z.?
   A. Discontinue valganciclovir because his CD4 count has been above 100 cells/mm³ for 3 months.
   B. Continue valganciclovir until the CD4 count has been above 100 cells/mm³ for 1 year.
   C. Finish 1 year of therapy with valganciclovir and then discontinue the medication if his CD4 count is still above 100 cells/mm³.
   D. Continue valganciclovir indefinitely.

10. K.T. is a 55-year-old woman who is hospitalized with a presumed Candida infection. She currently receives simvastatin, diazepam, lisinopril, dofetilide, and metoprolol. Which azole antifungal would be best to use to avoid interactions with the other medications K.T. is receiving?
    A. Itraconazole.
    B. Fluconazole.
    C. Voriconazole.
    D. Isavuconazonium.
11. T.E. is a 51-year-old man who has been HIV positive since 1998. He is hospitalized for cellulitis and reports that he has not taken his ART for at least a year. His current CD4 count is 112 cells/mm$^3$. He is allergic to penicillins and sulfa antibiotics. Which regimen is the best PCP prophylaxis for T.E.?
   A. Trimethoprim/sulfamethoxazole double strength by mouth daily.
   B. Dapsone 100 mg by mouth weekly.
   C. Atovaquone 1500 mg by mouth daily.
   D. Pentamidine 300 mg by nebulization once monthly.

12. O.D. is a 38-year-old HIV positive man originally from Puerto Rico who moved to the continental United States four years ago. He is hospitalized for fever, weight loss, chills, myalgia, and lymphadenopathy. He is initially treated for PCP but his symptoms worsen. A bronchoscopy is performed and the cultures are positive for *Histoplasma capsulatum*. What is the best treatment for O.D.?
   A. Amphotericin B lipid formulation for 1-2 weeks followed by itraconazole 200 mg daily for 12 weeks total.
   B. Micafungin 100 mg IV daily for 1-2 weeks followed by fluconazole 400 mg daily for 12 weeks total.
   C. Voriconazole 200 mg twice daily for 6 weeks total.
   D. Isavuconazole 200 mg every 8 hours for 2 days followed by 200 mg daily for 6 weeks total.

13. R.V. is a 35-year-old man who presents to the emergency department with a persistent cough, night sweats, and an unintentional 15 kg recent weight loss. He has been homeless for over 3 years and has been living at multiple shelters in the city. An interferon-gamma release assay test is positive and his sputum is AFB positive. He is not HIV-infected. Which one of the following would be the best empiric therapy for R.V.?
   A. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin and isoniazid 5 times weekly for 4 months.
   B. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin and isoniazid 5 times weekly for 4 months.
   C. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin, isoniazid, and ethambutol 3 times weekly for 4 months.
   D. Rifampin, isoniazid, pyrazinamide, and ethambutol 5 times weekly for 2 months followed by rifampin, isoniazid, and pyrazinamide 2 times weekly for 4 months.
**BPS Pharmacotherapy Specialty Examination Content Outline**

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. **Domain 1: Patient-Specific Pharmacotherapy**
   a. Task 1: Knowledge statements: 1–7, 11–12, 15; Task 4: Knowledge statements: 2–6
   b. Systems and Patient-Care Problems
      i. Human Immunodeficiency Virus
      ii. Opportunistic Infections in Patients with HIV
      iii. Tuberculosis
      iv. Antifungal Therapy

2. **Domain 2: Retrieval, Generation, Interpretation, and Dissemination of Knowledge in Pharmacotherapy, Task 2: Knowledge Statements: 1–5**
I. HUMAN IMMUNODEFICIENCY VIRUS

A. Transmission of HIV
   1. Sexual transmission
      a. Homosexual or heterosexual
      b. Increases with increased number of sexual partners
      c. Prevention
         i. Latex condom
         ii. Circumcision (males)
         iii. Preexposure prophylaxis (PrEP)
            (a) Use in those who are at substantial risk of acquiring HIV, including anyone in an ongoing relationship with an HIV-positive partner; anyone who is not in a mutually monogamous relationship with an HIV-negative partner and is a homosexual or bisexual man who has had anal sex without a condom or been given a diagnosis of a sexually transmitted disease in the past 6 months or a heterosexual man or woman who does not regularly use condoms during sex with partners of unknown HIV status who are at substantial risk of HIV infection; anyone who has injected illicit drugs in the past 6 months and who has shared injection equipment or been in drug treatment in the past 6 months.
            (b) Document negative HIV antibody.
            (c) Use tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg (Truvada) daily.
            (d) Test every 90 days for HIV antibody (and if prophylaxis is discontinued).
            (e) Check renal function every 6 months with tenofovir.
   2. Parenteral exposure to blood or blood products
      a. Intravenous drug abuser: Increased with increased needle sharing
      b. Hemophiliacs and blood transfusion recipients: Decreased since 1985
   3. Universal precautions (Table 1)
      a. Purpose is prevention of parenteral, mucous membrane, and non-intact skin exposures to bloodborne pathogens.
      b. Bodily fluids

Table 1. Universal Precautions

<table>
<thead>
<tr>
<th>Universal Precautions Apply to:</th>
<th>Universal Precautions Do Not Apply to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Feces</td>
</tr>
<tr>
<td>Bodily fluids containing visible blood</td>
<td>Nasal secretions</td>
</tr>
<tr>
<td>Semen and vaginal secretions</td>
<td>Sputum</td>
</tr>
<tr>
<td>Tissue</td>
<td>Sweat</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>Tears</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>Urine</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>Vomitus</td>
</tr>
<tr>
<td>Peritoneal fluid</td>
<td>Breast milk</td>
</tr>
<tr>
<td>Pericardial fluid</td>
<td>Saliva (precautions recommended for dentistry)</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td></td>
</tr>
</tbody>
</table>
c. General guidelines
   i. Take care when using and disposing of needles, scalpels, and other sharp instruments.
   ii. Use protective barriers (e.g., gloves, masks, and protective eyewear).
   iii. Wash hands and skin immediately if they are contaminated with body fluids to which universal precautions apply.
4. Perinatal transmission
   a. Antepartum: Through maternal circulation
   b. During delivery
   c. Postpartum: Breastfeeding
   d. Zidovudine therapy decreases risk of transmission from 23% to 3%–4% (less than 2% with combination therapy).

B. Diagnosis
   1. Step 1
      a. Fourth-generation HIV test
      b. Positive: 2–3 weeks after the infection
      c. Negative tests require no further testing; positive tests proceed to step 2.
      d. Sensitivity and specificity: Greater than 99%
      e. Fourth-generation tests: Abbott Architect HIV Ag/Ab Combo Assay; Bio-Rad GS HIV Combo Ag/Ab EIA
   2. Step 2
      a. HIV test that differentiates HIV-1 from HIV-2
      b. If positive: Diagnosis made
      c. If negative or indeterminate: Proceed to step 3
      d. Sensitivity and specificity: Greater than 99%
      e. Multispot HIV-1/HIV-2 Rapid Test
   3. Step 3
      a. HIV-1 nucleic acid amplification test (screening for HIV-1 RNA)
      b. If positive: Diagnosis made
      c. If negative: Negative for HIV-1
      d. HIV-1 NAT tests: APTIMA HIV-1 RNA Qualitative Assay; Procleix Ulitrio
   4. Test for HIV RNA (viral load)
      a. Detects HIV RNA in serum (tests for the virus, not for antibodies)
      b. Branched-chain DNA, Versant (Siemens)
         i. Signal amplification
         ii. Sensitive to 75 copies/mL of HIV RNA
      c. Reverse transcriptase polymerase chain reaction, Amplicor HIV-1 Monitor (Roche) or Abbott RealTime HIV-1 (Abbott): Sensitive to 50 copies/mL of HIV RNA
      d. Nucleic acid sequence–based amplification, NucliSens (bioMérieux): Sensitive to 40 copies/mL of HIV RNA
      e. Values expressed as copies of HIV RNA per milliliter or the log of copies of HIV RNA per milliliter
      f. Viral suppression, defined as HIV RNA below the level of detection (HIV RNA less than 20 copies/mL to 75 copies/mL), is the goal of treatment.
      g. While on treatment, changes greater than 3-fold (about 0.5 log) are statistically significant.
5. Use of HIV RNA testing (viral load)
   a. Most important use of the viral load is to monitor the effectiveness of therapy after initiation of antiretroviral therapy (ART).
   b. Newly diagnosed HIV infection (for baseline value to follow)
   c. Every 3–6 months without therapy
   d. From 2 to 4 (no more than 8) weeks after starting or changing therapy (should detect a significant decrease)
   e. Every 3–4 months while on therapy (checking for increase—therapy failure). May consider extension to every 6 months in patients on therapy and suppressed greater than 2 years with immune stability
   f. Whenever there is a clinical event or decrease in CD4 count

6. CD4 T-cell count
   a. Measure of immune function, used to determine the timing of ART, opportunistic infection prophylaxis, disease progression, and survival
   b. Normal values: 500–1300 cells/mm³
   c. Changes greater than 30% in CD4 counts are considered clinically significant.
   d. CD4 counts decrease, on average, 50–80 cells/mm³ per year in untreated HIV-infected patients.
   e. With potent combination ART, CD4 counts increase, on average, 50–100 cells/mm³ per year.
   f. Monitor at diagnosis (baseline), after ART is started to guide discontinuation of opportunistic infection prophylaxis, every 12 months for those consistently on therapy and with CD4 counts between 300 and 500 cells/mm³ for at least 2 years, and optional if CD4 is greater than 500 cells/mm³ in those virologically suppressed for at least 2 years. More frequent monitoring (every 3–6 months) may be needed based on clinical symptoms and viral load testing.

7. Who should be screened for HIV?
   a. All patients 13–64 years of age (in all health care settings)
   b. Adults and adolescents at high risk of HIV infection should be checked annually (intravenous drug users, those who have unprotected sex with several partners, men who have sex with men, men or women who have sex for money or drugs, people being treated for sexually transmitted diseases, recipients of several blood transfusions 1975–1985)
   c. Pregnant women

8. AIDS-defining conditions (Table 2)

### Table 2. AIDS-Defining Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infections, multiple or recurrent (&lt; 6 yr)</td>
<td></td>
</tr>
<tr>
<td>Candidiasis: bronchi, trachea, or lungs</td>
<td></td>
</tr>
<tr>
<td>Candidiasis: esophageal</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer: invasive (≥ 6 yr)</td>
<td></td>
</tr>
<tr>
<td>Coccidioidomycosis: disseminated or extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>Cryptococcosis: extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>Cryptosporidiosis: chronic intestinal (&gt; 1 mo in duration)</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus disease (other than liver, spleen, or nodes)</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus retinitis (with loss of vision)</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy: HIV related</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex: chronic ulcer(s) (&gt; 1 mo in duration); bronchitis, pneumonitis, or esophagitis</td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis: disseminated or extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>Isosporiasis: chronic intestinal (&gt; 1 mo in duration)</td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td></td>
</tr>
</tbody>
</table>

Lymphoma: Burkitt (or equivalent term)  
Lymphoma: immunoblastic (or equivalent term)  
Lymphoma: primary, of brain  
Mycobacterium avium complex or M. kansasii: disseminated or extrapulmonary  
M. tuberculosis: any site (pulmonary, disseminated, or extrapulmonary)  
Mycobacterium: other species or unidentified species; disseminated or extrapulmonary  
Pneumocystis jiroveci pneumonia  
Pneumonia: recurrent  
Progressive multifocal leukoencephalopathy  
Salmonella septicemia (recurrent)  
Toxoplasmosis of brain  
Wasting syndrome caused by HIV
C. Treatment of HIV

1. Reverse transcriptase inhibitors (RTIs) (nucleoside [NRTIs], nucleotide, and nonnucleoside [NNRTIs])
   a. Reverse transcriptase: Enzyme needed to copy viral RNA to DNA
   b. See Tables 3 and 4 for RTI characteristics.

2. Protease inhibitors (PIs)
   a. Protease: Enzyme needed to cleave polyproteins into mature viral protein components
   b. See Table 5 for PI characteristics.

3. Integrase inhibitors (INSTIs) (Table 6)
   a. Integrase: Enzyme needed for integration of viral DNA into the host cellular genome
   b. See Table 6 for INSTI characteristics.

4. Entry and post-attachment inhibitors (Table 7)
   a. Block binding and/or entry of the virus into human cells
   b. See Table 7 for entry and post-attachment inhibitor characteristics.

5. Prevention of maternal-fetal transmission
   a. Pregnant women with HIV receiving no ART
      i. All HIV-infected pregnant women should receive combination ART; initiate therapy as soon as possible, even in the first trimester.
      ii. Preferred regimens for HIV-infected pregnant women include a dual NRTI combination (abacavir/lamivudine, or tenofovir disoproxil fumarate/emtricitabine or lamivudine) and either a ritonavir-boosted PI (atazanavir/ritonavir or darunavir/ritonavir) or an INSTI (raltegravir).
      iii. All women should have HIV antiretroviral resistance testing completed before starting therapy.
      iv. Continue combination regimen through intrapartum period.
   b. Pregnant women with HIV receiving potent combination ART
      i. Continue current combination regimens if already receiving therapy. Consider replacing elvitegravir/cobicistat with raltegravir or a preferred PI combination. Avoid using dolutegravir in the first 8 weeks of pregnancy because of the risk of neural tube defects.
      ii. Continue combination regimen through intrapartum period.
   c. Pregnant women with HIV in labor (with or without therapy during pregnancy)
      i. Intravenous zidovudine should be administered to HIV-infected women with HIV RNA greater than 1000 copies/mL (or unknown HIV RNA) near delivery (consider also giving to women with HIV RNA levels between 50 and 1000 copies/mL). Intravenous zidovudine is not necessary for HIV-infected women who have HIV RNA of 50 copies/mL or less during late pregnancy and near delivery and no concerns about adherence to the cART regimen.
      ii. Continue combination ART as much as possible during labor.
   d. Infants born to mothers who are HIV positive
      i. Low risk of perinatal HIV transmission: Zidovudine 4-mg/kg/dose every 12 hours for 4 weeks, initiated within 6–12 hours of delivery
      ii. Higher risk of perinatal transmission or presumed HIV exposure: Zidovudine for 6 weeks (see dose above) plus nevirapine 8–12 mg/dose (based on weight) at birth, 48 hours later, and 96 hours after second dose OR triple ARV therapy with zidovudine, lamivudine, and nevirapine.

6. Prevention of postexposure infection
   a. Use universal precautions.
   b. Nonoccupational exposures: Treat if exposure of vagina, rectum, eye, mouth, mucous membrane, or non-intact skin with blood, semen, vaginal secretions, or breast milk of a person with a known HIV infection.
   c. Occupational exposures: Needlesticks or cuts (1 in 300 risk) and mucous membrane exposure (1 in 1000 risk)
   d. Postexposure prophylaxis can reduce HIV infection by about 80%.
e. Nonoccupational exposures: Begin within 72 hours.
f. Occupational exposures: Begin treatment within hours; if HIV status of source patient is unknown, start treatment while status is being evaluated.
g. Treatment should be administered for 4 weeks.
h. Recommended therapy for nonoccupational exposure is potent combination ART.
   i. Preferred regimen: Raltegravir twice daily or dolutegravir daily plus tenofovir/emtricitabine daily (do not use dolutegravir in women who are potentially pregnant or are early in their pregnancy).
   ii. Alternative regimen: Darunavir/ritonavir daily plus tenofovir/emtricitabine daily

Regimens for occupational postexposure prophylaxis

   i. Preferred regimen: Raltegravir twice daily plus tenofovir/emtricitabine
   ii. Alternative regimens
       (a) One of the following agents: Raltegravir, darunavir/ritonavir, etravirine, rilpivirine, atazanavir/ritonavir, or lopinavir/ritonavir plus one of the following combinations: tenofovir/emtricitabine, tenofovir/lamivudine, zidovudine/lamivudine, or zidovudine/emtricitabine
       (b) Elvitegravir, cobicistat, tenofovir, emtricitabine (Stribild)
### Table 3. Nucleoside and Nucleotide RTIs

<table>
<thead>
<tr>
<th></th>
<th>Abacavir (ABC) (Ziagen, Epzicom, Trizivir, Triumeq)</th>
<th>Emtricitabine (FTC) (Emtriva, Truvada, Atripla, Complera, Striibrid, Genovya)</th>
<th>Lamivudine (3TC) (Epivir, Compriva, Epzicom, Trizivir, Triumeq)</th>
<th>Zidovudine (ZDV) (AZT, Retrovir, Compriva, Trizivir)</th>
<th>Tenofovir Disoproxil Fumarate (TDF) (Viread, Truvada, Atripla, Compriva, Striibrid)</th>
<th>Tenofovir Alafenamide (TAF) (Vemlidy, Descovy, Genovya, Odefsey)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
<td>300-mg tablets</td>
<td>200-mg capsules</td>
<td>150-, 300-mg tablets</td>
<td>100-mg capsules, 300-mg tablets</td>
<td>300-mg tablets</td>
<td>25-mg tablets</td>
</tr>
<tr>
<td></td>
<td>20 mg/mL liquid</td>
<td>10 mg/mL liquid</td>
<td>10 mg/mL liquid</td>
<td>200 mg FTC/300 mg TDF</td>
<td>Truvada: 200 mg FTC/300 mg TDF</td>
<td>Descovy: 200 mg FTC/25 mg TAF</td>
</tr>
<tr>
<td></td>
<td>Trizivir: 300 mg of ABC/150 mg of 3TC/300 mg of ZDV</td>
<td>Truvada: 200 mg of FTC/300 mg TDF</td>
<td>Atripla: 150 mg of ABC/300 mg of ZDV</td>
<td>Atripla: 200 mg FTC/300 mg TDF</td>
<td>Atripla (see Efavirenz)</td>
<td>Genovya (see Elvitegravir)</td>
</tr>
<tr>
<td></td>
<td>Triumeq: 600 mg of ABC/50 mg of DTG, 300 mg of 3TC</td>
<td>Epzicom: 300 mg of ABC/50 mg of DTG</td>
<td>Comblera (see Rilpivirine)</td>
<td>Epzicom: 300 mg of ABC/50 mg of ZDV</td>
<td>Comblera (see Rilpivirine)</td>
<td>Genovya (see Elvitegravir)</td>
</tr>
<tr>
<td></td>
<td>Epzicom (see Lamivudine)</td>
<td>Striibrid: 300 mg of ABC/150 mg of 3TC/300 mg of ZDV</td>
<td>Striibrid (see Elvitegravir)</td>
<td>Striibrid (see Elvitegravir)</td>
<td>Striibrid (see Elvitegravir)</td>
<td>Biktarvy (see Bictegravir)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>300 mg BID or 600 mg/day</td>
<td>200 mg/day or 240 mg liquid/day</td>
<td>150 mg BID or 300 mg/day &lt; 50 kg: 4 mg/kg BID</td>
<td>200 mg TID or 300 mg BID</td>
<td>TDF: 300 mg PO daily</td>
<td>TAF: 25 mg PO daily, 10 mg PO daily with cobicistat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>82%</td>
<td>93%</td>
<td>86%</td>
<td>60%</td>
<td>40%</td>
<td>Take with food</td>
</tr>
<tr>
<td>Serum half-life</td>
<td>1.5 hr</td>
<td>10 hr</td>
<td>5–7 hr</td>
<td>1.1 hr</td>
<td>10–14 hr</td>
<td>Take with food</td>
</tr>
<tr>
<td>Intraocular half-life</td>
<td>12–26 hr</td>
<td>&gt; 20 hr</td>
<td>18–22 hr</td>
<td>7 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination</td>
<td>Metabolized by alcohol dehydrogenase and glucuronyl transferase</td>
<td>Renal excretion (86%)</td>
<td>Renally excreted unchanged (70%)</td>
<td>Metabolized to ZDV glucuronide (GZDV)</td>
<td>Renal excretion of GZDV</td>
<td>Eliminated primarily in urine and feces.</td>
</tr>
<tr>
<td>Major toxicity</td>
<td>Hypersensitivity, fever, rash, GI symptoms, malaise, fatigue, anorexia, and myocardial infarction</td>
<td>Diarrhea, nausea, headache, rash, and hyperpigmentation</td>
<td>Diarrhea, nausea, abdominal pain, insomnia, and headaches (minimal toxicity)</td>
<td>Bone marrow suppression, GI intolerance, headache, insomnia, asthenia, nail pigmentation, and myalgia</td>
<td>GL toxicity Headache Loss of bone mineral density Renal toxicity</td>
<td>GI toxicity Headache Less effects on bone mineral density and renal function</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Ethanol may increase ABC concentrations</td>
<td>TMP/SMZ may increase 3TC concentrations</td>
<td>Methylsulfamaglycylate P-glycoprotein substrate</td>
<td>P-glycoprotein substrate</td>
<td>Rifaximin, Rifaxabtin, Rifampicin P-glycoprotein substrate</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous information</td>
<td>Hypersensitivity reaction may be fatal; discontinue drug immediately Screen for HLA-B*5701 before initiation; cross-resistance with ddl and 3TC</td>
<td>Activity in resting macrophages Avoid combination products (Atripla, Complera, and Striibrid in renal dysfunction, and use appropriately adjusted individual agents instead</td>
<td>Resistance develops quickly with monotherapy Activity in resting macrophages</td>
<td>Activity in activated lymphocytes</td>
<td>More favorable effects on lipids than TAF.</td>
<td>Produg of tenofovir More favorable effects on markers of bone and renal health than TDF.</td>
</tr>
</tbody>
</table>

*a Dosage adjustment in hepatic insufficiency.

*b Dosage adjustment in renal insufficiency.

*c Dosage adjustment/avoid use in renal insufficiency: TDF: < 50–70 mL/min; TAF: < 30 mL/min.

AZT = azidothymidine (zidovudine); BID = twice daily; ddl = didanosine; DTG = dolutegravir; GI = gastrointestinal; PO = orally; RTI = reverse transcriptase inhibitor; TID = three times daily; TMP/SMZ = trimethoprim/sulfamethoxazole.
<table>
<thead>
<tr>
<th>RTI type</th>
<th>Doravirine (DOR) (Pifeltro, Delstrigo)</th>
<th>Efavirenz (EFV) (Sustiva, Atripla)</th>
<th>Etravirine (ETR) (Intence)</th>
<th>Nevirapine (NVP) (Viramune, Viramune XR)</th>
<th>Rilpivirine (RPV) (Edurant, Complera, Odefsey)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
<td>100-mg tablets Delstrigo: 300 mg 3TC/ 300 mg TDF/doravirine 100 mg</td>
<td>50-, 200-mg capsules 600-mg tablets Atripla: 200 mg of FTC/300 mg of TDF/ efavirenz 600 mg</td>
<td>100-, 200-mg tablets</td>
<td>200-mg tablets 400-mg XR tablets 50 mg/5 mL suspension</td>
<td>25-mg tablets Complera: 200 mg FTC/300 mg TDF/rilpivirine 25 mg Odefsey: 200 mg FTC/25 mg TAF, rilpivirine 25 mg</td>
</tr>
<tr>
<td>Dosing</td>
<td>100 mg PO daily</td>
<td>400–600 mg PO qHS</td>
<td>200 mg PO BID</td>
<td>200 mg/day for 14 days, then 200 mg PO BID or 400 mg PO daily (XR)*</td>
<td>25 mg PO daily</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>64% Take with or without food</td>
<td>42% Avoid with high-fat meal</td>
<td>Take with food</td>
<td>&gt; 90% Take with food</td>
<td></td>
</tr>
<tr>
<td>Serum half-life</td>
<td>15 hr</td>
<td>40–55 hr</td>
<td>41 hr</td>
<td>25–30 hr</td>
<td>50 hr</td>
</tr>
<tr>
<td>Elimination</td>
<td>Metabolized by CYP3A4, 6% excreted in urine</td>
<td>Metabolized by CYP3A4, 14%–34% excreted in urine, 16%–61% in feces</td>
<td>Metabolized by CYP3A4, CYP2C9, CYP2C19</td>
<td>Metabolized by CYP3A4; 80% excreted in urine (&lt; 5% unchanged), 10% in feces</td>
<td>Metabolized by CYP3A4</td>
</tr>
<tr>
<td>Major toxicity</td>
<td>Rash Nausea, diarrhea, abdominal pain Headache CNS symptoms (fatigue, dizziness, insomnia, abnormal dreams, somnolence)</td>
<td>Rash (less than delavirdine) CNS symptoms (insomnia, impaired concentration, nightmares, mania) Elevated LFTs</td>
<td>Rash Nausea Hypersensitivity reaction</td>
<td>Rash GI toxicity Elevated LFTs; hepatotoxicity</td>
<td>Rash Depression Insomnia Headache</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Avoid CYP3A inducers</td>
<td>Induces CYP3A4 and CYP2B6</td>
<td>Induces CYP3A4 Inhibits CYP2C9 and CYP2C19</td>
<td>Induces CYP3A4 Watch rifampin, rifabutin, OCs, protease inhibitors, triazolam, midazolam</td>
<td>PPIs (contraindicated), H₂-blockers, antacids</td>
</tr>
</tbody>
</table>

*Dosage adjustment in hepatic insufficiency.

CNS = central nervous system; CYP = cytochrome P450; ddI = didanosine; FTC = emtricitabine; LFT = liver function test; OC = oral contraceptive; PO = orally; PPI = proton pump inhibitor; qHS = every night; XR = extended release.
### Table 5. Protease Inhibitors

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
<td>100-, 150-, 200-, 300-mg capsules Evotaz: 300 mg/cobicistat (COBI) 150-mg tablets</td>
<td>75-, 150-, 300-, 400-, 600-mg tablets Prezobix: 800-mg/COBI 150-mg tablets</td>
<td>700-mg tablets; 50-mg/mL liquid; prodrug of amprenavir</td>
<td>100/25-, 200/50-mg tablets; 80/20-mg/mL liquid</td>
<td>100-mg tablets; capsules; 80-mg/mL liquid</td>
<td>Refrigerated capsules</td>
<td>200-mg capsules; 500-mg tablets</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>400 mg/day(^b) ATV 400 mg + RTV 100 mg daily If taken without efavirenz: ATV 300 mg + RTV 100 mg daily ATV 300 mg + COBI 150 mg daily</td>
<td>800 mg/day with RTV 100 mg daily or 600 mg BID with RTV 100 mg BID(^d) DRV 800 mg + COBI 150 mg daily</td>
<td>1400 mg BID or 1400 mg + RTV 100–200 mg/day or 700 mg + RTV 100 mg BID With efavirenz: 700 mg + RTV 100 mg BID(^d)</td>
<td>400/100 mg BID or 800/200 mg/day with food If taking efavirenz or nevirapine: 500 mg/125 mg BID</td>
<td>&quot;Boosting dose&quot; = 100–400 mg divided once or twice daily</td>
<td>1000 mg BID with ritonavir 100 mg; take within 2 hr of a meal(^f)</td>
<td>500 mg BID with RTV 200 mg BID(^g)</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>Food increases absorption and bioavailability; take with food</td>
<td>Food increases absorption and bioavailability; take with food</td>
<td>Take without respect to food (take with food if given with ritonavir)</td>
<td>Take solution with food; take tablets without respect to food</td>
<td>65%–75%; take with food</td>
<td>Take with food</td>
<td>Take without respect to food (take with food if given with ritonavir)</td>
</tr>
<tr>
<td>Serum half-life</td>
<td>7 hr</td>
<td>15 hr</td>
<td>7 hr</td>
<td>56 hr</td>
<td>35 hr</td>
<td>12 hr</td>
<td>6 hr</td>
</tr>
<tr>
<td>Elimination</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4 &gt; CYP2D6 &gt; CYP2C9/10</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Major toxicity</td>
<td>Indirect hyperbilirubinemia rash, elevated transaminases, prolonged PR interval and heart block, endocrine disturbances(^c)</td>
<td>Rash (sulfa); hepatotoxicity; endocrine disturbances(^c)</td>
<td>Rash; GI intolerance; oral paresthesias; elevated LFTs; endocrine disturbances(^c)</td>
<td>GI intolerance; fatigue; asthenia; pancreatitis; PR and QTc prolongation; endocrine disturbances(^c)</td>
<td>GI intolerance; pancreatitis (circumoral and extremities); taste disturbances; asthenia; endocrine disturbances(^c)</td>
<td>GI intolerance (mild); PR and QT prolongation; endocrine disturbances(^c)</td>
<td>Hepatotoxicity; rash (sulfa); intracranial hemorrhage; endocrine disturbances(^c)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Inhibits CYP3A4, PPIs, H(_2)-blockers, antacids</td>
<td>Inhibits CYP3A4 (^&lt;)RTV(^b)</td>
<td>Inhibits CYP3A4, CYP2D6 (^&lt;)RTV(^b)</td>
<td>Inhibits CYP3A4, CYP2D6 (^&lt;)RTV(^b)</td>
<td>Inhibits CYP3A4, CYP2D6 (^&lt;)RTV(^b)</td>
<td>Inhibits CYP3A4, CYP2D6 (^&lt;)RTV(^b)</td>
<td>Inhibits CYP3A4, CYP2D6</td>
</tr>
<tr>
<td>Miscellaneous information</td>
<td>Less lipid effects</td>
<td>Good for PI-resistant virus</td>
<td>Cross-resistance with IDV</td>
<td>Do not use with IDV</td>
<td>Good for PI-resistant virus; must give with RTV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Dosage adjustment in hepatic insufficiency.
\(^b\)Dosage adjustment in renal insufficiency.
\(^c\)Endocrine disturbances include insulin resistance (type 2 diabetes in 8%–10%), peripheral fat loss and central fat accumulation (in 50%), and lipid abnormalities (in 70%).

IDV = Indinavir; PI = protease inhibitor
### Table 6. Integrase Strand Transfer Inhibitors – INSTIs

<table>
<thead>
<tr>
<th></th>
<th>Bictegravir (BIC) (Biktarvy)</th>
<th>Dolutegravir (DTG) (Tivicay, Triumeq)</th>
<th>Elvitegravir (EVG) (Stribild, Genvoya)</th>
<th>Raltegravir (RAL) (Isentress Isentress HD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
<td>Biktarvy: Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg</td>
<td>50-mg tablets Triumeq: 600 mg of ABC, 50 mg of DTG, 300 mg of 3TC</td>
<td>Stribild: Elvitegravir 150 mg/cobicistat 150 mg/tenofovir 300 mg emtricitabine 200 mg a</td>
<td>25-, 100-, 400-mg tablets; Isentress HD: 600-mg tablets</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>50 mg PO once daily</td>
<td>50 mg PO once daily</td>
<td>Stribild: once daily Vitekta: once daily; dose depends on combination Genvoya: once daily</td>
<td>400 mg PO BID; Isentress HD: 1200 mg PO daily</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Metabolized by CYP3A and glucuronidation by UGT1A1</td>
<td>Metabolized by glucuronidation by UGT1A1/3 enzymes and by CYP3A</td>
<td>Metabolized by CYP3A and glucuronidation by UGT1A1/3 enzymes Cobicistat is metabolized by CYP3A and CYP2D6</td>
<td>Metabolized by hepatic glucuronidation by uridine 5’-diphospho-glucuronosyltransferase</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>50 mg PO once daily</td>
<td>50 mg PO once daily</td>
<td>Stribild: once daily Vitekta: once daily; dose depends on combination Genvoya: once daily</td>
<td>400 mg PO BID; Isentress HD: 1200 mg PO daily</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>Take with or without food</td>
<td>Take with or without food</td>
<td>Food increases absorption and bioavailability Take with food</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Serum half-life</strong></td>
<td>18 hr</td>
<td>14 hr</td>
<td>13 hr</td>
<td>9 hr</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Metabolized by CYP3A and glucuronidation by UGT1A1</td>
<td>Metabolized by glucuronidation by UGT1A1/3 enzymes and by CYP3A</td>
<td>Metabolized by CYP3A and glucuronidation by UGT1A1/3 enzymes Cobicistat is metabolized by CYP3A and CYP2D6</td>
<td>Metabolized by hepatic glucuronidation by uridine 5’-diphospho-glucuronosyltransferase</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Watch CYP3A and UGT1A1 inducers and inhibitors. Avoid rifampin, other rifamycins, St. John’s Wort and certain anticonvulsants. Contraindicated with doxetilide</td>
<td>Inhibitors and inducers of UGT1A3, UGT1A9, BCRP, and P-glycoprotein</td>
<td>Monitor closely if used with CYP3A inducers or inhibitors</td>
<td>Inducers of UGT1A1: rifampin, efavirenz, tipranavir/ritonavir</td>
</tr>
<tr>
<td><strong>Major toxicity</strong></td>
<td>Insomnia and diarrhea; Benign increases in creatinine and bilirubin</td>
<td>Insomnia and diarrhea Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)</td>
<td>Insomnia Cobi: Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)</td>
<td>Nausea, headache, diarrhea, pyrexia, creatine kinase elevation, insomnia</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Watch CYP3A and UGT1A1 inducers and inhibitors. Avoid rifampin, other rifamycins, St. John’s Wort and certain anticonvulsants. Contraindicated with doxetilide</td>
<td>Inhibitors and inducers of UGT1A3, UGT1A9, BCRP, and P-glycoprotein</td>
<td>Monitor closely if used with CYP3A inducers or inhibitors</td>
<td>Inducers of UGT1A1: rifampin, efavirenz, tipranavir/ritonavir</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Inhibits strand transfer of viral DNA to host cell DNA by the integrase enzyme</td>
<td>Inhibits strand transfer of viral DNA to host cell DNA by the integrase enzyme</td>
<td>Inhibits strand transfer of viral DNA to host cell DNA by the integrase enzyme Cobicistat is a potent CYP3A inhibitor used for pharmacokinetic enhancement; also inhibits tubular secretion of creatinine</td>
<td>Inhibits strand transfer of viral DNA to host cell DNA by the integrase enzyme</td>
</tr>
</tbody>
</table>

*aDosage adjustment in renal insufficiency.

3TC = lamivudine; ABC = abacavir; gp = glycoprotein; INSTI = integrase inhibitor; PO = orally
**Table 7.** Entry Inhibitors

<table>
<thead>
<tr>
<th>Class</th>
<th>Enfuvirtide (Fuzeon)</th>
<th>Ibalizumab (Trogarzo)</th>
<th>Maraviroc (MVC) (Selzentry)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
<td>90-mg vials</td>
<td>200-mg vials</td>
<td>150-, 300-mg tablets</td>
</tr>
<tr>
<td>Dosing</td>
<td>90 mg SC BID</td>
<td>2000 mg IV x1 followed by 800 mg IV every 2 weeks</td>
<td>150–600 mg PO BID (depending on concomitant drug interactions)*</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>N/A</td>
<td>N/A</td>
<td>23%–33%</td>
</tr>
<tr>
<td>Serum half-life</td>
<td>3.8 hr</td>
<td>64 hr</td>
<td>14–18 hr</td>
</tr>
<tr>
<td>Elimination</td>
<td>Metabolized by hydrolysis</td>
<td>Metabolized by CYP3A</td>
<td></td>
</tr>
<tr>
<td>Major toxicity</td>
<td>Hypersensitivity reactions; local injection site reactions (98%); pneumonia</td>
<td>Diarrhea, dizziness, nausea, rash Elevations in bilirubin, creatinine, glucose, lipase Blood dyscrasias</td>
<td>Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>None</td>
<td>None</td>
<td>CYP3A substrate (watch CYP3A inducers and inhibitors)</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Attachment of gp120 to CD4 receptor and coreceptors CCR5 or CXCR4 results in exposure of the specific peptide sequence of gp41; enfuvirtide binds to this gp41 peptide sequence, preventing fusion</td>
<td>Blocks HIV from binding to the CCR5 and CXCR4 co-receptors after HIV binds to the CD4 receptor</td>
<td>Binds to the CCR5 receptor of the CD4 T cell, preventing fusion and HIV entry</td>
</tr>
</tbody>
</table>

*aDosage adjustment in renal insufficiency.

gp = glycoprotein; N/A = not applicable; PO = orally; SC = subcutaneously.

**Patient Case**

1. F.G. is a 27-year-old man who is HIV positive but asymptomatic. His CD4 count is 550 cells/mm³, and his viral load is 5000 copies/mL by reverse transcriptase polymerase chain reaction. Which is the best treatment for F.G.?

   A. ART should not be given because his CD4 count is still above 500 cells/mm³.
   B. Initiate emtricitabine/tenofovir only because his CD4 count is still above 500 cells/mm³.
   C. Initiate combination therapy of abacavir, lamivudine, and atazanavir/ritonavir.
   D. Initiate combination therapy of tenofovir, emtricitabine, and raltegravir.

7. Treatment of the patient who is HIV positive
   a. Guidelines recommend HIV treatment for all infected patients, regardless of CD4 count (AI).
   b. Recommended initial regimens for most patients with HIV: The optimal ART for a treatment-naïve patient consists of two NRTIs in combination with an INSTI.
      i. Bictegravir/tenofovir alafenamide/emtricitabine
      ii. Dolutegravir/abacavir/lamivudine; only for patients who are HLA-B*5701 negative
      iii. Dolutegravir plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine
      iv. Raltegravir plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine
c. Recommended initial regimens in certain clinical situations:

i. NNRTI-based regimens

(a) Doravirine/tenofovir disoproxil fumarate/lamivudine or doravirine plus tenofovir alafenamide/emtricitabine

(b) Efavirenz/tenofovir disoproxil fumarate/emtricitabine

(c) Efavirenz plus tenofovir alafenamide/emtricitabine

(d) Rilpivirine/tenofovir disoproxil fumarate/emtricitabine or rilpivirine/tenofovir alafenamide/emtricitabine; only for patients with viral load less than 100,000 copies/mL and CD4 count greater than 200 cells/mm$^3$

ii. PI-based regimens

(a) Atazanavir/ritonavir or Atazanavir/cobicistat plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine; if TDF, not recommended for CrCl less than 70 mL/minute/1.73 m$^2$

(b) Darunavir/ritonavir or darunavir/cobicistat plus abacavir/lamivudine; only for patients who are HLA-B*5701 negative

(c) Darunavir/ritonavir or darunavir/cobicistat plus tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine; if TDF, not recommended for CrCl less than 70 mL/minute/1.73 m$^2$

iii. INSTI-based regimens:

(a) Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine or elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; only for patients with pre-ART CrCl greater than 70 mL/minute/1.73 m$^2$ if using tenofovir disoproxil fumarate or greater than 30 mL/minute/1.73 m$^2$ if using tenofovir alafenamide

(b) Raltegravir plus abacavir/lamivudine; only for patients who are HLA-B*5701 negative with a viral load less than 100,000 copies/mL

iv. Regimens to consider when ABC, TAF and TDF cannot be used:

(a) Dolutegravir plus lamivudine

(b) Darunavir/ritonavir plus raltegravir (only if HIV RNA less than 100,000 copies/mL and CD4 greater than 200/mm$^3$);

(c) Darunavir/ritonavir plus lamivudine

---

**Patient Case**

2. Six months after F.G. (from patient case 1) starts appropriate therapy, his CD4 count is 720 cells/mm$^3$, and his viral load is undetectable. Two years later, his CD4 count decreases to 310 cells/mm$^3$, and his viral load is 15,000 copies/mL. Resistance testing detects resistance to raltegravir. His HIV regimen is changed to abacavir, lamivudine, and darunavir/ritonavir. Which of the following tests must be performed before starting abacavir?

A. Liver function tests because of the risk of hepatotoxicity.

B. HLA-B*5701 allele screening because of the risk of a serious hypersensitivity reaction.

C. Hemoglobin A1C and a lipid panel because of the risk of endocrine disturbances.

D. Bilirubin because of the risk of hyperbilirubinemia.
II. OPPORTUNISTIC INFECTIONS: PATIENTS WITH HIV

![Graph showing the relationship between CD4 count and risk of HIV-related opportunistic infections.](image)

Figure 1. Relationship between CD4 count and risk of HIV-related opportunistic infections.

MAI = *Mycobacterium avium-intracellularare*.

### Patient Cases

3. Three years later, F.G. (from patient cases 1–2) has not responded to any of his ART regimens because of resistance or intolerance. His CD4 count has decreased to 135 cells/mm$^3$. For which infection is it most important that F.G. receive primary prophylaxis?
   - A. *Pneumocystis jiroveci* pneumonia (PCP, PJP).
   - B. Cryptococcal meningitis.
   - C. Cytomegalovirus (CMV).
   - D. *Mycobacterium avium* complex (MAC).

4. B.L. is a 44-year-old HIV-positive man who arrives at the emergency department severely short of breath. He is an extremely nonadherent patient and has not seen a health care provider in more than 3 years. A chest radiograph shows pulmonary infiltrates in both lung fields. The results of the laboratory tests are as follows: sodium 147 mEq/L, potassium 4.2 mEq/L, chloride 104 mEq/L, bicarbonate 25.2 mEq/L, glucose 107 mg/dL, blood urea nitrogen 38 mg/dL, serum creatinine 1.1 mg/dL, aspartate aminotransferase 28 IU/L, alanine aminotransferase 32 IU/L, lactate dehydrogenase 386 IU/L, alkaline phosphate 75 IU/L, pH 7.45, $P_{CO_2}$ 63 mm Hg, $P_{O_2}$ 32 mm Hg, and oxygen saturation 85%. His CD4 count is 98 cells/mm$^3$. Sputum Gram stain is negative, as is silver stain. Which is the best therapy for B.L.?
   - A. Pentamidine intravenously with adjuvant prednisone therapy for 21 days.
   - B. Trimethoprim/sulfamethoxazole orally for 21 days.
   - C. Trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days.
   - D. Atovaquone orally for 21 days.
A. Initiating Potent Combination ART in the Setting of Acute Opportunistic Infections


2. ART should begin within 2 weeks of acute opportunistic infections, except for tuberculosis (TB), in which therapy should begin within 2 weeks when the CD4 count is less than 50 cells/mm³ and by 8–12 weeks for all others, and cryptococcal meningitis, in which therapy should begin 5 weeks after diagnosis.

B. *Pneumocystis jiroveci* (formerly *carinii*) Pneumonia (PCP, PJP)

1. **Clinical presentation**
   a. Fever, shortness of breath, and nonproductive cough
   b. Elevated lactate dehydrogenase
   c. Diffuse pulmonary infiltrates
   d. In general, with CD4 counts less than 200 cells/mm³
   e. Hypoxemia with elevated alveolar-arterial (A-a) gradient and decreased $P_{O_2}$; A-a gradient = $150 - P_{O_2} - P_{CO_2}$

2. **Diagnosis**
   a. Induced sputum or bronchoalveolar lavage or transbronchial biopsy
   b. Methenamine silver stain of sputum sample

3. **Therapy**
   a. Trimethoprim/sulfamethoxazole (preferred)
      i. Dose: 15–20 mg/kg/day of trimethoprim divided every 6–8 hours for 21 days (intravenously for moderate to severe PCP); trimethoprim/sulfamethoxazole double strength 2 tablets three times daily (for mild to moderate PCP)
      ii. Adverse effects (80% of patients, with 20%–60% requiring discontinuation)
         (a) Nausea and vomiting
         (b) Rash
         (c) Anemia, thrombocytopenia, leucopenia
         (d) Renal impairment or hyperkalemia (also, small increases in serum creatinine occur because of competition between trimethoprim and creatinine for renal secretion)
      iii. Prophylactic dose
         (a) Preferred: Trimethoprim/sulfamethoxazole double strength or single strength once daily (pediatric dose, 150 mg/m² per dose of trimethoprim and 750 mg/m² per dose of sulfamethoxazole)
         (b) Alternative: Trimethoprim/sulfamethoxazole double strength three times/week
   b. Clindamycin and primaquine
      i. Dose: Clindamycin 600 mg every 6 hours or 900 mg every 8 hours intravenously plus primaquine 30 mg daily (for moderate to severe disease) or 450 mg every 6 hours or 600 mg every 8 hours orally and primaquine base 30 mg/day for 21 days (for mild to moderate disease)
      ii. Adverse effects
         (a) Rash
         (b) Anemia, methemoglobinemia
         (c) Diarrhea
   c. Pentamidine
      i. Dose: 4 mg/kg/day intravenously for 21 days (for moderate to severe disease)
      ii. Adverse effects
         (a) Hypotension
         (b) Rash
iii. Prophylactic dose: 300 mg by nebulization (Respirgard) once monthly (can predose with β-agonist to diminish respiratory irritation)
d. Trimethoprim and dapsone
i. Dose: 15 mg/kg/day of trimethoprim divided every 8 hours and dapsone 100 mg/day for 21 days (only for mild to moderate PCP)
ii. Adverse effects
   (a) Nausea and vomiting
   (b) Anemia
iii. Prophylactic dose: Dapsone 100 mg/day (pediatric dose, 1 mg/kg/day) alone or 50 mg/week with 50–75 mg of pyrimethamine and 25 mg of leucovorin weekly
e. Atovaquone (Mepron)
i. Dose: 750 mg twice daily for 21 days given with a high-fat meal (only for mild to moderate PCP)
ii. Pediatric dose (less than 40 kg [88 lb]) = 40 mg/kg/day divided twice daily
iii. Equal to trimethoprim/sulfamethoxazole for PCP but not an antibacterial
iv. Potential for decreased efficacy in patients with diarrhea (because of poor absorption)
v. Adverse effects
   (a) Nausea and vomiting
   (b) Rash
   (c) Transient increase in liver function tests
   (d) Insomnia, headache, fever
vi. Prophylactic dose = 1500 mg once daily (alternative to trimethoprim/sulfamethoxazole)
f. Adjuvant therapy: Corticosteroids
i. Used in patients with severe PCP (A-a gradient of 35 or more or P\textsubscript{O}\textsubscript{2} of 70 mm Hg or less); start within 72 hours
ii. Decreases mortality
iii. Dose: 40 mg twice daily of prednisone for 5 days, followed by 40 mg/day for 5 days, and then 20 mg/day for remainder of PCP therapy (use cautiously in patients with TB)

4. Prophylaxis
   a. Secondary prophylaxis in patients after PCP (may be discontinued if CD4 count is more than 200 cells/mm\textsuperscript{3} for 3 months or longer because of potent combination ART)
   b. Primary prophylaxis in patients with CD4 count less than 200 cells/mm\textsuperscript{3} (may be discontinued if CD4 count is more than 200 cells/mm\textsuperscript{3} for 3 months or longer because of potent combination ART)
   c. Consider stopping primary or secondary prophylaxis in patients with CD4 counts of 100-200 cells/mm\textsuperscript{3} if HIV plasma RNA level is below limits of detection for at least 3-6 months.

C. *Candida* Infections
1. Oral *Candida* infections (thrush)
   a. More than 90% of patients with AIDS sometime during their illness
   b. Signs and symptoms
      i. Creamy white, curdlike patches on the tongue and other oral mucosal surfaces
      ii. Pain; decreased food and fluid intake
2. *Candida* esophagitis
   a. Not always an extension of oral thrush (30% do not have oral thrush)
   b. Signs and symptoms: Painful swallowing, obstructed swallowing, substernal pain

3. Diagnosis
   a. Signs and symptoms of infection
   b. Fungal cultures, potassium hydroxide smear
   c. Endoscopic evaluation

4. Therapy
   a. Oropharyngeal candidiasis (treat 7–14 days)
      i. Fluconazole 100 mg orally daily.
      ii. Alternative: Itraconazole 200 mg orally daily or posaconazole 400 mg orally daily (after twice daily on day 1) or miconazole buccal tablets 50 mg orally daily or clotrimazole troches 10 mg orally five times daily or nystatin 5 mL (100,000 units/mL): swish and swallow four or five times daily
   b. Esophageal candidiasis (treat 14–21 days)
      i. Fluconazole 100–400 mg orally or intravenously daily or itraconazole 200 mg orally daily
      ii. Alternative: Voriconazole, caspofungin, micafungin, anidulafungin, amphotericin B deoxycholate, lipid formulation of amphotericin B, posaconazole or isavuconazole
   c. Vulvovaginal candidiasis
      i. Fluconazole 150 mg orally for one dose or topical azoles for 3–7 days
      ii. Alternative: Itraconazole 200 mg orally daily for 3–7 days

---

**Patient Cases**

5. G.H. is a 33-year-old HIV-positive man who presents to the clinic with a severe headache that has gradually worsened during the past 3 weeks. He also has memory problems and is always tired. He has refused ART in the past, and his most recent CD4 count was 75 cells/mm³. He is given a diagnosis of cryptococcal meningitis. Which is the best treatment for G.H.?
   A. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800 mg daily for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART in the first 1–2 weeks of therapy.
   B. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART after 5 weeks of antifungal therapy.
   C. Fluconazole 1200 mg/day for 10–12 weeks. Begin ART fluconazole 800 mg daily.
   D. Lipid-formulated amphotericin B 3–4 mg/kg/day plus fluconazole 800 mg/day for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART in the first 1-2 weeks of therapy.

6. After being treated for cryptococcal meningitis, G.H. is initiated on potent combination ART. For 2, 6, and 8 months after starting the therapy, his CD4 counts are 212, 344, and 484 cells/mm³, respectively. Which is the best follow-up therapy for G.H. now?
   A. Continue fluconazole maintenance therapy.
   B. Give maintenance therapy with fluconazole for at least 1 year; then, it can be discontinued because the CD4 counts have increased.
   C. Continue maintenance therapy with fluconazole until CD4 counts are greater than 500 cells/mm³.
   D. Discontinue maintenance therapy with fluconazole.
D. Cryptococcosis

1. *Cryptococcus neoformans*
2. Occurs in 6%–10% of patients with AIDS
3. In general, occurs in patients with CD4 counts less than 50 cells/mm³
4. Acute mortality is 10%–25%, and 12-month mortality is 30%–60%.
5. Worldwide distribution
   a. Found in aged pigeon droppings and nesting places (e.g., barns, window ledges)
   b. Organism must be aerosolized and inhaled; it then disseminates hematogenously.
6. Signs and symptoms
   a. Almost always meningitis (66%–84%)
   b. Usually present for weeks or months (1 day to 4 months; average, 31 days)
   c. Insidious onset
      i. Low-grade fever (80%–90%)
      ii. Headaches (80%–90%)
      iii. Altered sensorium (20%): Irritability, somnolence, clumsiness, impaired memory and judgment, behavioral changes
      iv. Seizures may occur late in the course (less than 10%).
      v. Minimal nuchal rigidity, meningismus, photophobia
7. Diagnosis
   a. Cerebrospinal fluid (CSF) changes including:
      i. Positive CSF cultures
      ii. CSF India ink
      iii. CSF cryptococcal antigen titer (91%)
      iv. Elevated opening pressure greater than 20 cm H₂O
   b. Serum cryptococcal antigen more than 1:8
8. Induction therapy (at least 2 weeks)
   a. Preferred:
      i. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
      ii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
   b. Alternatives:
      i. Amphotericin B lipid complex 5 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
      ii. Liposomal amphotericin B 3–4 mg/kg/day plus fluconazole 800 mg/day
      iii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800 mg/day
      iv. Liposomal amphotericin B 3–4 mg/kg/day alone
      v. Fluconazole 400–800 mg/day plus flucytosine 25 mg/kg every 6 hours
      vi. Fluconazole 1200 mg/day alone
9. Consolidation therapy (at least 8 weeks, beginning after successful induction therapy)
   a. Fluconazole 400 mg daily
   b. Alternative: Itraconazole 200 mg twice daily (less effective than fluconazole)
10. Maintenance therapy – Preferred: Fluconazole 200 mg/day for at least 1 year
11. Outcome
    a. Delay initiating combination ART in patients with cryptococcal meningitis for 5 weeks because of the immune reconstitution inflammatory syndrome (IRIS).
    b. Therapeutic response: 42%–75%
    c. Length of therapy is controversial, but antifungals should probably be continued as long as CSF and other body fluid cultures are positive and for 1 month after negative cultures.
    d. Relapse: 50%–90% (with about 100% mortality)
12. Prophylaxis
   a. Relapses usually occur within first year after therapy (less often with potent combination ART).
   b. Secondary prophylaxis: Fluconazole 200 mg/day (may consider discontinuing after a minimum of 1 year of chronic maintenance therapy if CD4 count is more than 100 cells/mm³ for 3 months or longer after potent combination ART; reinitiate if CD4 count decreases to less than 100 cells/mm³)
   c. Primary prophylaxis: Not indicated (decreases the incidence of cryptococcosis but does not decrease mortality and may lead to resistance)

Patient Case
7. J.C. is a 36-year-old HIV-positive woman with severe anemia. She has been tested for iron deficiency and has been taken off zidovudine and trimethoprim/sulfamethoxazole. She has also started to lose weight and to have severe diarrhea. A blood culture is positive for MAI. Which treatment is best for J.C.?
   A. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone.
   B. Azithromycin plus ethambutol for at least 12 months.
   C. Clarithromycin plus isoniazid for 2 weeks, followed by maintenance with clarithromycin alone.
   D. Ethambutol plus rifabutin indefinitely.

E. *M. avium* Complex
   1. Organism characteristics
      a. Complex is similar (main species are *M. avium* and *Mycobacterium intracellulare*, which are not differentiated microbiologically).
      b. Ubiquitous in soil and water and are transmitted through inhalation, ingestion, or inoculation by the respiratory or gastrointestinal (GI) tract
      c. Usually occurs in patients with HIV having a CD4 count less than 50 cells/mm³
      d. MAC is independently associated with risk of death, and treatment prolongs survival.
   2. Signs and symptoms (nonspecific)
      a. Weight loss, intermittent fevers, chills, night sweats, abdominal pain, diarrhea, chronic malabsorption, and progressive weakness
      b. Anemia
      c. Elevated alkaline phosphatase
   3. Diagnosis
      a. Blood or lymph node culture
      b. Bone marrow biopsy
      c. Stool cultures (do not treat if cultured only in the stool)
   4. Therapy
      a. Preferred therapeutic regimen is macrolide plus ethambutol: Clarithromycin 500 mg (7.5–15 mg/kg) twice daily or azithromycin 500–600 mg/day (10–20 mg/kg) if drug interactions or intolerance to clarithromycin, plus ethambutol 15 mg/kg/day for 12 months
      b. Other agents: Consider adding to preferred therapy if advanced immunosuppression (CD4 count less than 50 cells/mm³), high mycobacterial loads (more than 2 log CFU/mL of blood), or in the absence of effective ART.
         i. Rifabutin (Mycobutin) 300 mg/day (rifabutin dose chosen on the basis of other antiretrovirals because of drug-drug interactions)
         ii. A fluoroquinolone such as levofloxacin 500 mg oral daily or moxifloxacin 400 mg oral daily
         iii. An aminoglycoside such as amikacin 10–15 mg/kg intravenously daily or streptomycin 1 g intravenously or intramuscularly daily
c. Chronic maintenance therapy or secondary prophylaxis may be discontinued after 12 months of therapy if CD4 count is more than 100 cells/mm³ for 6 months or longer because of potent combination ART and if patient is asymptomatic. Restart if CD4 count drops below 100 cells/mm³.

5. Primary prophylaxis in patients with CD4 counts less than 50 cells/mm³ (may be discontinued if CD4 count is more than 100 cells/mm³ for 3 months or longer because of potent combination ART)
   a. Clarithromycin 500 mg orally twice daily: Lower incidence of MAC bacteremia (vs. placebo)
   b. Azithromycin 1200 mg orally once weekly
   c. Azithromycin 600 mg orally twice weekly
   d. Alternative: Rifabutin 300 mg/day (150 mg orally twice daily with food if there are GI adverse effects)

F. Cytomegalovirus
1. Characteristics of CMV infection
   a. Fifty-three percent of Americans age 18–25 years are CMV positive.
   b. Eighty-one percent of Americans older than 35 years are CMV positive.
   c. More than 95% of homosexual men are CMV positive.
   d. About 90% of CMV infections are asymptomatic (if illness occurs, it resembles mononucleosis).
   e. Virus remains latent in the host after initial infection but may reactivate if patient becomes immunocompromised (especially cell-mediated immunity).

2. Diagnosis of CMV infection: Usually made on the basis of clinical manifestations

3. Manifestations of CMV
   a. Retinitis
      i. Occurs in 10%–15% of patients with AIDS; is clinically most important CMV infection
      ii. In general, patients have CD4 counts less than 100 cells/mm³.
      iii. Begins unilaterally and spreads bilaterally
      iv. Early complaints: “Floaters,” pain behind the eye
      v. In general, progressive; no spontaneous resolution (blindness in weeks to months)
      vi. Twenty-six percent progression, even with treatment; retinal detachment very common
   b. Other manifestations
      i. Esophagitis or colitis
      ii. Pneumonitis
      iii. Neurologic

4. Therapy for CMV infections
   a. CMV retinitis
      i. Sight-threatening lesions
         (a) Valganciclovir 900 mg orally twice daily for 14–21 days, followed by 900 mg orally daily, plus intravitreal injections of ganciclovir or foscarnet for 1–4 doses over a period of 7–10 days
         (b) Alternative therapy (all regimens include intravitreal injections as listed above):
            (1) Ganciclovir 5 mg/kg intravenously every 12 hours for 14–21 days, followed by ganciclovir 5 mg/kg intravenously daily or valganciclovir 900 mg orally daily
            (2) Foscarnet 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours for 14–21 days, then 90–120 mg/kg intravenously daily
            (3) Cidofovir 5 mg/kg weekly intravenously for 2 weeks; then 5 mg/kg every other week with saline hydration and probenecid
ii. Peripheral lesions
   (a) Valganciclovir 900 mg orally twice daily for 14–21 days, followed by 900 mg orally daily.
   (b) Alternative therapy:
      (1) Ganciclovir 5 mg/kg intravenously 5–7 times weekly
      (2) Foscarnet 90–120 mg/kg intravenously daily
      (3) Cidofovir 5 mg/kg every other week intravenously with saline hydration and probenecid
b. Other CMV infections
i. Esophagitis or colitis
   (a) Ganciclovir 5 mg/kg intravenously every 12 hours, followed by valganciclovir 900 mg orally twice daily when tolerated
   (b) Alternative therapy:
      (1) Foscarnet 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours
      (2) Valganciclovir 900 mg orally twice daily (if tolerable)
ii. Pneumonitis – Use ganciclovir or foscarnet at retinitis doses.
iii. Neurologic – Combination of ganciclovir and foscarnet at retinitis doses
5. Consider waiting up to 2 weeks after initiating CMV therapy to start ART in a treatment-naive patient
6. Prophylaxis
a. Secondary prophylaxis is necessary for all patients (see individual drugs for specific doses); it may be discontinued if the CD4 count is more than 100 cells/mm³ for 3–6 months or longer because of potent combination ART. Reinitiate secondary prophylaxis if the CD4 count decreases to less than 100 cells/mm³.
b. Primary prophylaxis not recommended. In patients with CD4 counts less than 50 cells/mm³, regular funduscopic examinations are recommended.

G. Toxoplasmosis
1. Description
   a. Toxoplasma gondii (protozoan)
   b. Felines are the hosts for sporozoite production (change litter box daily, wash hands after changing litter box or have someone else change the litter box, and, ideally, keep the cat indoors).
   c. From 15% to 68% of adults in the United States are seropositive for T. gondii.
   d. Secondary to undercooked beef, lamb, or pork (stress avoidance in patients with HIV)
   e. Case-defining illness in 2.1% of patients with AIDS
2. Signs and symptoms
   a. Fever, headache, altered mental status
   b. Focal neurologic deficits (60%): Hemiparesis, aphasia, ataxia, visual field loss, nerve palsies
   c. Seizures (33%)
   d. CSF: Mild pleocytosis, increased protein, normal glucose
3. Diagnosis
   a. Brain biopsy: Only definitive diagnosis but generally reserved for patients who do not respond to specific therapy or when other workup suggests an etiology other than toxoplasmosis
   b. Antibodies or T. gondii isolation in serum or CSF
   c. Magnetic resonance imaging scan or computed tomographic scan: Multiple, bilateral, hypodense, ring-enhancing mass lesions (magnetic resonance imaging scan more sensitive than computed tomographic scan)
4. Therapy
   a. Preferred therapy
      i. Pyrimethamine 50–75 mg/day (loading dose of 200 mg) plus
      ii. Sulfadiazine 1000–1500 mg every 6 hours (watch crystalluria)
         (a) Bone marrow suppression: Thrombocytopenia, granulocytopenia, anemia
         (b) Add folinic acid (leucovorin) 10-25 mg/day to reduce bone marrow effects of pyrimethamine.
         (c) Duration: 6 weeks or after signs and symptoms resolve
   b. Alternative therapy
      i. Clindamycin 600 mg intravenously or orally every 6 hours plus pyrimethamine (see above) – Use for sulfa intolerance or nonresponse to preferred therapy
      ii. Trimethoprim/sulfamethoxazole 5 mg/kg of trimethoprim intravenously or orally twice daily
      iii. Atovaquone 1500 mg orally twice daily plus pyrimethamine/leucovorin (see above)
      iv. Atovaquone 1500 mg orally twice daily plus sulfadiazine (see above)
      v. Atovaquone 1500 mg orally twice daily

5. Prophylaxis
   a. Relapse rates approach 80% without maintenance therapy.
   b. Toxoplasma-seropositive patients with a CD4 count of 100 cells/mm³ or less should receive primary prophylaxis.
   c. Primary prophylaxis
      i. Trimethoprim/sulfamethoxazole double strength once daily or dapsone/pyrimethamine/leucovorin or atovaquone with or without pyrimethamine at doses used for PCP prophylaxis
      ii. May be discontinued if the CD4 count is more than 200 cells/mm³ for 3 months or longer because of potent combination ART
      iii. Consider stopping primary prophylaxis in patients with CD4 counts of 100-200 cells/mm³ if HIV plasma RNA level is below limits of detection for at least 3-6 months.
   d. Secondary prophylaxis
      i. Pyrimethamine 25–50 mg/day plus leucovorin 10–25 mg/day with sulfadiazine 2–4 g/day
      ii. Clindamycin 600 mg orally every 8 hours plus pyrimethamine (see above) – Use for sulfa intolerance or non-response to preferred therapy.
      iii. Trimethoprim/sulfamethoxazole double strength orally twice daily
      iv. Atovaquone 750–1500 mg orally twice daily plus pyrimethamine/leucovorin (see above)
      v. Atovaquone 750–1500 mg orally twice daily plus sulfadiazine (see above)
      vi. Atovaquone 750–1500 mg orally twice daily
      vii. May be discontinued if the CD4 count is more than 200 cells/mm³ for 6 months or longer because of potent combination ART

III. TUBERCULOSIS

   A. Mycobacterium tuberculosis
   1. Factors associated with acquiring TB
      a. Exposure to people with active pulmonary TB
      b. Geographic location
      c. Low socioeconomic status
      d. Nonwhite race
      e. Male sex
      f. HIV infection
      g. Foreign birth
2. Epidemiology (Figure 2)

**Number of persons with reported cases of tuberculosis, 1986-2017**

![Graph showing the number of reported tuberculosis cases from 1986 to 2017 for all persons, US-born persons, and foreign-born persons.]

**Figure 2.** Epidemiology of tuberculosis.

B. Pathophysiology (Figure 3)

1. Person-to-person transmission: Airborne droplets carrying *M. tuberculosis* are inhaled.
2. Infection primarily pulmonary but can occur in other organ systems

![Diagram illustrating the pathophysiology of tuberculosis, showing the inhaled droplet bypassing the mucociliary system and becoming implanted in the bronchioles or alveoli, followed by activated alveolar macrophages ingesting and destroying over 90% of the inhaled tubercle bacilli. Remaining 10% multiply within the macrophages and are released when the macrophage dies. Released bacilli attract monocytes and macrophages forming the primary tubercle – growth occurs within the macrophages with destruction of neither bacilli or macrophages occurring.]

**Figure 3.** Pathophysiology of tuberculosis.

*TST* = tuberculin skin test
C. Diagnosis (Table 8)

Table 8. Diagnosis of Tuberculosis

<table>
<thead>
<tr>
<th>Nonspecific Signs and Symptoms</th>
<th>Radiology</th>
<th>Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Chest radiograph: patchy or nodular infiltrates in upper lobes; cavitary lesions</td>
<td>Sputum smear for AFB</td>
</tr>
<tr>
<td>Malaise</td>
<td></td>
<td>Sputum culture for <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFB = acid-fast bacillus.

1. Tuberculin skin test (TST) (Table 9)
   a. Recommended dose is 5 tuberculin units/0.1 mL.
   b. Mantoux method
      i. Intradermal injection of tuberculin into forearm
      ii. Measure diameter of induration after 48–72 hours.
      iii. Use two-step TST for initial testing of people who will be tested periodically (e.g., health care workers).
   c. False-negative tests occur in 15%–20% of people infected with *M. tuberculosis*, primarily in those recently infected or anergic.
   d. Only 8% of people vaccinated with bacille Calmette-Guérin (BCG) at birth will react 15 years later.

Table 9. Testing for Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>Likelihood of Infection with <em>M. tuberculosis</em> (see below)</th>
<th>Risk of Progressing to Tuberculosis if Infected (see below)</th>
<th>Criterion for Positive Skin Test (mm)</th>
<th>Recommended testing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely</td>
<td>Low to intermediate</td>
<td>≥ 10</td>
<td>IGRA recommended if history of BCG vaccine or unlikely to return to have TST read (otherwise IGRA suggested) TST is acceptable alternative</td>
</tr>
<tr>
<td>Likely</td>
<td>High</td>
<td>≥ 5</td>
<td>IGRA or TST (data insufficient to recommend one over the other)</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Low to high</td>
<td>≥ 15</td>
<td>Do not test with either IGRA or TST (may be done for employee health surveillance)</td>
</tr>
</tbody>
</table>

Groups with increased likelihood to be infected (i.e., “likely”)
- Household contact or recent exposure of an active case
- Mycobacteriology laboratory personnel
- Immigrants from high-burden countries
- Residents and employees of high-risk congregate settings

Risk of Developing Tuberculosis

Low:
- No risk factors

Intermediate:
- Diabetes
- Chronic renal failure
- Intravenous drug use

High:
- Children < 5 years
- HIV infection
- Immunosuppressive therapy
- Abnormal chest x-ray consistent with prior TB
- Silicosis

* For children under 5 years of age use TST rather than an IGRA in all situations
2. Interferon-gamma release assays (IGRA)
   a. QuantiFERON-TB Gold and T-SPOT.TB
   b. Blood test that detects the release of interferon gamma in response to *M. tuberculosis* infection
   c. Less sensitivity but greater specificity than the TST for predicting future active infection

3. Booster effect
   a. The TB test can restimulate hypersensitivity in those exposed in the past.
   b. Occurs within 1 week of the test and persists for more than 1 year
   c. Those with small TB test reactions can be retested in 1 week; if positive, result should be attributed to boosting of a subclinical hypersensitivity; chemoprophylaxis is not necessary.

### Patient Case
8. J.M. is a 42-year-old man who has a yearly TST because he works at a long-term care facility. Forty-eight hours after the TST is placed, he has an 18-mm induration. This is the first time he has reacted to this test. His chest radiograph is negative. Which is best in view of J.M.’s positive TST?

   A. No treatment is necessary, and J.M. should have another TST skin test in 1 year.
   B. J.M. should have another TST skin test in 1 week to see whether this is a booster effect.
   C. J.M. should be monitored closely, but no treatment is necessary because he is older than 35 years.
   D. J.M. should be initiated on isoniazid 300 mg/day orally for 9 months.

### D. Therapy
1. Treatment of latent TB infection
   a. The goal is to prevent latent (asymptomatic) infection from progressing to clinical disease.
   b. Treatment of latent TB infection is recommended for the following people:
      i. HIV infected persons
      ii. Close contacts of people with a diagnosed infectious TB
      iii. People with abnormal chest radiographs that show fibrotic lesions, likely to represent old, healed TB
      iv. Immunosuppressed persons (e.g., organ transplant recipients, taking the equivalent of more than 15 mg/day of prednisone for more than 1 month, receiving TNF-alpha antagonists)
      v. Foreign-born people from high-prevalence countries (immigration within 5 years)
      vi. Injection drug users
      vii. People working at or living in high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospital, and other health care facilities)
      viii. Mycobacteriology laboratory personnel
      ix. Children under 4 years of age, or children and adolescents exposed to adults in high-risk categories
   c. Dosing regimens
      i. Patients who are not infected with HIV
         (a) Isoniazid 300 mg/day or 900 mg twice weekly for 6–9 months (9 months preferred, especially for children and pregnant women)
         (b) Rifampin 600 mg/day for 4 months
         (c) Rifapentine 900 mg plus isoniazid 900 mg/week for 12 weeks (with directly observed therapy)
         (d) Rifampin 600 mg/day plus isoniazid 300 mg/day for 3 months (not recommended by the Centers for Disease Control and Prevention)
ii. Patients who are coinfected with HIV
   (a) Administer isoniazid 300 mg/day for 9 months
   (b) Alternative: Isoniazid 900 mg twice weekly for 9 months with directly observed therapy
       (lower strength of evidence)
iii. Areas with multidrug-resistant isolates: Two drugs with activity against the isolate for 6–12 months

**Patient Case**

9. R.J. is a 32-year-old HIV-positive man who presents to the clinic with increased weight loss, night sweats, and a cough productive of sputum. He is currently receiving darunavir/ritonavir 800 mg/100 mg daily, tenofovir 300 mg daily, emtricitabine 200 mg daily, fluconazole 200 mg/day orally, and trimethoprim/sulfamethoxazole double strength daily. A sputum sample is positive for acid-fast bacillus. R.J. lives in an area with a low incidence of multidrug-resistant TB. Which is the best initial treatment?

A. Initiate isoniazid, rifampin, and pyrazinamide with no change in HIV medications.
B. Initiate isoniazid, rifampin, and pyrazinamide; increase the dosage of darunavir/ritonavir; and use a higher dosage of rifamycin.
C. Initiate isoniazid, rifabutin, pyrazinamide, and ethambutol, with a lower dosage of rifabutin.
D. Initiate isoniazid, rifabutin, pyrazinamide, and ethambutol, and decrease the dosage of darunavir/ritonavir.

2. Treatment of active TB infection (Tables 10 and 11)
   a. Principles of treatment
      i. Regimens must contain many drugs to which the organisms are susceptible.
      ii. Drug therapy must continue for a sufficient period.

**Table 10. Pharmacotherapeutic Agents in the Treatment of Tuberculosis**

<table>
<thead>
<tr>
<th>First-Line Agents</th>
<th>Second-Line Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Amikacin/kanamycin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Capreomycin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Cycloserine</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td>Para-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Rifabutin</td>
</tr>
<tr>
<td></td>
<td>Rifapentine</td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
</tr>
</tbody>
</table>

b. Therapeutic options for treating active TB (Note: Any regimen administered two, three, or five times/week should be done by directly observed therapy.)
### Table 11. Treatment of Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Patients without HIV</th>
<th>Patients with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommended</td>
<td>Antibiotic</td>
</tr>
<tr>
<td><strong>Intensive Phase</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Isoniazid&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(daily or five times weekly)</td>
</tr>
<tr>
<td><strong>Continuation Phase</strong></td>
<td>Isoniazid</td>
<td>Rifampin</td>
</tr>
<tr>
<td><strong>Optional (less efficacy)</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Antibiotic</td>
<td>Regimen</td>
</tr>
<tr>
<td><strong>Intensive Phase</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Isoniazid</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>(three times weekly or daily for two weeks followed by two times weekly)</td>
<td></td>
</tr>
<tr>
<td><strong>Continuation Phase</strong></td>
<td>Isoniazid</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>(three times weekly or twice weekly)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>If TB isolate is susceptible to both INH and RIF, then ethambutol can be dropped from the intensive phase.

<sup>b</sup>Pyridoxine should be given to all those receiving isoniazid and at increased risk of neuropathy (e.g., pregnant women, breastfeeding infants, HIV infected persons, patients with diabetes, alcoholism, malnutrition, or chronic renal failure, persons of advanced age).

<sup>c</sup>Extend to 7 months if cavitary lesions on chest x-ray and positive sputum culture after intensive phase.

<sup>d</sup>Extend to 7 months if patient not receiving ART.

<sup>e</sup>Efficacy diminishes as the number of weekly doses decreases.

**c. Concurrent therapy in patients with HIV**

i. For ART-naive patients, ART should be initiated within 2 weeks when the CD4 count is less than 50 cells/mm<sup>3</sup> and by 8–12 weeks for all others.

ii. PIs and NNRTIs (except for efavirenz or nevirapine) should not be administered concurrently with rifampin; INSTIs can be administered with rifampin (except elvitegravir and bictegravir), but doses need to be altered; NRTIs can be administered with rifampin, except for tenofovir alafenamide (which should not be administered with any rifamycin).

iii. A washout period of 1–2 weeks may be necessary once rifampin is discontinued before PIs, elvitegravir, or NNRTIs are initiated.

iv. Rifabutin can be substituted for rifampin; patients may take NNRTIs with rifabutin, but rifabutin doses may need to be increased to 450–600 mg/day (see HIV guidelines).

v. Patients may take PIs with rifabutin, but the rifabutin dose should be decreased to 150 mg every day or every other day (300 mg three times weekly may be an option).

vi. Elvitegravir and bictegravir should not be used with rifabutin.

vii. Patients taking rifabutin and PIs, INSTIs, or NNRTIs should have HIV RNA concentrations performed periodically.

vii. Rifapentine should only be given to patients receiving either an efavirenz- or raltegravir-based regimen.

**d. Known drug resistance to isoniazid:** Administer rifampin, pyrazinamide, ethambutol, and moxifloxacin or levofloxacin for 2 months; rifabutin may be substituted for rifampin in patients with HIV. Continuation phase should be completed with rifampin (or rifabutin) plus ethambutol plus moxifloxacin (or levofloxacin) for 7 months.

**e. Known drug resistance to rifampin:** Administer isoniazid, pyrazinamide, and ethambutol for 9–12 months; streptomycin may be added for the first 2 months to shorten the total treatment time to 9 months.
f. Total duration of therapy should be based on number of doses received, not on calendar time.
   i. Pulmonary TB: 6 months
   ii. Pulmonary TB and culture positive after 2 months of TB treatment: 9 months
   iii. Extrapulmonary TB with central nervous system (CNS) infection: 9–12 months
   iv. Extrapulmonary TB with bone or joint involvement: 6–9 months
   v. Extrapulmonary TB in other sites: 6 months

Patient Cases
10. Which represents the best follow-up for R.J. (from Patient Case 9)?
    A. Treatment with the initial drugs should continue for 6 months.
    B. Treatment can be decreased to just isoniazid and a rifamycin after 2 months for a total treatment of 18–24 months.
    C. Treatment can be decreased to just isoniazid and a rifamycin after 2 months for a total treatment of 6 months; HIV RNA concentrations should be observed closely during therapy.
    D. Treatment can be decreased to isoniazid, a rifamycin, and either pyrazinamide or ethambutol after 2 months for a total treatment of 6 months; HIV RNA concentrations should be observed closely during therapy.

11. L.F. is a 55-year-old man (73 kg) who was involved in a motor vehicle accident with subsequent bilateral pneumothoraces. He is admitted to the ICU and mechanically ventilated. He is started on levofloxacin which after 3 days is switched to piperacillin/tazobactam and vancomycin. After 5 days of broad spectrum antibiotics his temperature continues to spike. A blood culture is positive for Candida krusei. What is the best treatment for L.F.?
    A. Fluconazole 400 mg IV daily for 7 days following the first negative blood culture.
    B. Micafungin 100 mg IV daily for 14 days following the first negative blood culture.
    C. Amphotericin B lipid formulation 3 mg/kg/day for 14 days following the first negative blood culture.
    D. Voriconazole 200 mg IV twice daily for 7 days following the first negative blood culture.

IV. FUNGAL PHARMACOTHERAPY

A. Candida
   1. Background
      a. C. albicans, C. krusei, C. parapsilosis, C. tropicalis, C. glabrata, C. auris
      b. Risk factors:
         i. Broad spectrum antibiotics
         ii. Central catheters, urinary catheters, etc. (remove if found to be the source of infection)
         iii. Prosthetic devices
         iv. Immunocompromised (chemotherapy, radiation, corticosteroid, HIV, etc.)
   2. Therapy
      a. Oral/esophageal candidiasis (see II. Opportunistic Infections: Patients With HIV, C. Candida Infections)
      b. Candidemia
         i. Echinocandin (caspofungin, anidulafungin, or micafungin)
         ii. Fluconazole: only use if known or suspected fluconazole-sensitive organism (400 mg/day)
         iii. Amphotericin B lipid formulation – for resistance or intolerance to other antifungals
         iv. Treat for 14 days after first negative blood culture
c. Endocarditis
   i. Amphotericin B lipid formulation ± flucytosine or high dose echinocandin
   ii. Fluconazole (or voriconazole or posaconazole) can be used as step down therapy for sensitive isolates
   iii. Replace the valve and treat for 6 weeks
   iv. Consider chronic suppressive therapy with fluconazole for prosthetic valve endocarditis

d. Osteomyelitis/Septic arthritis
   i. Fluconazole for 6-12 months
   ii. Echinocandin for 2 weeks followed by fluconazole for 6-12 months
   iii. Amphotericin B lipid formulation for 2 weeks followed by fluconazole for 6-12 months
   iv. Same recommendations for septic arthritis except total therapy is only 6 weeks

e. Urinary tract infections
   i. Remove indwelling catheters, nephrostomy tubes, stents, etc.
   ii. Asymptomatic: treat only if patient is neutropenic or undergoing urologic manipulation
   iii. Symptomatic
      (a) Fluconazole for 2 weeks
      (b) Amphotericin B (1-7 days) or flucytosine (7-10 days) for fluconazole resistant organisms
      (c) Other azoles and echinocandins do not achieve adequate urinary concentrations

f. Invasive Candidiasis in the Intensive Care Unit
   i. Empiric treatment
      (a) Use for patients with unexplained fever and risk factors: Candida colonization, severe illness, broad spectrum antibiotics, recent abdominal surgery, necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroids, central venous catheter
      (b) Echinocandin therapy recommended
      (c) Fluconazole use only in patients without recent azole use or colonization with azole-resistant organisms
      (d) Amphotericin B lipid formulation if patient intolerant to other antifungals
      (e) Duration: 2 weeks if patient responds or 4-5 days with no response
   ii. Prophylaxis
      (a) Fluconazole 400 mg daily in ICUs where the incidence of invasive Candidiasis is >5% of patients
      (b) Echinocandins can be used alternatively

B. Histoplasmosis
   1. Background
      a. Histoplasma capsulatum
      b. Endemic regions: lower Mississippi and Ohio valleys
      c. Organisms in excrement are aerosolized and inhaled
      d. Signs and symptoms: lymphadenopathy, splenomegaly, fever, weight loss, headache, chills, cough, chest pain, myalgias, fatigue
   2. Therapy
      a. 50% mortality even with therapy – relapses are frequent
      b. Moderate to severe illness: amphotericin B lipid formulation (5 mg/kg/day) for 1-2 weeks followed by itraconazole to complete 12 weeks of therapy
      c. Mild illness: itraconazole 200 mg twice daily for 12 weeks (may need to extend to 12-24 months in patients with chronic or disseminated disease)
C. Coccidioidomycosis  
1. Background  
   a. *Coccidioides immitis*  
   b. Endemic regions: California, Arizona, Nevada, New Mexico, Utah, Texas  
   c. Organisms in soil are aerosolized and inhaled  
   d. Signs and symptoms: cough, sputum production, chest pain, malaise, fever, chills, night sweats, anorexia, weakness, arthralgias  
2. Therapy  
   a. Consider not treating in immunocompetent host  
   b. Fluconazole 400 mg daily or itraconazole 400 mg daily for 3-6 months  
   c. Severe/diffuse/disseminated disease: amphotericin B lipid formulation (5 mg/kg/day) until improvement then fluconazole or itraconazole for at least a year  

D. Blastomycosis  
1. Background  
   a. *Blastomyces dermatitidis*  
   b. Endemic regions: Southeastern states, Ohio and Mississippi river basins, and Great Lakes region including the St. Lawrence seaway  
   c. Sources: soil – organisms in soil are aerosolized and inhaled  
   d. Signs and symptoms: cough, sputum production, chest pain, malaise, fever, chills, weakness, arthralgias  
   e. Cutaneous manifestations (occurs in 40-80% of patients): small papulopustular lesions that spread to form a crusted, heaped-up lesion or an ulcerative pustular lesion  
2. Therapy  
   a. Itraconazole 200 mg twice daily for 24 weeks  
   b. Severe/life threatening disease: amphotericin B lipid formulation (5 mg/kg/day) until improvement then itraconazole for 6-12 months  

E. Aspergillosis  
1. Background  
   a. *Aspergillus fumigatus*  
   b. Ubiquitous in the environment  
   c. Sources: grows in stored hay/grain, decaying vegetation, soil, compost piles, and manure – common during hospital renovation / construction, in potted plants, and air conditioner filters – organisms are aerosolized and inhaled  
   d. Allergic bronchopulmonary aspergillosis – in asthma patients, aspergillosis causes hypersensitivity reaction and granuloma formation (treat with prednisone)  
   e. Pneumonia – secondary to prolonged neutropenia; high fever and dense pulmonary infiltrates – rapidly progressing and universally fatal in bone marrow transplant patients  
2. Therapy  
   a. Voriconazole 4 mg/kg intravenous twice daily or 200-300 mg orally twice daily  
   b. Alternatives: isavuconazole 200 mg daily or amphotericin B lipid formulation (3-5 mg/kg/day)  
   c. Echinocandins only if azoles and amphotericin are contraindicated  
   d. Treat for 6-12 weeks  
3. Prophylaxis  
   a. Recommended for at-risk patients with prolonged neutropenia, graft versus host disease or lung transplant  
   b. Voriconazole or posaconazole or micafungin (use voriconazole, itraconazole, or inhaled amphotericin for 3-4 months after lung transplant)
F. Mucormycosis
   1. Background
      b. Ubiquitous in the environment
      c. Sources: decaying organic matter – organisms are aerosolized and inhaled
      d. Signs and symptoms: fever, cough, shortness of breath (pulmonary); can also cause sinusitis with associated symptoms or cutaneous infections
   2. Therapy
      a. Amphotericin B lipid formulation (5 mg/kg/day) until improvement then isavuconazole or posaconazole
      b. Treat until resolution of infection (usually months)

Patient Case
12. A.B. is a 55-year-old woman who presents to your clinic with toenail discoloration with a few of her toenails separating from the nail bed. She is diagnosed with onychomycosis. What is the best treatment for A.B.?
   A. Fluconazole 200 mg orally daily for 14 days.
   B. Itraconazole 200 mg orally daily for 28 days.
   C. Miconazole cream applied twice daily to toenails for 2 months.
   D. Terbinafine 250 mg orally daily for 3 months.

G. Superficial fungal infections
   1. Background
      a. Caused by dermatophytes (*Microsporum, Trichophyton, Epidermophyton*)
      b. More common in males than females
      c. More common in tropical, humid climates
      d. Transmitted person to person, via soil contact and via animal contact
   2. Tinea capitis – infection of the scalp
      a. Peak incidence of 3-9 years of age, more common in nonwhites
      b. Spores invade the hair shaft leading to hair loss without inflammation or spores spread beyond the hair shaft leading to inflammation
      c. Therapy:
         i. Griseofulvin
         ii. Terbinafine
         iii. Itraconazole, fluconazole
         iv. Selenium sulfide 2.5% shampoo (reduces spread of infection and reinfection)
   3. Tinea pedis – infection of the foot
      a. Increase in frequency with age; more common in men than women, and in those who wear shoes
      b. Moccasin like distribution (difficult to treat) or intertrigenous involvement which may lead to secondary bacterial infection
      c. Therapy:
         i. Topical antifungal agent twice daily until clear
         ii. Terbinafine, itraconazole, or fluconazole for severe or resistant cases
   4. Tinea cruris – infection of the groin and thigh
      a. More common in males than females
      b. Predisposing factors include obesity, tight-fitting clothes, wet swimsuits, etc.
      c. Therapy:
         i. Topical antifungals twice daily for 3-4 weeks
         ii. Loose-fitting cotton underwear and good hygiene
5. Tinea corporis – “ringworm”
   a. Common in hot, humid climates – transmitted person to person
   b. Asymptomatic or pruritic annular plaque – scaling, crusting, vesicle formation and papules on nonhairy skin
   c. Therapy:
      i. Topical antifungal twice daily for 2-4 weeks
      ii. Terbinafine or itraconazole for extensive skin involvement

6. Onychomycosis – nail infection
   a. Increases with age – affects 5% of the population
   b. Predisposing factors include superficial fungal infection of feet or hands, repeated minor trauma with heat and moisture
   c. Nail discoloration, subungual hyperkeratosis, separation of nail from bed
   d. Therapy:
      i. Terbinafine
      ii. Itraconazole (pulse or continuous therapy)
      iii. Onychomycosis specific topical agents: efinaconazole, tavaborole, or ciclopirox
      iv. Duration: fingernails: 6 weeks; toenails: 12 weeks (longer if using topical agents)

**Patient Case**

13. C.A. is a 66-year-old man with a history of advanced non–small cell lung cancer. After his most recent chemotherapy, he became severely neutropenic and received a diagnosis of *Aspergillus* pneumonia. C.A. has acute renal failure related to his chemotherapy and is receiving warfarin, diltiazem, dronedarone, atorvastatin, pantoprazole, and carbamazepine. Which antifungal would be the best therapy for C.A.?
   A. Lipid amphotericin.
   B. Micafungin.
   C. Fluconazole.
   D. Voriconazole.

**V. ANTIFUNGAL AGENTS**

A. Amphotericin B (Fungizone, Abelcet, Amphotec, AmBisome)
   1. Mechanism of action: Binds to ergosterol in the fungal cell membrane, altering membrane permeability and causing cell lysis
   2. Spectrum of activity
      a. *Candida, Blastomyces dermatitidis, Coccidioides immitis, C. neoformans, Paracoccidioides, Histoplasma capsulatum, Sporothrix, Aspergillus*, mucormycoses
      b. Clinical use
         i. Cryptococcal meningitis
         ii. Systemic fungal infections caused by sensitive fungi
         iii. Limited use clinically with newer antifungals
   3. Adverse effects (less common with lipid formulations)
      a. Renal toxicity (glomerular and tubular)
         i. Glomerular filtration rate decreases by about 40% within 2 weeks and usually stabilizes at 20%–60% of normal.
         ii. In general, reversible unless total dose is more than 4–5 g
         iii. Manifestations: Renal tubular acidosis, urine casts, azotemia, oliguria, magnesium, and potassium wasting
iv. Prevention
(a) Correct salt depletion: 3 L normal saline for 24 hours or 500 mL of normal saline before and after amphotericin dose
(b) Avoid diuretics and liberalize salt intake; risk-benefit with other disease states
b. Thrombophlebitis prevention
i. Dilute to 0.1 mg/mL and infuse for at least 4 hours; a faster infusion (i.e., 45 minutes to 2 hours) may be tolerated.
ii. Use a central site.
iii. Adding heparin may decrease phlebitis.
c. Anemia
d. Fever and chills
i. Mechanism: Amphotericin B induces prostaglandin synthesis.
ii. Premedications
(a) Hydrocortisone: 25 mg intravenously before the dose or in the bottle decreases fever and chills (higher doses are not significantly better)
(b) Ibuprofen (10 mg/kg up to 600 mg 30 minutes before infusion): Significantly more fever and chills in placebo (87%) than in ibuprofen group (48%)
(c) Acetylsalicylic acid, acetaminophen, diphenhydramine: Never shown to be effective (but not specifically studied)
e. Rigors treatment
i. Meperidine 50 mg: Stops reaction within 30 minutes (mean, 10.8 minutes)
ii. If the patient consistently needs meperidine, then prophylactic doses may be appropriate.

4. Dosing
a. Start therapy with 0.25 mg/kg (some suggest 5–10 mg) administered for 4–6 hours.
b. Increase gradually to desired milligram per kilogram concentration (i.e., 5- to 10-mg increments).
c. May increase rapidly in fulminant infections or immunocompromised patients
d. Amphotericin can be given on alternate days by doubling the daily dose to a maximum of 1.5 mg/kg.

5. Lipid amphotericin formulations (liposome, lipid complex, and colloidal dispersion; Table 12)
a. Lipid formulations are designed to maintain therapeutic efficacy, but they diminish renal and infusion-related toxicity.

Table 12. Amphotericin Formulations

<table>
<thead>
<tr>
<th>Lipid type</th>
<th>Amphotericin B Deoxycholate</th>
<th>Abelcet</th>
<th>Amphocet</th>
<th>AmBisome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.7–1 mg/kg/day</td>
<td>5 mg/kg/day for 2 hours</td>
<td>3–4 mg/kg/day for 3–4 hours</td>
<td>3–5 mg/kg/day</td>
</tr>
<tr>
<td>Test dose</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Chills or rigors (%)</td>
<td>54–56</td>
<td>18</td>
<td>77</td>
<td>18</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>44–47</td>
<td>14</td>
<td>55</td>
<td>17</td>
</tr>
<tr>
<td>Nephrotoxicity (%)</td>
<td>34–47</td>
<td>28</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Hypokalemia (%)</td>
<td>12–29</td>
<td>5</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Hypomagnesemia (%)</td>
<td>11–26</td>
<td>N/A</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>
b. Mainly taken up by macrophages in the lung, liver, spleen, bone marrow, and circulating monocytes

c. Liposomes target fungal cell membranes much more than human cell membranes.

d. Amphotericin dissociates from the liposome over time, decreasing its toxicity (only free drug is toxic).

e. Primary use in patients with aspergillosis and cryptococcal meningitis who cannot tolerate amphotericin B deoxycholate

f. Potential use for invasive candidiasis

B. Azole Antifungals

1. Mechanism of action: Inhibits the synthesis of ergosterol, a component of the fungal cell membrane, vital for normal growth

2. Fluconazole (Diflucan)
   a. Spectrum of activity
      i. *Candida* spp. (poor activity against *C. glabrata* and no activity against *C. krusei*), *Cryptococcus, Blastomyces, Histoplasma,* dermatophytes
   ii. Clinical use
      a. *Candida* infections (primarily *C. albicans* and *C. parapsilosis*)
      b. Cryptococcal meningitis

b. Pharmacokinetics
   i. Well absorbed orally (bioavailability 100%); also available intravenously
   ii. Half-life is about 30 hours; primarily eliminated unchanged in the urine

c. Adverse effects
   i. Nausea, abdominal pain, headache, reversible alopecia
   ii. Elevated liver function tests

d. Drug interactions (CYP3A4 inhibitor at more than 400 mg/day and CYP2C9 inhibitor at lower doses)
   i. Cyclosporine
   ii. Phenytoin
   iii. Warfarin

e. Dosing
   i. Oral candidiasis: 100–200 mg/day
   ii. Esophageal candidiasis: 200–400 mg/day
   iii. Invasive candidiasis: 400–800 mg/day
   iv. Acute cryptococcal meningitis: 400–800 mg/day
   v. Cryptococcal meningitis prophylaxis: 200 mg/day

3. Itraconazole (Sporanox)
   a. Spectrum of activity
      i. *Candida* spp. (usually just *C. albicans*), *Cryptococcus, Aspergillus, Blastomyces, Histoplasma,* dermatophytes
   ii. Clinical use
      a. Onychomycosis
      b. Histoplasmosis
      c. Aspergillosis
      d. Blastomycosis

b. Pharmacokinetics
   i. Oral absorption about 55% when given with food
   ii. Half-life is about 20 hours; extensively metabolized; hydroxy itraconazole is active.
c. Adverse effects
   i. Nausea, abdominal pain, headache, rash
   ii. Elevated liver function tests, potential fulminant hepatitis
   iii. Caution in heart failure (avoid doses of 400 mg/day or greater; do not use for treatment of onychomycosis if heart failure)
d. Drug interactions (CYP2C9, CYP2C19 and CYP3A4 inhibitor)
   i. Antacids, H₂-blockers, proton pump inhibitors, didanosine (GI absorption)
   ii. Cyclosporine
   iii. Digoxin (decreases digoxin volume of distribution)
   iv. Phenytoin
   v. Warfarin
   vi. PIs
   vii. HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors
e. Dosing: 100–200 mg/day. Oral capsules with food; oral solution without food
f. Therapeutic Drug Monitoring (TDM)
   i. TDM appropriate for most patients receiving itraconazole
   ii. Trough concentrations taken 7–14 days after starting therapy or making dose adjustments.
   iii. Target concentrations > 0.5 mg/L for prophylaxis and > 1 mg/L for treatment.

4. Voriconazole (Vfend)
   a. Spectrum of activity
      i. Candida spp., Aspergillus, Fusarium, Scedosporium, Histoplasma, Cryptococcus
      ii. Clinical use
         (a) Resistant Candida infections (especially C. glabrata and C. krusei)
         (b) Aspergillosis
         (c) Histoplasmosis
   b. Pharmacokinetics
      i. Oral absorption about 95%; also available intravenously
      ii. Half-life is about 6 hours; extensively metabolized; CYP2C9, CYP3A4, CYP2C19
   c. Adverse effects
      i. Abnormal vision 30% (abnormal vision, color changes, photophobia). Short-term (20–30 minutes) effects on retina. Dose related. Not studied for more than 28 days of therapy
      ii. Elevated liver function tests, rash, nausea
d. Drug interactions (CYP3A4 and CYP2C9 inhibitor and substrate; see Table 13)
e. Dosing
   i. Aspergillosis: Loading dose, 6 mg/kg two times intravenously (infuse for 2 hours); maintenance dose, 4 mg/kg every 12 hours intravenously (infuse for 2 hours)
   ii. Candidiasis and candidemia: 400 mg orally or intravenously every 12 hours for two doses, then 200 mg every 12 hours
      (a) For patients who are receiving phenytoin, increase dose to 5 mg/kg every 12 hours intravenously or 200–400 mg every 12 hours orally.
      (b) Dose reduction for moderate or severe cirrhosis: After loading dose, decrease dose by 50% in Child-Pugh class A/B. No information for patients in Child-Pugh class C
      (c) No adjustment of the oral dose for renal insufficiency; patients with CrCl less than 50 mL/minute/1.73 m² should not receive the intravenous product because of accumulation of the intravenous vehicle sulfobutyl ether-β-cyclodextrin
      (d) Therapeutic drug monitoring indicated because of polymorphism in CYP2C19 metabolism
f. Therapeutic Drug Monitoring (TDM)
   i. TDM appropriate for most patients receiving voriconazole (esp. pediatrics, patients with toxicity, and patients receiving interacting drugs).
   ii. Consider monitoring when transitioning from IV to oral (esp. in obesity)
   iii. Trough concentrations taken 4-5 days after starting therapy or making dose adjustments.
   iv. Target concentrations > 0.5 mg/L for prophylaxis and > 1-2 mg/L for treatment.

Table 13. Drug Interactions Reported with Voriconazole

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin (CYP inducer)</td>
<td>↓ Voriconazole</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td>Rifabutin (CYP inducer)</td>
<td>↓ Voriconazole</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td>Carbamazepine (CYP inducer)</td>
<td>↓ Voriconazole</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td>Barbiturates, long acting (CYP inducers)</td>
<td>↓ Voriconazole</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>↑ Ergot alkaloids</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td>Sirolimus (CYP3A4 substrate)</td>
<td>↑ Sirolimus</td>
<td>Coadministration contraindicated</td>
</tr>
</tbody>
</table>
| Cyclosporine (CYP3A4 substrate)           | ↑ Cyclosporine     | Reduce cyclosporine dose by half when initiating voriconazole
|                                           |                    | Monitor levels closely                               |
|                                           |                    | Increase cyclosporine dose as necessary when voriconazole is discontinued |
| Tacrolimus (CYP3A4 substrate)             | ↑ Tacrolimus       | Reduce tacrolimus dose to one-third of initial dose when initiating voriconazole
|                                           |                    | Monitor levels closely                               |
|                                           |                    | Increase tacrolimus dose as necessary when voriconazole is discontinued |
| Omeprazole (CYP2C19 inhibitor, CYP2C19 and CYP3A4 substrate) | ↑ Voriconazole | In patients receiving omeprazole doses ≥ 40 mg, reduce omeprazole dose by half |
|                                           | ↑ Omeprazole       |                                                     |
| Warfarin (CYP2C9 substrate)               | ↑ Warfarin         | Closely monitor PT/INR and adjust warfarin dose as needed |
|                                           | ↑ PT               |                                                     |

INR = international normalized ratio; PT = prothrombin time.

5. Posaconazole (Noxafil)
   a. Spectrum of activity
      i. *Candida* spp., *Cryptococcus*, *Trichosporon*, *Aspergillus*, *Fusarium*, *Zygomycetes*
      ii. Clinical use
         (a) *Candida* infections
         (b) Aspergillosis
         (c) Zygomycoses
         (d) Fusariosis
b. Pharmacokinetics
   i. Oral absorption of suspension increased by a high-fat meal
   ii. Oral tablet formulation: Food has less impact on absorption.
   iii. Half-life is about 24–30 hours; primarily eliminated unchanged in the feces

c. Adverse effects
   i. Nausea, vomiting, diarrhea
   ii. Elevated liver function tests, rash, hypokalemia, thrombocytopenia
   iii. Corrected QT (QTc) interval prolongation

d. Drug interactions: CYP3A4 inhibitor; decreased posaconazole absorption with proton pump inhibitors and H₂-blockers

e. Dosing: Oropharyngeal candidiasis, 100 mg/day; refractory oropharyngeal candidiasis, 400 mg twice daily; prophylaxis of invasive fungal infections in neutropenic and patients with graft-versus-host disease, 200 mg three times daily (suspension), 300 mg daily (tablet or intravenous)

6. Isavuconazonium (Cresemba)
   a. Spectrum of activity
      i. Candida spp., Cryptococcus, Aspergillus, Mucorales, Fusarium, Histoplasma, Blastomyces
      ii. Clinical use
         (a) Aspergillosis
         (b) Mucormycosis
   b. Pharmacokinetics
      i. Prodrug that is rapidly hydrolyzed in the blood to isavuconazole
      ii. Oral absorption is complete (take with or without food) and protein binding is greater than 99%.
      iii. Half-life is about 130 hours; metabolized primarily by CYP3A4
   c. Adverse effects
      i. Nausea, vomiting, diarrhea
      ii. Elevated liver function tests, hypokalemia, cough, peripheral edema, back pain
   d. Drug interactions: CYP3A4 substrate and moderate inhibitor; P-glycoprotein mild inhibitor; increased isavuconazole with PIs; decreased isavuconazole with rifampin
   e. Dosing: 372 mg (200 mg isavuconazole) every 8 hours for six doses (loading dose) followed by 372 mg (200 mg isavuconazole) daily (maintenance dose)

C. Echinocandins
   1. Mechanism of action: Inhibits synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall
   2. Caspofungin (Cancidas), micafungin (Mycamine), anidulafungin (Eraxis)
      a. Spectrum of activity
         i. Candida spp. (weak against C. parapsilosis), Aspergillus
         ii. Clinical use
            (a) Candida: Invasive candidiasis, candidemia, intra-abdominal abscesses, peritonitis, and pleural space infections
            (b) Esophageal candidiasis
            (c) Invasive aspergillosis (refractory to or intolerant of other therapies)
      b. Pharmacokinetics
         i. Only available intravenously
         ii. Half-life of about 1–2 days; caspofungin and micafungin hepatically metabolized; anidulafungin chemically degraded in the blood
      c. Adverse effects: Infusion site–related reactions, headache, GI symptoms
d. Drug interactions
   i. Caspofungin: Avoid concomitant use with cyclosporine or tacrolimus.
   ii. Micafungin: Avoid concomitant sirolimus or nifedipine.
   iii. Anidulafungin: None

e. Dosing
   i. Caspofungin: 70 mg once intravenously, followed by 50 mg/day intravenously (lower dose for
      Child-Pugh class B: 70 mg loading, then 35–50 mg daily)
   ii. Micafungin: Candidemia 100 mg/day; esophageal candidiasis or aspergillosis 150 mg/day
   iii. Anidulafungin: 200 mg once intravenously, followed by 100 mg/day intravenously
REFERENCES

**Human Immunodeficiency Virus**


**Opportunistic Infections in Patients with HIV**


**Tuberculosis**


**Fungal Pharmacotherapy**


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**
The patient should be treated at this time; a potent combination ART should be initiated in all HIV-infected patients, regardless of CD4 count (Answer A is incorrect). Combination therapy of tenofovir, emtricitabine, and raltegravir is a recommended initial therapeutic regimen (Answer D is correct). Regimens without an NNRTI, PI, or INSTI are not indicated for HIV (Answer B is incorrect). The regimen of abacavir, lamivudine, and atazanavir/ritonavir is not a recommended or alternative option. It should only be used if recommended or alternative options are not appropriate and should definitely not be first-line therapy (Answer C is incorrect).

2. **Answer: B**
A patient taking abacavir should be screened for the presence of the *HLA-B*^*5701* allele before initiating therapy. If the patient is positive for this allele, the risk of hypersensitivity reactions is increased (Answer B is correct). Although abacavir may increase AST and ALT concentrations, the incidence of hepatotoxicity is extremely low and these labs do not need to be checked before starting therapy. (Answer A is incorrect). Endocrine disturbances (e.g., hyperglycemia, fat redistribution, lipid abnormalities) are more associated with PIs (Answer C is incorrect). Abacavir does not cause hyperbilirubinemia; therefore, the patient need not be monitored for this (although a patient taking atazanavir does) (Answer D is incorrect).

3. **Answer: A**
When the CD4 count decreases to 135 cells/mm^3^, the patient should receive primary prophylactic treatment against PCP (CD4 count less than 200 cells/mm^3^) (Answer A is correct). Primary prophylaxis is necessary for MAC when the CD4 count is less than 50 cells/mm^3^ (Answer D is incorrect). For CMV, patients with CD4 counts less than 50 cells/mm^3^ should receive regular funduscopic examinations (Answer C is incorrect). In general, primary prophylaxis is not used for cryptococcal meningitis (Answer B is incorrect).

4. **Answer: C**
Although pentamidine would be an appropriate therapeutic option for a patient who is HIV positive with PCP, the optimal empiric therapy is trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days (Answer A is incorrect and answer C is correct). The regimen may be changed to trimethoprim/sulfamethoxazole orally after the patient has clinical improvement. Although trimethoprim/sulfamethoxazole is the drug of choice for PCP, adjuvant prednisone therapy is indicated because the patient’s A-a gradient is 55, and his PO_2_ is less than 70 mm Hg (Answer B is incorrect). Atovaquone is indicated only for patients with mild to moderate PCP who cannot tolerate trimethoprim/sulfamethoxazole. This patient does not meet this criterion (Answer D is incorrect).

5. **Answer: B**
Patients with cryptococcal meningitis should ideally be treated with liposomal amphotericin and fluconazole for at least 2 weeks, followed by fluconazole for at least 8 weeks (Answer B is correct). Although amphotericin B deoxycholate with fluconazole is an alternative, this is not the best option (Answer A is incorrect). Fluconazole alone is also an alternative but should only be used when none of the amphotericin products is an option for therapy (Answer C is incorrect). Because of the higher mortality when ART is begun early in cryptococcal meningitis therapy, initiation of ART should be delayed until 5 weeks after beginning appropriate antifungal therapy (Answer D is incorrect).

6. **Answer: B**
Maintenance therapy for cryptococcal meningitis with fluconazole can be discontinued after a minimum of 1 year of long-term maintenance therapy if the CD4 count increases to more than 100 cells/mm^3^ for 3 months or longer after potent combination ART (Answer B is correct and answer D is incorrect). Because this patient’s CD4 counts have been greater than 100 cells/mm^3^ for at least 3 months, maintenance therapy can be discontinued after he has been treated for 1 year (Answers A and C are incorrect).

7. **Answer: B**
For the treatment of MAC, azithromycin plus ethambutol for at least 12 months is the best therapeutic combination; this combination includes one of the newer macrolides and a second agent (ethambutol is usually the preferred second agent) (Answer B is correct). Therapy
may be discontinued after 12 months if CD4 counts increase with potent combination ART and if the patient is asymptomatic. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone, is incorrect because there is no induction therapy followed by maintenance monotherapy for MAC (Answer A is incorrect). A therapeutic regimen of clarithromycin plus isoniazid is not the best because isoniazid has no activity against MAC (Answer C is incorrect). Although ethambutol plus rifabutin has activity against MAC, the current recommendations are that all therapeutic regimens include either azithromycin or clarithromycin; therefore, the ethambutol plus rifabutin regimen is not the treatment of choice (Answer D is incorrect).

8. Answer: D
A patient with an induration greater than 15 mm after a TST for TB needs to be assessed for treatment. Because this patient works at a high-risk congregate setting (i.e., the long-term care facility), he needs to be treated (Answer A is incorrect). The booster effect is a phenomenon associated with an initial small reaction causing immunologic stimulation, followed by a larger reaction with a subsequent test (Answer B is incorrect). This patient had an initial large reaction (18-mm induration). Age is not a factor to consider in treating latent TB (Answer C is incorrect). Initiating isoniazid 300 mg/day orally for 9 months is the best recommendation for managing this patient’s positive TST (Answer D is correct).

9. Answer: C
This patient’s HIV medications should be changed (rifampin will induce the metabolism of darunavir and ritonavir) (Answer A is incorrect). He should not receive a PI or an NNRTI (except for efavirenz) with rifampin. Patients who are HIV positive should be initiated on four drugs for TB, and darunavir should not be used with rifampin (Answer B is incorrect). The best recommendation is isoniazid, rifabutin, pyrazinamide, and ethambutol, with a lower dose of rifabutin; it includes the four drugs for TB and a lower dose of rifabutin (because of darunavir/ritonavir inhibition) (Answer C is correct). The darunavir/ritonavir dose does not need to be changed when rifabutin is added (Answer D is incorrect).

10. Answer: C
For this patient, only the rifamycin and isoniazid need to be continued after 2 months of therapy with the four drugs for TB (Answer A is incorrect). The regimen can be simplified to a rifamycin and isoniazid after 2 months, but the recommended treatment duration is 6 months (Answers B and D are incorrect). The concentrations of HIV RNA should be monitored closely because of potential alterations in drug concentrations of the PI (Answer C is correct).

11. Answer: B
Candida krusei is an organism that is frequently resistant to azole antifungals, including fluconazole and voriconazole; therefore, those agents should not be used in this situation (answers A and D are incorrect). The best choice would be either an echinocandin or amphotericin product (although the newer azoles, posaconazole, and isavuconazole do have some activity against C. krusei). Given its lower side effect profile and lack of adjustments needed for renal or hepatic dysfunction, micafungin is the best choice in this situation (answer B is correct). The length of therapy is also correct, treatment for 14 days after the first negative blood culture. Although an amphotericin B lipid formulation would be a second-line option, the higher incidence of side effects associated with its use make it not the best choice (answer C is incorrect).

12. Answer: D
Onychomycosis needs to be treated for a long period of time, generally 3 months. Although fluconazole is active against the organisms that cause onychomycosis and systemic therapy is generally best, a 14-day course would not be long enough to effectively treat the infection (answer A is incorrect). Itraconazole is one of the drugs of choice for onychomycosis, in either a continuous or pulse therapeutic regimen. However, once again, 28 days is not long enough for treatment (answer B is incorrect). There are a number of different topical antifungal medications that can be used for onychomycosis. However, miconazole cream is not one of them. Also, topical treatment requires longer therapy than systemic treatment (answer C is incorrect). Terbinafine is one of the drugs of choice for onychomycosis and the treatment duration, 3 months, is correct (answer D is correct).

13. Answer: B
Micafungin has activity against Aspergillus and is the best option for this patient because it does not require
dosage adjustment for renal dysfunction and has limited drug interactions (Answer B is correct). Lipid amphotericin has activity against *Aspergillus* and could be used for this infection, but because of its renal toxicity, lipid amphotericin is not the best choice in this patient with acute renal failure (Answer A is incorrect). Fluconazole has no activity against *Aspergillus* and could potentially interact with some of the drugs the patient is receiving (Answer C is incorrect). Voriconazole has activity against *Aspergillus*, but it significantly interacts with several of the drugs the patient is receiving (atorvastatin, dronedarone, warfarin, carbamazepine), making it a less than ideal choice in this patient (Answer D is incorrect).
**HIV/Infectious Diseases**

**ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**

1. **Answer: D**

   Transmission of HIV to a child is decreased if the mother’s viral load is decreased. The benefits of therapy far outweigh the risk (Answer A is incorrect). A potent combination ART regimen given throughout the pregnancy is the most appropriate therapeutic regimen for an asymptomatic patient with HIV who is pregnant (even in the first trimester) and has a low CD4 count and high viral load (Answer D is correct). Although zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and to the child for 6 weeks, was the regimen originally studied to decrease HIV transmission, potent combination ART is indicated because of the patient’s low CD4 count and high viral load; therefore, single-drug therapy is inappropriate (Answer B is incorrect). Although zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and to the child for 6 weeks, was the regimen originally studied to decrease HIV transmission, potent combination ART is indicated because of the patient’s low CD4 count and high viral load; therefore, single-drug therapy is inappropriate (Answer B is incorrect). A single dose of nevirapine at the onset of labor will not affect viral load or lower the risk of HIV transmission as much as potent combination ART throughout the pregnancy (Answer C is incorrect).

2. **Answer: A**

   The patient should be told that dolutegravir can cause insomnia (Answer A is correct). This patient should be told to talk to a pharmacist about the current combination therapy because there are many drug interactions with antiretroviral agents. Neither dolutegravir nor tenofovir inhibit CYP3A4 (Answer C is incorrect). In addition, informing the patient to cut the dose in half if there are adverse effects is incorrect because antiretroviral drugs, should never be used below the recommended dose (Answer B is incorrect). Informing the patient that tenofovir and emtricitabine cause additive peripheral neuropathy is incorrect because neither of these drugs is associated with that adverse effect (Answer D is incorrect).

3. **Answer: B**

   Patients with cryptococcal meningitis should always receive maintenance therapy (Answer A is incorrect). One of the principles of treating AIDS-related illnesses is that the infections are seldom curable, and generally long-term secondary prevention is required. Weekly amphotericin B has been studied for secondary prophylaxis, but fluconazole is the better agent because of its ease of administration and lower toxicity (Answer B is correct and answer C is incorrect). The agents that are effective for PCP prophylaxis have no activity against Cryptococcus (Answer D is incorrect).

4. **Answer: C**

   The number of patients needed to treat with isoniazid over rifampin to prevent one progression to active disease is $200 = 1/(0.008 - 0.003)$ (Answers A and B are incorrect and answer C is correct). The only information needed is the absolute risk in both groups, which is provided (Answer D is incorrect).

5. **Answer: D**

   Pyrimethamine plus clindamycin and leucovorin for 6 weeks is the correct choice for treating toxoplasmosis in a patient who is HIV positive, not taking antiretrovirals, and taking dapsone for PCP prophylaxis (Answer D is correct). Atovaquone is not first-line therapy, although data support its effectiveness in combination with sulfadiazine or pyrimethamine (Answer A is incorrect); trimethoprim/sulfamethoxazole is not effective for treatment or secondary prophylaxis of toxoplasmosis (Answer B is incorrect). Pyrimethamine and sulfadiazine are the first-line agents for toxoplasmosis; however, leucovorin should always be used with pyrimethamine to prevent myelosuppression (Answer C is incorrect).

6. **Answer: D**

   Fluconazole has no activity against aspergillus, so it would not be an option for therapy (Answer A is incorrect). Although voriconazole has activity against aspergillus, there is a significant interaction with rifampin, resulting in lower voriconazole concentrations (Answer B is incorrect). Voriconazole does have activity against aspergillus, but levels are significantly decreased in a patient receiving rifampin (Answer C is incorrect). Amphotericin lipid formulation would be the best option because of its activity against aspergillus and lack of drug interaction with any of the TB medications (Answer D is correct).

7. **Answer: B**

   Because the patient is symptomatic and her sputum is acid-fast bacillus positive, she should be treated for an active TB infection. The recommended therapy for active TB is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 more months (Answer B is correct).
Patients should be initiated on at least three antibiotics for the first 2 months (Answers A and C are incorrect). Although fluoroquinolones have some activity against TB, their use as first-line monotherapy is inappropriate (Answer D is incorrect).

8. **Answer: C**

Data are continuous and probably normally distributed (given the large population of 350 patients in the study); therefore, a parametric test is indicated. The t-test is the best parametric test for comparing two groups (Answer C is correct). Although an analysis of variance is a parametric test, it is used to compare more than two groups (Answer A is incorrect). A chi-square test is used to compare nominal or categorical data between two groups (Answer B is incorrect). The end points in this study are continuous and should therefore not be compared using this statistical test. The Wilcoxon rank sum test is a nonparametric analog to the t-test (Answer D is incorrect).

9. **Answer: A**

Valganciclovir therapy should be continued in an HIV-positive patient with CMV retinitis until the patient's CD4 count is above 100 cells/mm³ for at least 3 months (Answer A is correct, answers B, C and D are incorrect). There is no minimum duration of therapy for CMV retinitis, as there is with MAC or cryptococcal infections. Therapy would need to be reinitiated if his CD4 count fell back below 100 cells/mm³. In patients with CMV retinitis, all lesions must be inactive and the decision to stop maintenance treatment made in collaboration with an ophthalmologist.

10. **Answer: B**

All azole antifungals interact with CYP enzymes. However, fluconazole has less CYP3A4 inhibition than the other azole antifungals (Answer B is correct). It interacts with CYP2C9 at lower doses, but it interacts with CYP3A4 only at doses of 400 mg/day or higher. All other azole antifungals interact with CYP3A4 at typical therapeutic doses (Answer A, C and D are incorrect).

11. **Answer: C**

Because the patient has a sulfa allergy, trimethoprim/sulfamethoxazole is not an option, even though the dose is correct (Answer A is incorrect). All of the other agents are potential options. However, the dapsone dose is incorrect. When used alone it must be dosed daily (Answer B is incorrect). Moreover, pentamidine is difficult to administer because it must be done by nebulization (Answer D is incorrect). Therefore, the best choice is atovaquone (Answer C is correct).

12. **Answer: A**

Given the fact that this patient is hospitalized and his infection is worsening, this can be considered a moderate to severe case of Histoplasmosis. The correct regimen is 1-2 weeks of an amphotericin B lipid formulation followed by itraconazole to complete a 12-week course (Answer A is correct). The echinocandins appear to be ineffective against Histoplasma so micafungin should not be used (answer B is incorrect). Although both voriconazole and isavuconazole have activity against Histoplasma they currently aren't recommended based on limited to no clinical data to back up their use. Voriconazole also has a lot of drug interactions (as does itraconazole) and isavuconazole is much more expensive (answers C and D are incorrect).

13. **Answer: B**

This patient has active tuberculosis as demonstrated by his symptoms, positive sputum, and positive IGRA test. Patients with active tuberculosis should be treated with 4 drugs (rifampin, isoniazid, pyrazinamide, ethambutol) for 2 months and 2 drugs (rifampin and isoniazid) for 4 months (answers C and D are incorrect). Although a regimen administered 2 and 3 times weekly is optional, it is not the recommended therapy (answer A is incorrect). Ideally, active tuberculosis treatment should be given either daily or 5 times weekly (Answer B is correct).