HIV/Infectious Diseases

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Learning Objectives

1. Formulate an appropriate regimen to prevent or treat human immunodeficiency virus infections, including initiation 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. Classify the various antifungal agents and explain their role in common fungal infections.

Self-Assessment Questions

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

1. K.E. is a 29-year-old asymptomatic patient who is human immunodeficiency virus (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 baby for 6 weeks.
   C. No drug therapy is required now, but administer a single dose of nevirapine at the onset of labor.
   D. Administer a potent combination antiretroviral therapy (ART) regimen that includes zidovudine throughout the pregnancy.

2. R.E. is a 33-year-old man who has been HIV positive since 2005. Recently, his CD4 counts started to decrease significantly, and his viral load started to increase. He is initiated on tenofovir, emtricitabine, and atazanavir/ritonavir. Which is the best counseling for R.E.?
   A. Watch for yellowing of the skin and eyes because atazanavir can cause hyperbilirubinemia.
   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 atazanavir and tenofovir inhibit cytochrome P450 (CYP) 3A4.
   D. Tenofovir and emtricitabine cause additive peripheral neuropathy, so let your pharmacist know if you experience tingling in your extremities.

3. One year later, R.E. is concerned that his ART is not working and asks whether he should make some changes. Which statement best represents what to tell him?
   A. His therapy should be changed only if he is deteriorating clinically (e.g., having more opportunistic infections).
   B. His therapy should be changed if his viral load increases significantly after initial suppression to undetectable concentrations.
   C. If he is concerned about his regimen not being effective, then atazanavir/ritonavir should be changed to fosamprenavir/ritonavir.
   D. Resistance usually occurs with emtricitabine, so this should be changed to lamivudine.

4. F.V. is a 46-year-old man who has been HIV positive for 15 years. He has been receiving potent combination ART for the past 5 years, including zidovudine, lamivudine, and lopinavir/ritonavir. He is now experiencing hyperglycemia, fat redistribution, and lipid abnormalities. Which is the best management strategy for F.V.’s drug-related symptoms?
   A. Change regimen to tenofovir, emtricitabine, and rilpivirine.
   B. Change regimen to abacavir, lamivudine, and raltegravir.
   C. Add simvastatin for the lipid abnormalities and treat according to the recommendations from the National Cholesterol Education Program.
D. Add pioglitazone for the glucose abnormalities and treat according to the recommendations from the American Diabetes Association.

5. 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/mm$^3$. His laboratory profile is performed with the following results: Gram stain negative, white blood cell count 2 cells/mm$^3$, protein 35 mg/dL, glucose 75 mg/dL (peripheral 110 mg/dL), India ink positive, and cryptococcal antigen 1:1024. Which is the best therapy for P.P.?
   A. Fluconazole 200 mg/day orally for 8 weeks.
   B. Amphotericin B deoxycholate 0.3 mg/kg/day alone for 2 weeks.
   C. Amphotericin B deoxycholate 0.3 mg/kg/day plus flucytosine 37.5 mg/kg every 6 hours for 4 weeks.
   D. Amphotericin B deoxycholate 0.7 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks.

6. A study is performed to compare 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.

7. 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. Her most recent CD4 count was 85 cells/mm$^3$, but that was 4 months ago. She currently takes no antiretroviral agents but does take dapsone for Pneumocystis jiroveci pneumonia (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.

8. 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. Flucytosine.
   D. Micafungin.

9. 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 purified protein derivative (PPD) 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 PPD 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 300 mg/day orally for 6 months.
   B. Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 more months.
   C. Isoniazid and rifampin for 6 months.
   D. Levofloxacin 750 mg/day orally for both TB and other bacterial causes of pneumonia.
10. 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 efavirenz—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.
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
            (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 either a gay or bisexual man who has had anal sex without a condom or been diagnosed with an STD 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 injects illicit drugs in the past 6 months and who have shared injection equipment or been in drug treatment in the past 6 months.
            (b) Document negative HIV antibody.
            (c) Use tenofovir 300 mg plus emtricitabine 200 mg (Truvada) daily.
            (d) Test every 90 days for HIV antibody (and if prophylaxis is discontinued).
   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 nonintact skin exposures to bloodborne pathogens
      b. Bodily fluids

<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>
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<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 (i.e., 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-0 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 Ulitro
   4. Test for HIV RNA
      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. For all tests, less than 200 copies/mL is considered undetectable.
      g. Changes greater than threefold (about 0.5 log) are clinically 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 (also check CD4 count)
      d. From 2 to 4 (no more than 8) weeks after starting or changing therapy (should detect a significant decrease)
      e. Every 3–6 months while on therapy (checking for increase—therapy failure); (also check CD4 count)
      f. Whenever there is a clinical event or decrease in CD4 count
6. 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

7. 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 to 6 months) may be needed based on clinical symptoms and viral load testing.

8. Case definition for HIV, 2008 (Table 2)

Table 2. Case Definition for HIV, 2008

<table>
<thead>
<tr>
<th>Stage</th>
<th>Laboratory Evidence</th>
<th>Clinical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Laboratory confirmation of HIV infection and CD4 count of ≥500/µL or CD4 percentage of ≥29</td>
<td>None required (but no AIDS-defining condition)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Laboratory confirmation of HIV infection and CD4 count of 200–499/µL or CD4 percentage of ≥14–28</td>
<td>None required (but no AIDS-defining condition)</td>
</tr>
<tr>
<td>Stage 3 (AIDS)</td>
<td>Laboratory confirmation of HIV infection and CD4 count of &lt;200/µL or CD4 percentage of &lt;14</td>
<td>Or documentation of an AIDS-defining condition (with laboratory confirmation of HIV infection)</td>
</tr>
<tr>
<td>Stage unknown</td>
<td>Laboratory confirmation of HIV infection and No information on CD4 count or percentage</td>
<td>And no information on presence of AIDS-defining conditions</td>
</tr>
</tbody>
</table>

*Laboratory confirmation: Positive result from an HIV antibody screening test (e.g., reactive enzyme immunoassay) confirmed by a positive result from a supplemental HIV antibody test (e.g., Western blot or indirect immunofluorescence assay test) or positive result or report of a detectable quantity (i.e., within the established limits of the laboratory test) from any of the following HIV virologic (i.e., nonantibody) tests.
9. Acquired immunodeficiency syndrome (AIDS)-defining conditions (Table 3)

Table 3. AIDS-Defining Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Bacterial infections, multiple or recurrent (&lt;13 years)</td>
<td>Lymphoid interstitial pneumonia or pulmonary</td>
</tr>
<tr>
<td>Candidiasis: bronchi, trachea, or lungs</td>
<td>lymphoid hyperplasia complex (&lt;13 years)</td>
</tr>
<tr>
<td>Candidiasis: esophageal</td>
<td>Lymphoma: Burkitt (or equivalent term)</td>
</tr>
<tr>
<td>Cervical cancer: invasive</td>
<td>Lymphoma: immunoblastic (or equivalent term)</td>
</tr>
<tr>
<td>Coccidiodymycosis: disseminated or extrapulmonary</td>
<td>Lymphoma: primary or brain</td>
</tr>
<tr>
<td>Cryptococcosis: extrapulmonary</td>
<td>Mycobacterium avium complex or M. kansasii:</td>
</tr>
<tr>
<td>Cryptosporidiosis: chronic intestinal (&gt;1 month in duration)</td>
<td>disseminated or extrapulmonary</td>
</tr>
<tr>
<td>Cytomegalovirus disease (other than liver, spleen, or nodes)</td>
<td>M. tuberculosis: any site (pulmonary or extrapulmonary)</td>
</tr>
<tr>
<td>Cytomegalovirus retinitis (with loss of vision)</td>
<td>1. Cytomegalovirus retinitis (with loss of vision)</td>
</tr>
<tr>
<td>Encephalopathy: HIV related</td>
<td>2. Enterovirus infections</td>
</tr>
<tr>
<td>Herpes simplex: chronic ulcer(s) (&gt;1 month in duration); bronchitis,</td>
<td>a. Enterovirus infections</td>
</tr>
<tr>
<td>pneumonia, myelitis, or esophagitis</td>
<td>b. Enterovirus infections (Arbovirus)</td>
</tr>
<tr>
<td>Histoplasmosis: disseminated or extrapulmonary</td>
<td>c. Enterovirus infections (Viruses)</td>
</tr>
<tr>
<td>Isosporiasis: chronic intestinal (&gt;1 month in duration)</td>
<td>d. Enterovirus infections (Non-Arbovirus)</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>3. Cytomegalovirus disease (other than liver, spleen, or nodes)</td>
</tr>
</tbody>
</table>

C. Primary HIV Infection

1. Characteristics of the primary HIV infection
   a. About 40%–60% develop symptoms from the primary infection.
   b. Abrupt onset: Duration 3–14 days
   c. Occurs 5 days to 3 months after HIV exposure (generally within 2–4 weeks)
   d. Fevers, sweats, lethargy, malaise, myalgias, arthralgias, headache, photophobia, diarrhea, sore throat, lymphadenopathy
   e. Treatment of an acute HIV infection is generally not recommended.

2. Progression of HIV
   a. HIV replicates actively at all stages of the infection.
   b. $10^9$ to $10^{10}$ virions are produced every day.
   c. Half-life of virions is about 6 hours.

3. Immunization of patients with HIV (no live virus vaccines if CD4 count is less than 200 cells/mm$^3$)
   a. Influenza virus vaccine: Annually before the influenza season
   b. Pneumococcal vaccine: Once (ideally, before CD4 count is less than 200 cells/mm$^3$)
   c. Hepatitis B vaccine: For all susceptible patients
   d. Hepatitis A vaccine: For all at-risk patients
D. Treatment of HIV

1. Reverse transcriptase inhibitors (RTIs) (nucleoside [NRTIs], nucleotide, and nonnucleoside [NNRTIs])
   a. Reverse transcriptase: Enzyme required to copy viral RNA to DNA
   b. See Tables 4 and 5 for RTI characteristics.

2. Protease inhibitors (PIs)
   a. Protease: Enzyme required to cleave polyproteins into mature viral protein components
   b. See Table 6 for PI characteristics.

3. Entry inhibitors (Table 7)
   a. Block binding and entry of the virus into human cells
   b. See Table 7 for entry inhibitor characteristics.

4. Integrase inhibitors (INSTIs) (Table 7)
   a. Integrase: Enzyme required for integration of viral DNA into the host cellular genome
   b. See Table 7 for INSTI characteristics.

5. Prevention of maternal-fetal transmission
   a. Pregnant women with HIV receiving no ART
      i. Women who meet the criteria for beginning HIV therapy in adults should receive a potent
         three-drug combination ART (to prevent resistance); initiate therapy as soon as possible, even
         in the first trimester.
      ii. Women who do not meet the criteria for beginning HIV therapy should still receive potent
         combination ART (to prevent transmission); delay therapy until after first trimester, but no
         later than 28 weeks’ gestation, though earlier therapy can be considered.
      iii. Use zidovudine as a component of therapy unless there is severe toxicity or resistance, or
           unless the woman is already on a fully suppressive regimen.
      iv. Avoid efavirenz in women of childbearing age to prevent first-trimester exposure.
      v. Women who have received ART in the past but who are currently on no therapy should have
         HIV antiretroviral resistance testing completed before starting therapy.
      vi. Continue combination regimen through the intrapartum period (with zidovudine infusion
          added) and treat baby for 6 weeks.
   b. Pregnant women with HIV receiving potent combination ART
      i. Continue current combination regimens (preferably with zidovudine) if already receiving
         therapy. Avoid efavirenz in the first trimester.
      ii. Continue combination regimen through intrapartum period (with zidovudine infusion added)
          and treat baby for 6 weeks.
   c. Pregnant women with HIV in labor (with or without therapy during pregnancy)
      i. At labor, zidovudine 2 mg/kg intravenously for 1 hour, followed by a 1-mg/kg/hour infusion
         until cord is clamped. Discontinue oral zidovudine but continue any other oral antiretrovirals
         (except for stavudine).
      ii. Continue ART as much as possible during labor.
   d. Infants born to mothers who are HIV positive
      i. Zidovudine 4-mg/kg/dose every 12 hours for 6 weeks
      ii. Infants born to mothers who did not receive antiretrovirals during pregnancy: 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
6. Prevention of postexposure infection
   a. Use universal precautions.
   b. Nonoccupational exposures: Treat if exposure of vagina, rectum, eye, mouth, mucous membrane, or nonintact 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. Regimens for occupational postexposure prophylaxis
      i. Preferred regimen: raltegravir 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
         or
         (b) Elvitegravir, cobicistat, tenofovir, emtricitabine (Stribild)
<table>
<thead>
<tr>
<th>Nucleoside RTIs</th>
<th>Form</th>
<th>Dosing</th>
<th>Serum half-life</th>
<th>Intracellular half-life</th>
<th>Major toxicity</th>
<th>Drug interactions</th>
<th>Miscellaneous information</th>
<th>Pharmacokinetic properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>300-mg tablets</td>
<td>150 mg BID</td>
<td>12–26 hours</td>
<td>12–26 hours</td>
<td>Hypersensitivity, fever, rash, nausea, diarrhea</td>
<td>Ethanol may increase ABC concentrations</td>
<td>Hypersensitivity reaction may be fatal: discontinue drug immediately</td>
<td>Metabolized by alcohol dehydrogenase and glucuronotransferase</td>
</tr>
<tr>
<td>RTI Type</td>
<td>Form</td>
<td>Dosing</td>
<td>Oral Bioavailability</td>
<td>Serum half-life</td>
<td>Elimination</td>
<td>Major Toxicity</td>
<td>Drug Interactions</td>
<td>Miscellaneous Information</td>
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<tr>
<td>Nevirapine (NVP) (Viramune, Viramune XR)</td>
<td>Nucleoside</td>
<td>200–200-mg tablets</td>
<td>85%</td>
<td>5.8 hours</td>
<td>Metabolized by CYP3A4 and CYP2C19 to nevirapine glucuronide</td>
<td>Rash (less than delavirdine), Headache, Rash, Elevation of AST/ALT, Rash, Nausea</td>
<td>Induces CYP3A4 and CYP2C19</td>
<td>Extensive cross-resistance in class</td>
</tr>
<tr>
<td>Delavirdine (DLV) (Rescriptor)</td>
<td>Nucleoside</td>
<td>100–200-mg tablets</td>
<td>42%</td>
<td>5–8 hours</td>
<td>Metabolized by CYP3A4, CYP2C19, and CYP2C9 to 5′-epoxide and 5′- glucuronide</td>
<td>Rash (less than delavirdine), CNS symptoms (insomnia, impaired concentration, nightmares, mania)</td>
<td>Reduces CYP3A4 and CYP2C19 with administration of didanosine and zidovudine (ddI)</td>
<td>Extensive cross-resistance in class</td>
</tr>
<tr>
<td>Efavirenz (EFV) (Sustiva, Atripla)</td>
<td>Nucleoside</td>
<td>400–400 mg PO qHS</td>
<td>40%</td>
<td>&gt;24 hours</td>
<td>Metabolized by CYP3A4</td>
<td>Rash, Nausea, Headache, Hypersensitivity reaction, Elevated AST/ALT</td>
<td>Induces CYP3A4 and CYP2C19</td>
<td>Extensive cross-resistance in class</td>
</tr>
<tr>
<td>Rilpivirine (RPV) (Edurant, Complera)</td>
<td>Nucleoside</td>
<td>200–200 mg PO BID</td>
<td>90%</td>
<td>10–14 hours</td>
<td>Metabolized by CYP3A4</td>
<td>Rash, GI toxicity, Depression, Abnormal LFTs, Hepatotoxicity</td>
<td>Induces CYP3A4 and CYP2C19</td>
<td>Extensive cross-resistance in class</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate (TDF) (Viread, Truvada, Atripla, Complera, Stribild)</td>
<td>Nucleoside</td>
<td>25–200 mg PO daily</td>
<td>40%</td>
<td>14–15 hours</td>
<td>Metabolized by CYP3A4, 51% excreted in urine (&lt;5% unchanged), 44% in feces</td>
<td>Rash, GI toxicity, Abnormal LFTs, Hepatotoxicity</td>
<td>Induces CYP3A4 and CYP2C19</td>
<td>Extensive cross-resistance in class</td>
</tr>
</tbody>
</table>

**Dosage adjustment in hepatic insufficiency.**

**Drug interactions:**
- PPIs (contraindicated), H₂-blockers,
- antacids
- Increases ddI concentration; separate administration
- May be effective against HIV-1 resistant to other RTIs

**Miscellaneous information:**
- Do not initiate in patients with CD4+ counts >250 cells/mm³ or in men with CD4+ counts >400 cells/mm³ (liver toxicity)
- Use with caution if viral load >100,000 copies/mL
- May cause lactic acidosis with hepatic steatosis (mitochondrial toxicity may be less)

**Table 5:** Nonnucleoside and Nucleotide RTIs

**RTI type**
- Nonnucleoside
- Nucleotide

**Form**
- Oral tablets
- Extended-release tablets
- Capsules

**Dosing**
- PO TID
- PO BID
- PO qHS

**Oral Bioavailability**
- 42–80%

**Serum half-life**
- 5–30 hours

**Elimination**
- Metabolized by CYP3A4, 51% excreted in urine (<5% unchanged), 44% in feces

**Major Toxicity**
- Rash, Headache, Rash, Elevation of AST/ALT, Rash, Nausea

**Drug Interactions**
- Inhibits CYP3A4 and CYP2C19
- Induces CYP3A4

**Miscellaneous Information**
- Can dissolve in water for patients who cannot swallow
- Effective against HIV-1 resistant to other RTIs
- Use with caution if viral load >100,000 copies/mL
- May cause lactic acidosis with hepatic steatosis (mitochondrial toxicity may be less)

**Dosage adjustment in renal insufficiency.**

**Dosage adjustment in hepatic insufficiency.**

**RTI type**
- Nonnucleoside
- Nucleotide

**Form**
- Oral tablets
- Extended-release tablets
- Capsules

**Dosing**
- PO TID
- PO BID
- PO qHS

**Oral Bioavailability**
- 42–80%

**Serum half-life**
- 5–30 hours

**Elimination**
- Metabolized by CYP3A4, 51% excreted in urine (<5% unchanged), 44% in feces

**Major Toxicity**
- Rash, Headache, Rash, Elevation of AST/ALT, Rash, Nausea

**Drug Interactions**
- Inhibits CYP3A4 and CYP2C19
- Induces CYP3A4
- Separates administration with didanosine and didanosine

**Miscellaneous Information**
- Can dissolve in water for patients who cannot swallow
- Effective against HIV-1 resistant to other RTIs
- Use with caution if viral load >100,000 copies/mL
- May cause lactic acidosis with hepatic steatosis (mitochondrial toxicity may be less)
### Table 6. Protease Inhibitors

| Drug                  | Form          | Dosing                  | Major toxicity                                      | Drug interactions | Miscellaneous       | Less lipid effects | Less transaminase inhibition | Less PR and QT prolongation | Less less lipid effects in patients with diabetes | Less less lipid effects in patients with endocrine disturbances |
|-----------------------|---------------|-------------------------|-----------------------------------------------------|-------------------|---------------------|--------------------|-----------------------------|-----------------------------|--------------------------------------------------------------------------------|
| Tipranavir            | 250-mg capsules, 100-mg/ml solution, 80-mg/ml oral suspension, 200-mg tablets | 100 mg BID with RTV 100 mg BID 100 mg BID | Rash, pruritus, elevated transaminases, peripheral neuropathy, endocrine disturbances, hypotension, fever, chills, erythema, rash | No major drug interactions | Fluid retention | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus |
| Saquinavir (SQV)      | 100-mg capsules, 50-mg tablets | 200 mg BID with RTV 125 mg BID 125 mg BID | Rash, hyperlipidemia, rash, diarrhea, hepatotoxicity, peripheral neuropathy, endocrine disturbances, hypotension, fever, chills, erythema | No major drug interactions | Fluid retention | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus |
| Ritonavir (RTV)       | 100-mg capsules, 50-mg tablets, 125-mg tablets | 100 mg BID with RTV 50 mg BID 50 mg BID | Rash, hyperlipidemia, rash, diarrhea, hepatotoxicity, peripheral neuropathy, endocrine disturbances, hypotension, fever, chills, erythema | No major drug interactions | Fluid retention | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus |
| Atazanavir (ATV)      | 100-mg capsules, 50-mg tablets | 100 mg BID with RTV 50 mg BID 50 mg BID | Rash, hyperlipidemia, rash, diarrhea, hepatotoxicity, peripheral neuropathy, endocrine disturbances, hypotension, fever, chills, erythema | No major drug interactions | Fluid retention | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus |
| Lopinavir/                        | 200-mg tablets | 100 mg BID with RTV 50 mg BID 50 mg BID | Rash, hyperlipidemia, rash, diarrhea, hepatotoxicity, peripheral neuropathy, endocrine disturbances, hypotension, fever, chills, erythema | No major drug interactions | Fluid retention | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus |
| Nelfinavir (NFV)                        | 100-mg capsules, 50-mg tablets | 100 mg BID with RTV 50 mg BID 50 mg BID | Rash, hyperlipidemia, rash, diarrhea, hepatotoxicity, peripheral neuropathy, endocrine disturbances, hypotension, fever, chills, erythema | No major drug interactions | Fluid retention | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus | Good for PI-resistant virus |

**Dosage adjustment in hepatic insufficiency:**
- If severe liver disease: reduce dosage

**Dosage adjustment in renal insufficiency:**
- If severe renal disease: reduce dosage

**Endocrine disturbances include insulin resistance (type 2 diabetes mellitus in 8%–10%), hyperglycemia, and lipodystrophy (in 70%).**

**Drug interactions:**
- Induces CYP3A4, PPIs, H2-blockers, antacids
- Inhibits CYP3A4, CT2D6
- Decreases absorption

**Miscellaneous information:**
- Cross-resistance with other protease inhibitors
- Do not use with IDV

**Other miscellaneous information:**
- Drug interactions: See drug interaction chart for dosage adjustment
- Pharmacokinetic information: See pharmacokinetic chart for dosage adjustment

**Clinical implications:**
- Good for treatment of PI-resistant virus
- Good for treatment of PI-resistant virus
- Good for treatment of PI-resistant virus

**References:**
- [ACCP Updates in Therapeutics® 2015: The Pharmacotherapy Preparatory Review and Recertification Course](http://example.com)
**Table 7.** Entry Inhibitors and Integrase Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Enfuvirtide (Fuzeon)</th>
<th>Maraviroc (MVC) (Selzentry)</th>
<th>Dolutegravir (DTG) (Tivicay, Triumeq)</th>
<th>Elvitegravir (EVG) (Stribild, VitECTA)</th>
<th>Raltegravir (RAL) (Isentress)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Entry inhibitor</td>
<td>Entry inhibitor</td>
<td>Integrase inhibitor</td>
<td>Integrase inhibitor</td>
<td>Integrase inhibitor</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>90-mg vials</td>
<td>150-, 300-mg tablets</td>
<td>50-mg tablets</td>
<td>Tablets with elvitegravir 150 mg/</td>
<td>25-, 100-, 400-mg tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Triumeq: 600 mg of ABC, 50 mg of DTG, 300 mg of 3TC</td>
<td>cobicistat 150 mg/tenofovir 300 mg emtricitabine 200 mg*</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>90 mg SC BID</td>
<td>150–600 mg PO BID (depending on concomitant drug interactions)*</td>
<td>50 mg PO once daily</td>
<td>Stribild: once daily VitECTA: once daily; dose depends on combination</td>
<td>400 mg PO BID</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>N/A</td>
<td>23%–33%</td>
<td>Take with or without food</td>
<td>Food increases absorption and bioavailability</td>
<td>Take with food</td>
</tr>
<tr>
<td><strong>Serum half-life</strong></td>
<td>3.8 hours</td>
<td>14–18 hours</td>
<td>14 hours</td>
<td>13 hours</td>
<td>9 hours</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Metabolized by hydrolysis</td>
<td>Metabolized by CYP3A</td>
<td>Metabolized by glucuronidation by UGT1A1/3 enzymes and by CYP3A</td>
<td>Metabolized by CYP3A and glucuronidation by UGT1A1/3 enzymes</td>
<td>Metabolized by hepatic glucuronidation by uridine 5′-diphospho--glucuronosyltransferase</td>
</tr>
<tr>
<td><strong>Major toxicity</strong></td>
<td>Hypersensitivity reactions; local injection-site reactions (98%); pneumonia</td>
<td>Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension</td>
<td>Insomnia and diarrhea Benign increases in creatinine (inhibits creatinine secretion and bilirubin (blocks bilirubin clearance)</td>
<td>Renal toxicity (avoid concomitant nephrotoxic agents); discontinue if CrCl is less than 50 mL/minute</td>
<td>Nausea, headache, diarrhea, pyrexia, creatine kinase elevation</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>None</td>
<td>CYP3A substrate (watch CYP3A inducers and inhibitors)</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, and rifabutin</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></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 gp4 peptide sequence, preventing fusion</td>
<td>Binds to the CCR5 receptor of the CD4 T cell, preventing fusion and HIV entry</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</td>
</tr>
</tbody>
</table>

*Dosage adjustment in renal insufficiency.

3TC = lamivudine; ABC = abacavir; BID = twice daily; CrCl = creatinine clearance; CYP = cytochrome P450; N/A = not applicable; PO = orally; qHS = every night; SC = subcutaneously; TID = three times daily.
Patient Case
1. F.G. is a 27-year-old man who is HIV positive but asymptomatic. One year ago, his CD4 count was 815 cells/mm³, and his viral load was 1500 copies/mL (by reverse transcriptase polymerase chain reaction). F.G. continues to be monitored; his CD4 count has decreased (most recent was 240 cells/mm³), and his viral load has increased (most recent was 60,000 copies/mL by reverse transcriptase polymerase chain reaction). Which is the best treatment for F.G.?
   A. ART should not be given because F.G.’s CD4 count is still above 200 cells/mm³.
   B. Initiate F.G. on zidovudine alone because his CD4 count is still above 200 cells/mm³.
   C. Initiate F.G. on combination therapy of zidovudine, lamivudine, and nevirapine.
   D. Initiate F.G. on combination therapy of tenofovir, emtricitabine, and atazanavir/ritonavir.

7. Treatment of the patient who is HIV positive
   a. Initiating potent combination ART in an antiretroviral-naive patient
      i. Any patient who is HIV positive (regardless of viral load or CD4 count) with the following conditions
         (a) Pregnancy
         (b) History of AIDS-defining illness
         (c) HIV-associated nephropathy
         (d) HIV/hepatitis B coinfection
      ii. Any HIV-positive patient with the following CD4 counts
         (a) Less than 350 cells/mm³ (strongest recommendation)
         (b) CD4 350–500 cells/mm³ (lower strength of recommendation)
         (c) More than 500 cells/mm³ (lowest strength of recommendation)
      iii. Any HIV-positive patient at risk of transmitting HIV to sexual partners
   b. Recommended therapy regardless of baseline viral load or CD4 count: The optimal ART for a treatment-naive patient consists of two NRTIs in combination with a third active drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir, or an INSTI
      i. NNRTI-based regimen: efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)
      ii. PI-based regimens
         (a) Atazanavir/ritonavir plus tenofovir/emtricitabine (ATV/r plus TDF/FTC)
         (b) Darunavir/ritonavir plus tenofovir/emtricitabine (DRV/r plus TDF/FTC)
      iii. INSTI-based regimens
         (a) Dolutegravir/abacavir/lamivudine (DTG plus ABC/3TC); only for patients who are HLA-B*5701 negative
         (b) Dolutegravir/tenofovir/emtricitabine (DTG plus TDF/FTC)
         (c) Elvitegravir/cobicistat plus tenofovir/emtricitabine (EVG/cobi/TDF/FTC); only for patients with pre-ART CrCl >70 mL/min
         (d) Raltegravir/Tenofovir/Emtricitabine (RAL plus TDF/FTC)
   c. Recommended therapy only for patients with viral load <100,000 copies/mL
      i. NNRTI-based regimens
         (a) Efavirenz/abacavir/lamivudine (EFV plus ABC/3TC); only for patients who are HLA-B*5701 negative
         (b) Rilpivirine/tenofovir/emtricitabine (RPV/TDF/FTC); only for patients with CD4 count >200 cells/mm³
      ii. PI-based regimen: Atazanavir/ritonavir plus abacavir/lamivudine (ATV/r plus ABC/3TC); only for patients who are HLA-B*5701 negative
iii. Recommended therapy only for patients with viral load <100,000 copies/mL: Efavirenz or atazanavir/ritonavir plus abacavir/lamivudine; rilpivirine plus tenofovir/emtricitabine (only if CD4 count > 200 cells/mm³)

d. Alternative therapy: Based on individual patient characteristics and needs, an “alternative regimen” may be the optimal regimen for a given patient.
   i. PI-based regimens
      (a) Darunavir/ritonavir plus abacavir/lamivudine (DRV/r plus ABC/3TC); only for patients who are HLA-B*5701 negative
      (b) Lopinavir/ritonavir plus abacavir/lamivudine or tenofovir/emtricitabine (LPV/r [once or twice daily] plus ABC/3TC); only for patients who are HLA-B*5701 negative
      (c) Lopinavir/ritonavir plus abacavir/lamivudine or tenofovir/lamivudine (LPV/r [once or twice daily] plus TDF/FTC)
   ii. INSTI-based regimen: Raltegravir plus abacavir/lamivudine (RAL plus ABC/3TC); only for patients who are HLA-B*5701 negative

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**Patient Cases**

2. Six months after he starts appropriate therapy, F.G.’s CD4 count is 620 cells/mm³, and his viral load is undetectable. Two years later, his CD4 count decreases to 310 cells/mm³, and his viral load is 15,000 copies/mL. Resistance testing is performed, and resistance is detected to atazanavir but not the other PIs. Which change is best for F.G.’s therapy?
   A. Stress adherence and continue the same regimen.
   B. Change atazanavir/ritonavir to efavirenz.
   C. Change tenofovir and emtricitabine to abacavir and lamivudine.
   D. Change the entire regimen to abacavir, lamivudine, and darunavir/ritonavir.

3. Which is the best parameter to monitor if F.G. is to receive darunavir/ritonavir?
   A. Peripheral neuropathy.
   B. Drug interactions with drugs metabolized by CYP1A2.
   C. Endocrine disturbances such as hyperglycemia, fat redistribution, and lipid abnormalities.
   D. Nephrolithiasis.

---

f. Change therapy for the following reasons:
   i. Practical reasons
      (a) Reduce pill burden
      (b) Decrease adverse events
      (c) Change food or fluid requirements
      (d) Minimize drug interactions
      (e) Optimize therapy during or before pregnancy
      (f) Reduce costs
   ii. Virologic failure
      (a) Not achieving HIV RNA less than 200 copies/mL
      (b) Two consecutive HIV RNA levels more than 200 copies/mL after 24 weeks of therapy
      (c) HIV RNA levels more than 200 copies/mL after initial suppression to undetectable levels
iii. Immunologic failure
   (a) No specific definition
   (b) Some studies have used the following:
      (1) Failure to increase 50–100 cells/mm³ above the baseline CD4 cell count during the first year of therapy
      (2) Failure to increase the CD4 count above 350 cells/mm³ in 4–7 years

   g. Regimen switching for practical reasons
   i. Review past treatment history and resistance testing. Consider consulting an HIV specialist.
   ii. Do not switch without assurance that the new regimen will be as active as the current one.
   iii. Within-class switches due to adverse events usually maintain suppression.
   iv. If there is no drug resistance, switches to lower-toxicity, lower–pill burden regimens generally results in similar if not better outcomes.
   v. Monitor the patient closely during the first 3 months after a switch.

   h. Options for treatment failure
   i. Perform resistance testing (while patient is on failing regimen or within 4 weeks of discontinuing).
      (a) More accurate result if HIV RNA levels are >1,000 copies/mL
      (b) If HIV RNA levels are >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered.
   ii. Prior therapy with no resistance
      (a) Check adherence and address underlying causes. Consider reinitiating the same regimen.
      (b) Initiate a new regimen.
      (c) Intensify one therapy or boost one therapy based on pharmacokinetic parameters.
   iii. Prior therapy with resistance: Start a new regimen with at least two and preferably three fully active agents.
   iv. Extensive therapy with resistance: Resuppress viral load maximally or at least adequately to prevent clinical progression.
   v. New regimen with at least two fully active agents is not possible: Continue current regimen.

   i. Resistance testing
      i. Types of testing
         (a) Genotypic
            (1) Testing for the presence of mutations known to cause drug resistance
            (2) Comparing the HIV-1 pol gene with a wild-type gene
            (3) Recommended to guide therapy in patients with virologic failure while on their first or second regimen
         (b) Phenotypic
            (1) Test for inhibitory concentration needed to decrease HIV replication by 50% (IC₅₀)
            (2) Values are reported as fold changes in sensitivity.
            (3) An increase of less than fourfold in IC₅₀ is defined as sensitive.
            (4) A four- to tenfold increase in IC₅₀ is defined as intermediate.
            (5) An increase of more than tenfold in IC₅₀ is defined as resistant.
            (6) Added to genotypic testing in patients with complex drug resistance mutation patterns
      ii. Indications
         (a) Recommended: Upon entrance into care
         (b) Recommended: Virologic failure during potent combination ART
         (c) Recommended: All pregnant women with HIV
         (d) Recommended: Suboptimal suppression of viral load after initiation of potent combination ART
(e) Recommended: Acute HIV infection before initiating therapy to determine whether a drug-resistant virus was transmitted
(f) Genotypic testing recommended for treatment-naive patients
(g) Phenotypic testing recommended for treatment-experienced patients with complex resistance patterns

iii. Benefits
(a) Resistance testing is an independent indicator of virologic outcome (better short-term viral load response in those who had testing completed).
(b) May also benefit patients by limiting drug exposures, toxicities, and expense

iv. Limitations
(a) The effect of resistance testing is limited in heavily treated patients.
(b) The HIV RNA value must be greater than 1000 copies/mL (500–1000 copies/mL acceptable).
(c) Current need for expert interpretation
(d) Difficult-to-detect small mutant populations (less than 20%)
(e) Cost: About $400–$500 per test

II. OPPORTUNISTIC INFECTIONS: PATIENTS WITH HIV

Figure 1. Relationship between CD4 count and risk of HIV-related opportunistic infections.
MAI = *Mycobacterium avium-intracellulare.*

A. Overview of HIV-Associated Opportunistic Infections
1. Principle 1: The fungal, parasitic, and viral infections acquired by people who are infected with HIV are rarely curable. At best, the infection is controllable during an acute episode but usually requires long-term suppressive therapy.
2. Principle 2: Most HIV-associated infections represent endogenous reactivation of previously acquired organisms and do not represent a threat to others.
3. Principle 3: Concurrent or consecutive infections with different organisms are a common clinical occurrence in severely immunosuppressed people with HIV infection.
4. Principle 4: The observed frequency of certain parasitic and fungal infections depends on the prevalence of asymptomatic infection with these pathogens in the local population.
5. Principle 5: Infections associated with HIV are severe, often disseminated and atypical, and characterized by a high density of organisms.
6. Principle 6: Certain B-cell–associated infections are seen with greater frequency in people with HIV infections (e.g., pneumococcal infection).

**Patient Cases**

4. Three years later, F.G. (from Patient Case questions 1–3) has not responded to any of his ART regimens because of resistance or intolerance. His CD4 count has decreased to 135 cells/mm³. For which infection is it most important that F.G. receive primary prophylaxis?
   A. *Pneumocystis jirovecii* pneumonia (PCP).
   B. Cryptococcal meningitis.
   C. Cytomegalovirus (CMV).
   D. *Mycobacterium avium* complex (MAC).

5. B.L. is a 44-year-old man positive for HIV 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*<sub>O2</sub> 63 mm Hg, *P*<sub>CO2</sub> 32 mm Hg, and oxygen saturation 85%. Sputum Gram stain is negative; silver stain is also negative. Which is the best therapy for B.L.?
   A. Pentamidine intravenously with adjuvant prednisone therapy for 21 days.
   B. Trimethoprim/sulfamethoxazole for 21 days.
   C. Trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days.
   D. Atovaquone for 21 days.

B. 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.

C. *Pneumocystis jirovecii* pneumonia (PCP)
   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*<sub>O2</sub>; A-a gradient = 150 – *P*<sub>O2</sub> – *P*<sub>CO2</sub>
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. Prophylaxis 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 or 300 mg every 6 hours or 450 mg every 8 hours orally and primaquine base 30 mg/day for 21 days
      ii. Adverse effects
         a) Rash
         b) Anemia, methemoglobinemia
         c) Diarrhea
   c. Pentamidine
      i. Dose: 4 mg/kg/day intravenously for 21 days
      ii. Adverse effects
         a) Hypotension
         b) Rash
         c) Electrolyte disturbances
         d) Hypoglycemia or hyperglycemia
         e) Pancreatitis
      iii. Prophylaxis 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
   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 Po2 of 70 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/mm3 for 3 months or longer because of potent combination ART)
   b. Primary prophylaxis in patients with CD4 count less than 200 cells/mm3 (may be discontinued if CD4 count is more than 200 cells/mm3 for 3 months or longer because of potent combination ART)

D. 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 (oral candidiasis is easy to treat [3–14 days’ duration], but it relapses within 30 days)
   a. Nystatin
      i. Indicated for mucous membrane and cutaneous Candida infections
      ii. Use for initial episodes in patients with CD4 count more than 50 cells/mm3.
      iii. 5 mL (100,000 units/mL); swish and swallow four times daily.
      iv. Poor adherence
   b. Clotrimazole (alternative to nystatin)
      i. Use for initial episodes in patients with CD4 count more than 50 cells/mm3.
      ii. Clotrimazole (Mycexel) troches 10 mg five times daily
      iii. Poor adherence (generally better tolerated than nystatin)
   c. Fluconazole
      i. Indicated for oropharyngeal and esophageal candidiasis
      ii. 2% relapse on fluconazole versus 28% on placebo
      iii. 10% of patients develop fluconazole-resistant infections.
      iv. 100–400 mg/day
d. Itraconazole
  i. Indicated for oropharyngeal and esophageal candidiasis
  ii. Oral solution: 200 mg/day
  iii. Significant drug-drug interactions

Patient Case
6. G.H. is a 33-year-old man positive for HIV 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 and is successfully treated. Which is the best follow-up therapy for G.H.?

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 PCP prophylaxis.

E. 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. Therapy
     a. Preferred: Lipid amphotericin 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for at least 2 weeks, followed by fluconazole 400 mg/day for at least 8 weeks
     b. Alternative
        i. Lipid amphotericin 5 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for at least 2 weeks, followed by fluconazole 400 mg/day for at least 8 weeks
ii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for at least 2 weeks, followed by fluconazole 400 mg/day for at least 8 weeks
iii. Lipid amphotericin 3–4 mg/kg/day plus fluconazole 800 mg/day for at least 2 weeks, followed by fluconazole 400 mg/day for at least 8 weeks
iv. Lipid amphotericin 3–4 mg/kg/day alone for at least 2 weeks, followed by fluconazole 400 mg/day for at least 8 weeks
v. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800 mg/day for 2 weeks, followed by fluconazole 800 mg/day for at least 8 weeks
vi. Fluconazole 400–800 mg/day plus flucytosine 25 mg/kg every 6 hours for 6 weeks
vii. Fluconazole 800–2000 mg/day for 10–12 weeks

9. Outcome
   a. Therapeutic response: 42%–75%
   b. 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.
   c. Relapse: 50%–90% (with about 100% mortality)

10. 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 Cases

7. 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. Maintenance therapy with fluconazole should be given for at least 1 year; then, it can be discontinued because the CD4 counts have increased.
   C. Maintenance therapy with fluconazole should be continued until CD4 counts are greater than 500 cells/mm³.
   D. Maintenance therapy with fluconazole can be discontinued.

8. J.C., a 36-year-old woman positive for HIV, has 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 MAC. Which treatment is best for J.C.?
   A. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone.
   B. Azithromycin ethambutol for at least 12 months.
   C. Clarithromycin plus isoniazid for 2 weeks, followed by maintenance with clarithromycin alone.
   D. Ethambutol plus rifabutin indefinitely.
F. *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
      i. Organisms gain access through the gastrointestinal tract.
      ii. After access, the organism spreads hematogenously.
   c. Usually occurs in patients with HIV having a CD4 count less than 50 cells/mm³

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 culture
   b. Bone marrow biopsy
   c. Stool cultures (do not treat if cultured only in the stool)

4. Therapy
   a. MAC is independently associated with risk of death, and treatment prolongs survival.
   b. 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
   c. Other agents: Consider adding to preferred therapy if advanced immunosuppression (CD4 count <50 cells/mm³), high mycobacterial loads (>2 log colony-forming units/mL of blood), or in the absence of effective ART.
      i. Rifabutin (Mycobutin) 150–600 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
   d. 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 antiretroviral therapy)
   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. Rifabutin 300 mg/day (150 mg orally twice daily with food if there are gastrointestinal adverse effects)
      i. Two times longer until a positive MAC culture (vs. placebo)
      ii. Decreased incidence of symptoms related to MAC
      iii. Adverse effects: rash, gastrointestinal disturbances, neutropenia, body fluid discoloration
      iv. Do not give alone to patients with active TB.
G. Cytomegalovirus (CMV)

1. Characteristics of CMV infection
   a. Fifty-three percent of Americans between 18 and 25 years of age 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).
   f. Before highly active antiretroviral therapy, 90% of patients with AIDS developed CMV infections, and 25% experienced life- or sight-threatening disease.

2. Diagnosis of CMV infection
   a. Serology (detects exposure to CMV)
   b. Virus isolation
      i. Tissue culture: Takes up to 6 weeks
      ii. Shell vial technique: Takes only 16 hours; organism is incubated overnight and then detected by immunofluorescence microscopy with monoclonal antibodies.
   c. Cytology and histology
      i. Large (cytomegalic) cell with a large, central, basophilic, intranuclear inclusion (“owl’s eye”)
      ii. Low yield

3. Manifestations of CMV
   a. Gastrointestinal
      i. Colitis: 5%–10% of patients with AIDS
      ii. Esophagitis and gastritis uncommon
      iii. Hepatitis: 33%–50% with histologic evidence but minimal clinical importance
      iv. Maintenance drugs not needed
   b. Pneumonia
      i. CMV is commonly in bronchial secretions; of questionable importance
      ii. Chest radiography results are similar to those seen with PCP.
      iii. Symptoms: Shortness of breath; dyspnea on exertion; dry, nonproductive cough
      iv. Treat if:
         (a) Documented tissue infection
         (b) CMV is only pathogen
         (c) Deteriorating illness
      v. About 50%–60% of patients will respond; no need for maintenance
   c. 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

4. Therapy for CMV infections
   a. Ganciclovir (Cytovene-IV, Cytovene), valganciclovir (Valcyte)
      i. Competes with deoxynucleosides, inhibiting viral DNA synthesis
      ii. Must be triphosphorylated; the rate-limiting step in this process is the first phosphorylation.
         CMV induces the production of the enzymes necessary for the monophosphorylation of ganciclovir but not acyclovir.
iii. Valganciclovir is a prodrug rapidly converted to ganciclovir in the intestinal wall and liver (bioavailability about 60%).

iv. Adverse effects
(a) 65% have adverse effects, and 76% have moderate to severe neutropenia (25% less than 1000 cells/mm$^3$, 16% less than 500 cells/mm$^3$).
   (1) In general, after 10 days
   (2) Ganciclovir plus zidovudine: 82% will have severe hematologic toxicity.
   (3) Patients receiving ganciclovir can tolerate no more than 300 mg/day of zidovudine.
(b) Thrombocytopenia (9% less than 20,000 cells/mm$^3$)
(c) Confusion, convulsions, dizziness, headache, thought disorders
(d) Nausea, vomiting, diarrhea, abnormal liver function tests
(e) Possible reproductive toxicity

v. Dose
(a) Induction: Valganciclovir 900 mg orally twice daily for 14–21 days (alternative: ganciclovir 5 mg/kg intravenously every 12 hours for 14–21 days)
(b) Maintenance: Valganciclovir 900 mg/day orally (alternative: ganciclovir 5 mg/kg/day intravenously)
(c) All (100%) patients will relapse in 1–8 weeks without maintenance.
(d) Intravenous maintenance therapy requires establishment of central venous access.

b. Foscarnet
i. Inhibits viral-induced DNA polymerase; no effect on human DNA polymerase
ii. Effective against all herpes viruses (especially CMV), HBV ($\pm$), and HIV
iii. Foscarnet and ganciclovir are equally effective against CMV, but foscarnet decreases (by about 4 months) mortality because of its anti-HIV effects.
iv. Foscarnet is active against ganciclovir resistant CMV with mutations in the UL97 region of the viral genome.
v. Adverse effects
(a) Renal impairment
   (1) Especially occurs if the patient is dehydrated or taking other renal toxic drugs
   (2) A two- to threefold elevation in serum creatinine (more than 50% had to discontinue)
   (3) Usually reversible
   (4) Prevented by administering 2.5 L/day of normal saline
(b) Decrease in hemoglobin and hematocrit
(c) Altered serum electrolytes (calcium, phosphorus, magnesium)
(d) Penile ulcerations
vi. Preparation and dose
(a) Commercial preparation is available in 500-mL glass bottles at 24 mg/mL; 24 mg/mL should be administered centrally. For peripheral administration, use 12 mg/mL.
(b) One gram of foscarnet contains about 600 mg of sodium chloride.
(c) Induction: 60 mg/kg every 8 hours or 90 mg/kg every 12 hours for 14–21 days (administer for 1 hour)
(d) Maintenance: 90–120 mg/kg/day (administer for 2 hours)
(e) Decrease dose by 3.5 mg/kg for each 0.1 mL/minute/kg of CrCl below 1.6 mL/minute/kg.
(f) Maintenance therapy requires establishment of central venous access.

c. Cidofovir (Vistide)
i. Acts as a nucleoside monophosphate, inhibiting viral DNA polymerase
ii. Intracellular activation required
iii. Cidofovir is active against ganciclovir-resistant CMV with mutations in the UL97 region of the viral genome

iv. Adverse effects
   (a) Renal impairment
   (b) Manifested as proteinuria and elevated creatinine concentrations
   (c) Decreased with concurrent probenecid (2 g, 3 hours before infusion and 1 g, 2 and 8 hours after infusion, to decrease renal secretion) and saline hydration
   (d) Probenecid may cause nausea, vomiting, headache, fever, and flushing.

v. Neutropenia (15% of patients)

vi. Dose
   (a) Induction: 5 mg/kg/week for 2 weeks
   (b) Maintenance: 5 mg/kg every other week
   (c) Maintenance therapy does not require the establishment of central venous access.
   (d) Adequate saline hydration plus probenecid (2 g, 3 hours before infusion and 1 g, 2 and 8 hours after infusion) must be administered with drug.
   (e) Avoid regimen in patients with sulfa allergy because of cross-hypersensitivity with probenecid.

5. Prophylaxis
   a. Secondary prophylaxis is required for all patients (see individual drugs for specific doses); it may be discontinued if the CD4 count is more than 100 cells/mm$^3$ for 3–6 months or longer because of potent combination ART. Reinitiate secondary prophylaxis if the CD4 count decreases to less than 100 cells/mm$^3$.
   b. Primary prophylaxis not recommended. In patients with CD4 counts less than 50 cells/mm$^3$, regular funduscopic examinations are recommended.

H. 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 not done
   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. Standard therapy
      i. Pyrimethamine 50–75 mg/day (loading dose, 200 mg in two doses) 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
      (a) Dosage: 600–1200 mg intravenously every 6 hours for 6 weeks; after 3 weeks, can change to oral 600 mg every 8 hours
      (b) Used in combination with pyrimethamine/leucovorin for sulfa intolerance or by itself when bone marrow suppression occurs
   ii. Atovaquone
      (a) Dosage: 1500 mg orally twice daily
      (b) Used in combination with pyrimethamine/leucovorin or in combination with sulfadiazine or alone
   iii. Azithromycin
      (a) Dosage: 900–1200 mg/day orally
      (b) Used in combination with pyrimethamine (do not use alone for acute therapy)

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. For primary prophylaxis, use trimethoprim/sulfamethoxazole double strength once daily or dapsone/pyrimethamine/leucovorin or atovaquone with or without pyrimethamine at doses used for PCP prophylaxis (may be discontinued if the CD4 count is more than 200 cells/mm³ for 3 months or longer because of potent combination ART).
   d. For secondary prophylaxis, use the following (may be discontinued if the CD4 count is more than 200 cells/mm³ for 6 months or longer because of potent combination ART):
      i. Pyrimethamine 25–50 mg/day plus leucovorin 10–25 mg/day with sulfadiazine 2–4 g/day
      ii. Clindamycin 600 mg every 8 hours can be substituted if sulfa intolerance occurs.
      iii. Atovaquone 750 mg orally every 6–12 hours with or without pyrimethamine/leucovorin or sulfadiazine

III. TUBERCULOSIS

A. M. 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. AIDS
      g. Foreign birth
   2. Epidemiology (Figure 2)
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, although can occur in other organ systems

- Activated alveolar macrophages ingest and destroy over 90% of the inhaled tubercle bacilli.
- Remaining 10% multiply within the macrophages and are released when the macrophage dies.

- Inhaled droplet bypasses mucociliary system and becomes implanted in the bronchioles or alveoli.
- Released bacilli attract monocytes and macrophages forming the primary tubercle – growth occurs within the macrophages with destruction of neither bacilli or macrophages occurring.

- In susceptible patients bacilli continue to grow – the caseous center enlarges destroying adjacent lung tissue.

- In patients with diminished cell-mediated immunity the delayed hypersensitivity reaction is greater and the caseous center expands.

- With continued delayed hypersensitivity reaction (immunosuppressed patients) the caseous center liquefies which provides a viable environment for bacillary growth – now growth occurs extracellularly.

- Patients with normal immune systems destroy bacilli escaping from the caseous center leading to little to no tissue destruction.

- Note: This caseous liquefaction and bacillary growth can occur even in “normal” patients – therefore antimicrobial therapy is necessary.

- Approximately 10% of those infected develop clinical tuberculosis.

- Erosion of bronchial tissue occurs and cavities form.

- Bacilli die in the caseous center Positive PPD Asymptomatic.

- Bacilli remain dormant in the caseous center Positive PPD Asymptomatic (for life?)

Figure 3. Pathophysiology of tuberculosis.

PPD = purified protein derivative.
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</td>
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<tr>
<td>Weight loss</td>
<td></td>
<td></td>
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<tr>
<td>Fever, chills</td>
<td></td>
<td></td>
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<tr>
<td>Night sweats</td>
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<tr>
<td>Pleuritic pain</td>
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</table>

AFB = acid-fast bacillus.

1. Skin test for PPD (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 PPD 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. Two hundred fifty tuberculin units per 0.1 mL of solution can be used, but this is not recommended by the Centers for Disease Control and Prevention.
   e. Only 8% of people vaccinated with Bacille Calmette-Guérin at birth will react 15 years later.

Table 9. Recommendation for Purified Protein Derivative Skin Test

<table>
<thead>
<tr>
<th>Criterion for Positive Skin Test (mm)</th>
<th>Applicable Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Patients with chest radiograph consistent with TB Close contacts of patients with newly diagnosed infectious TB Patients with HIV infection Patients with documented defects in cellular immunity Patients receiving prednisone ≥15 mg/day for ≥1 month</td>
</tr>
<tr>
<td>10</td>
<td>Recent immigrants (within the past 5 years) from countries with a high prevalence of TB (even if they had BCG) Intravenous drug abusers Residents and employees of prisons or jails, nursing homes, hospitals, and homeless shelters Patients with diseases known to be associated with a higher risk of TB (diabetes mellitus, silicosis, leukemias and lymphomas, chronic renal failure), gastrectomy, and jejunointestinal bypass Children &lt;4 years old</td>
</tr>
<tr>
<td>15</td>
<td>Patients with no identifiable risk factors</td>
</tr>
</tbody>
</table>

BCG = Bacille Calmette-Guérin; TB = tuberculosis.
2. Interferon gamma release assays and targeted blood tests
   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 PPD test for predicting future active infection
   d. Can be used interchangeably with PPD: Most beneficial to verify a positive PPD in patients with a history of Bacille Calmette-Guérin vaccine or for patients who will not or cannot return for a PPD reading

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

9. J.M. is a 42-year-old man who has a yearly PPD skin test because he works at a long-term care facility. Forty-eight hours after the PPD 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 PPD?

   A. No treatment is necessary, and J.M. should have another PPD skin test in 1 year.
   B. Another PPD skin test should be performed 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. The treatment of latent TB infection should be instituted in the following groups with a positive PPD skin test:
      i. Close contacts of people with newly diagnosed infectious TB
      ii. Health care workers at facilities treating patients with TB
      iii. Foreign-born people from high-prevalence countries (immigration within 5 years)
      iv. Homeless people
      v. People working at or living in long-term care facilities
      vi. Patients with HIV infection
      vii. Recent converters (within a 2-year period)
      viii. People with abnormal chest radiographs that show fibrotic lesions, likely to represent old, healed TB
      ix. People with medical conditions that have been reported to increase the risk of TB: intravenous drug use, diabetes mellitus, silicosis, Hodgkin disease, leukemia, immunosuppressive therapy, corticosteroids, end-stage renal disease
   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)
         (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 two times/week 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

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**Patient Case**

10. R.J. is a 32-year-old man positive for HIV infection who presents to the clinic with increased weight loss, night sweats, and a cough productive of sputum. He is currently receiving fosamprenavir/ritonavir 700 mg/100 mg twice daily, zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, fluconazole 200 mg/day orally, and trimethoprim/sulfamethoxazole double strength daily. A sputum sample is obtained, which 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 fosamprenavir/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 fosamprenavir/ritonavir.

---

2. Treatment of active TB infection (Table 10)

   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.

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

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

   b. Therapeutic options for patients without HIV infection. (Note: Any regimen administered two, three, or five times/week should be done by directly observed therapy.)
      i. Option 1: Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months (daily, five times weekly, three times weekly, or twice weekly), followed by isoniazid and rifampin for 4 months (daily, five times weekly, three times weekly, or twice weekly)
ii. Option 2: Isoniazid, rifampin, and ethambutol for 2 months (daily or five times/week), followed by isoniazid and rifampin for 7 months (daily, five times/week, or two times/week)

c. Therapeutic options for patients with HIV
   i. Option 1: Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months (daily or five times/week), followed by isoniazid and rifampin for 4 months (daily or five times/week or three times/week)
   ii. Option 2: Isoniazid, rifampin, and ethambutol for 2 months (daily or five times/week), followed by isoniazid and rifampin for 7 months (daily or five times/week)

d. 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/mm³ and by 8–12 weeks for all others.
   ii. PIs and NNRTIs (except for efavirenz or nevirapine) should not be administered concurrently with rifampin; NRTIs can be administered with rifampin.
   iii. A washout period of 1–2 weeks may be necessary once rifampin is discontinued before PIs or NNRTIs are initiated.
   iv. Rifabutin can be substituted for rifampin; patients may take NNRTIs with rifabutin, but 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. Patients taking rifabutin and PIs or NNRTIs should have HIV RNA concentrations performed periodically.

e. 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.

f. 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.

g. 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 to 9 months
   v. Extrapulmonary TB in other sites: 6 months

**Patient Case**

11. Which represents the best follow-up for R.J.?
   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.
IV. ANTIFUNGAL THERAPY

Patient Case
12. 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 he was given 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 of the following antifungals would be the best therapy for C.A.?

A. Lipid amphotericin.
B. Micafungin.
C. Fluconazole.
D. Voriconazole.

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
      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 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)

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)
   a. Lipid formulations are designed to maintain therapeutic efficacy, but they diminish renal- and infusion-related toxicity.

Table 11. Amphotericin Formulations

<table>
<thead>
<tr>
<th></th>
<th>Amphotericin B Deoxycholate</th>
<th>Abelcet</th>
<th>Amphotec</th>
<th>AmBisome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid type</td>
<td>Multilamellar vesicle with ribbonlike structure (lipid complex)</td>
<td>Colloidal dispersion in aqueous solution (disk-shaped bilayer)</td>
<td>Unilamellar liposome</td>
<td></td>
</tr>
<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>Nephrototoxicity (%)</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>NA</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

b. Mostly 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. Ketoconazole (Nizoral): Use only if no option for using alternative antifungals.
   a. Spectrum of activity
      i. *Candida* spp., *Blastomyces*, histoplasmosis, *Coccidioides*, *Sporothrix*, dermatophytes
      ii. Clinical use: Histoplasmosis, superficial *Candida* and other infections, blastomycosis, coccidioidomycosis
   b. Adverse effects
      i. Nausea, abdominal pain, headache, rash
      ii. Adrenal insufficiency, decreased libido, impotence, gynecomastia, menstrual irregularities (inhibits steroidogenesis)
      iii. Elevated liver function tests, potential fulminate hepatitis
   c. Drug interactions (CYP3A4 substrate and inhibitor)
      i. Antacids, histamine-2 (H2)-blockers, proton pump inhibitors, didanosine (gastrointestinal absorption)
      ii. Rifampin (decreases ketoconazole concentrations)
      iii. Cyclosporine
      iv. Phenytoin
      v. Warfarin
      vi. Methylprednisolone, midazolam, alprazolam, simvastatin, lovastatin
      vii. Protease inhibitors
   d. Dosing: 200–400 mg/day

3. 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

4. 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 fulminate hepatitis
   iii. Caution in heart failure (avoid doses ≥400 mg/day; do not use for treatment of onychomycosis if heart failure)
d. Drug interactions (CYP3A4 inhibitor at more than 400 mg/day and CYP2C9 inhibitor at lower doses)
   i. Antacids, H₂-blockers, proton pump inhibitors, didanosine (gastrointestinal absorption)
   ii. Cyclosporine
   iii. Digoxin (decreases digoxin volume of distribution)
   iv. Phenytoin
   v. Warfarin
   vi. Protease inhibitors
   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

5. 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 12)
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 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.

Table 12. 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></td>
<td>↑ Rifabutin</td>
<td></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>Pimozide (CYP3A4 substrate)</td>
<td>↑ Pimozide</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td></td>
<td>↑ Risk QT prolongation</td>
<td></td>
</tr>
<tr>
<td>Quinidine (CYP3A4 substrate)</td>
<td>↑ Quinidine</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td></td>
<td>↑ Risk QT prolongation</td>
<td></td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>↑ Ergot alkaloids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Risk ergotism</td>
<td></td>
</tr>
<tr>
<td>Sirolimus (CYP3A4 substrate)</td>
<td>↑ Sirolimus</td>
<td>Coadministration contraindicated</td>
</tr>
<tr>
<td>Cyclosporine (CYP3A4 substrate)</td>
<td>↑ Cyclosporine</td>
<td>Reduce cyclosporine dose by half when initiating voriconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor levels closely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase cyclosporine dose as necessary when voriconazole is discontinued</td>
</tr>
<tr>
<td>Tacrolimus (CYP3A4 substrate)</td>
<td>↑ Tacrolimus</td>
<td>Reduce tacrolimus dose to one-third of initial dose when initiating voriconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor levels closely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase tacrolimus dose as necessary when voriconazole is discontinued</td>
</tr>
<tr>
<td>Omeprazole (CYP2C19 inhibitor, CYP2C19 and CYP3A4 substrate)</td>
<td>↑ Voriconazole</td>
<td>In patients receiving omeprazole doses ≥40 mg, reduce omeprazole dose by half</td>
</tr>
<tr>
<td></td>
<td>↑ Omeprazole</td>
<td></td>
</tr>
<tr>
<td>Warfarin (CYP2C9 substrate)</td>
<td>↑ Warfarin</td>
<td>Closely monitor PT/INR and adjust warfarin dose as needed</td>
</tr>
<tr>
<td></td>
<td>↑ PT</td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; INR = international normalized ratio; PT = prothrombin time.

6. 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. New 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)

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, gastrointestinal 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**


**Antifungal Therapy**


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**
The patient should be treated at this time; a potent combination ART definitely should be initiated when CD4 counts fall below 350 cells/mm³ and can be initiated in patients with CD4 counts greater than 350 cells/mm³ (although this is a lower strength of recommendation). The combination therapy of tenofovir, emtricitabine, and atazanavir/ritonavir is a preferred initial therapeutic regimen. Monotherapy is not indicated for HIV. Although treatment with zidovudine, lamivudine, and nevirapine is an acceptable alternative, it should not be first-line therapy.

2. **Answer: D**
A change in potent combination ART should be made when the viral load becomes detectable after a period of levels below detection. Some clinicians would wait and monitor the patient closely if the viral load increased to 10,000 copies/mL. However, these patients generally will require changes in therapy in the future. Testing is showing resistance to atazanavir. Because of that, changes in ART must be made. Simply stressing adherence and continuing the same regimen is inappropriate. Ideally, a new regimen should contain at least two, preferably three fully active drugs. In general, changing a single antiretroviral in a failing regimen is not recommended because of the risk of rapid development of resistance. Changing only one drug in a regimen should be done only for intolerance. Therefore, initiating an entirely new regimen of abacavir, lamivudine, and darunavir/ritonavir is best because changing all three agents simultaneously limits the possibility of resistance to the new regimen occurring quickly.

3. **Answer: C**
A patient taking darunavir/ritonavir should be monitored for endocrine disturbances (e.g., hyperglycemia, fat redistribution, lipid abnormalities) because all PIs can cause endocrine disturbances. Because darunavir/ritonavir does not cause peripheral neuropathy (although didanosine, zalcitabine, and stavudine do), this does not need to be monitored. Drug interaction with drugs metabolized by CYP1A2 is not of concern because darunavir is an inhibitor of CYP3A4, and ritonavir is an inhibitor of CYP2D6 and CYP3A4. Darunavir does not cause nephrolithiasis; thus, the patient does not need to be monitored for this (although a patient taking indinavir does).

4. **Answer: A**
When the CD4 count decreases to 135 cells/mm³, the patient should receive primary prophylactic treatment against PCP (CD4 count less than 200 cells/mm³). Primary prophylaxis is necessary for MAC when the CD4 count is less than 50 cells/mm³. For CMV, patients with CD4 counts less than 50 cells/mm³ should receive regular funduscopic examinations. In general, primary prophylaxis is not used for cryptococcal meningitis.

5. **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. 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 the patient's PO₂ is less than 70. Atovaquone is indicated only for patients with mild to moderate PCP who cannot tolerate trimethoprim/sulfamethoxazole. This patient does not meet this criterion.

6. **Answer: B**
Patients with cryptococcal meningitis should always receive secondary prophylaxis. One of the principles of treating AIDS-related illnesses is that the infections are seldom curable, and generally, long-term preventable therapy is required. Weekly amphotericin B has been studied for secondary prophylaxis, but fluconazole is the best agent for secondary prophylaxis. The agents that are effective for PCP prophylaxis have no activity against *Cryptococcus*.

7. **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/mm³ for 3 months or longer after potent combination ART. 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.

8. 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). 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. A therapeutic regimen of clarithromycin plus isoniazid is not the best because isoniazid has no activity against MAC. 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.

9. Answer: D
A patient with an induration of greater than 15 mm after a PPD skin test for TB needs to be assessed for treatment. Because this patient’s PPD skin test was negative last year, he is considered a recent converter and needs to be treated. He would also need to be treated if there were patients with TB at the long-term care facility. The booster effect is a phenomenon associated with an initial small reaction causing immunologic stimulation, followed by a larger reaction with a subsequent test. This patient had an initial large reaction (18-mm induration). Age is not a factor to consider in treating latent TB. Initiating isoniazid 300 mg/day orally for 9 months is the best recommendation for managing this patient’s positive PPD.

10. Answer: C
This patient’s HIV medications should be changed (rifampin will induce the metabolism of fosamprenavir and ritonavir). He should not receive a PI (except for full-dose ritonavir) or an NNRTI (except for efavirenz) with rifampin. Patients who are HIV positive should be initiated on four drugs for TB, and fosamprenavir should not be used with rifampin. 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 fosamprenavir/ritonavir inhibition). The fosamprenavir/ritonavir dose does not need to be changed when adding rifabutin.

11. Answer: C
For this patient, only rifampin and isoniazid need to be continued after 2 months of therapy with the four drugs for TB. The regimen can be simplified to a rifampycin and isoniazid after 2 months, but the recommended treatment duration is 6 months. The concentrations of HIV RNA should be monitored closely because of potential alterations in drug concentrations of the PI.

12. 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. 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. Fluconazole has no activity against Aspergillus and also may potentially interact with the some of the drugs the patient is receiving. Voriconazole has activity against Aspergillus, but it significantly interacts with a number of the drugs the patient is receiving (atorvastatin, dronedarone, warfarin, carbamazepine), making it a less than ideal choice in this patient.
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. A potent combination ART that includes zidovudine 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 (although if the woman is on a fully suppressed regimen without zidovudine, that regimen should be continued without changes). Although zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and to the baby 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. 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. Single-dose nevirapine is indicated in women in labor who were not treated during their pregnancy.

2. **Answer: A**

The patient should be told that atazanavir can cause hyperbilirubinemia. This patient should be told to talk to a pharmacist about the current combination therapy because there are many drug interactions with antiretroviral agents. However, although atazanavir inhibits CYP3A4, tenofovir does not (it is an NRTI, not a PI). In addition, informing the patient to cut the dose in half if there are adverse effects is incorrect because antiretroviral drugs, especially PIs, should never be used below the recommended dose. Informing the patient that tenofovir and emtricitabine cause additive peripheral neuropathy is incorrect because neither of these drugs is associated with that adverse effect.

3. **Answer: B**

There are many other reasons to change ART in addition to clinical deterioration. These include an inability to decrease viral load to undetectable levels, the detection of virus after initial suppression to undetectable levels, a failure to increase the CD4 count by 50–100 cells/mm$^3$ during the first year of therapy, and a failure to increase the CD4 count above 350 cells/mm$^3$ while on therapy. If there is a question of ineffective ART, single drugs should be changed only with caution (consider changing the entire regimen). Resistance does not occur more commonly with emtricitabine than with other antiretroviral agents.

4. **Answer: A**

A change in therapy is indicated for the patient taking potent combination ART and experiencing hyperglycemia, fat redistribution, and lipid abnormalities. Although adding lipid-lowering agents may be indicated to lower cardiovascular risks, simvastatin should not be used with lopinavir or ritonavir because of the drug interaction (increased simvastatin concentrations lead to an increased risk of myalgias). Pravastatin is a better choice (even though it may decrease ritonavir concentrations). Although adding an insulin-sensitizing agent may be indicated, pioglitazone should not be used with lopinavir or ritonavir because of the drug interaction (increased pioglitazone concentrations and potential induction of PI metabolism by pioglitazone). At this time, changing agents (if possible) to an effective regimen that does not cause endocrine disturbances is the best option. The NRTIs that can increase lipid levels include stavudine, zidovudine, and abacavir; therefore, these agents should be avoided. Abacavir is also associated with an increased incidence of myocardial infarction. All of the ritonavir-boosted PIs can increase lipid concentrations, as can efavirenz; therefore, these agents should be avoided. The best option is therefore tenofovir, emtricitabine, and rilpivirine.

5. **Answer: D**

The current recommended regimen for treating cryptococcal meningitis in patients positive for HIV is amphotericin B 0.7 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for 2 weeks, followed by fluconazole 400 mg/day. Fluconazole alone is recommended only for mild to moderate cryptococcal meningitis, and the dose should be 400 mg/day. Studies have shown that early mortality is greater with fluconazole alone than with amphotericin B alone. When amphotericin B is used alone for cryptococcal meningitis, the dose should be 0.7 mg/kg per day, not 0.3 mg/kg per day. The flucytosine dose of 37.5 mg/kg every 6 hours is high and is
especially likely to cause bone marrow suppression in patients who are HIV positive.

6. **Answer: C**

The number of patients needed to treat with isoniazid over rifampin to prevent one progression to active disease is \( 200 = \frac{1}{0.008 - 0.003} \). The only information needed is the absolute risk in both groups, which is provided.

7. **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. Atovaquone is not first-line therapy, although data support its effectiveness in combination with sulfadiazine or pyrimethamine; trimethoprim/sulfamethoxazole is not effective for treatment or secondary prophylaxis of toxoplasmosis. Pyrimethamine and sulfadiazine are the first-line agents for toxoplasmosis; however, leucovorin should always be used with pyrimethamine to prevent myelosuppression.

8. **Answer: D**

Fluconazole does not have activity against aspergillus, so it would not be an option for therapy. Although voriconazole has activity against aspergillus, there is a significant interaction with rifampin, resulting in lower voriconazole concentrations. Flucytosine does not have activity against aspergillus. Micafungin would be the best option because of its activity against aspergillus and lack of drug interaction with any of the TB medications.

9. **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. Patients should be initiated on at least three antibiotics for the first 2 months. Although fluoroquinolones have some activity against TB, their use as first-line monotherapy is inappropriate.

10. **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. Although an analysis of variance is a parametric test, it is used to compare more than two groups. A chi-square test is used to compare nominal or categorical data between two groups. 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.