Chapter 41: Human Immunodeficiency Virus Infection

INTRODUCTION

- **Table 41-1** presents the case definition for adult, adolescent, and children, respectively, for *human immunodeficiency virus* (HIV) infection.

TABLE 41-1

Surveillance Case Definition for HIV Infection Stage Based on CD4+ T-Lymphocyte Counts, United States, 2014

	Age on Date of CD4+ T-Lymphocyte Test[a]					
	<1 year		1–5 years		≥6 years	
Stage	Cells/μL (×10^6/L)	%	Cells/μL (×10^6/L)	%	Cells/μL (×10^6/L)	%
1	≥1500	≥34	≥1000	≥30	≥500	≥26
2	750–1499	26–33	500–999	22–29	200–499	14–25
3 (AIDS)	<750	<26	<500	<22	<200	<14
AIDS Indicator Conditions						
Bacterial infections, multiple or recurrent (specific to children <6 years) Candidiasis of bronchi, trachea, or lungs Candidiasis, esophageal Cervical cancer, invasive (specific to adults, adolescents, children >6 years)			Lymphoma, Burkitt Lymphoma, immunoblastic Lymphoma, primary, or brain			
Coccidioidomycosis, disseminated or extrapulmonary			*Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary			
Cryptococcosis, extrapulmonary			*Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)			
Cryptosporidiosis, chronic intestinal (duration >1 month)			*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary			
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month			*Pneumocystis jirovecii* pneumonia (PCP)			
Cytomegalovirus retinitis (with loss of vision)			Pneumonia, recurrent (specific to adults, adolescents, children >6 years)			
Encephalopathy, HIV-related			Progressive multifocal leukoencephalopathy			
Herpes simplex: chronic ulcer(s) (duration >1 month); or bronchitis, pneumonitis, or esophagitis, onset at age >1 month			*Salmonella* septicemia, recurrent Toxoplasmosis of brain, onset at age >1 month Wasting syndrome due to HIV			
Histoplasmosis, disseminated or extrapulmonary isosporiasis, chronic intestinal (duration >1 month) Kaposi's sarcoma						

[a]Age-specific CD4+ T-lymphocyte count or CD4+ T-lymphocyte percentage of total lymphocytes

ETIOLOGY AND PATHOGENESIS

- Infection with HIV occurs through three primary modes: sexual, parenteral, and perinatal. Sexual intercourse, primarily anal and vaginal intercourse, is the most common vehicle for transmission. The highest risk appears to be from receptive anorectal intercourse at about 1.4 transmissions per 100 sexual acts. Condom use reduces the risk of transmission by approximately 80%. Individuals with genital ulcers or sexually transmitted diseases are at great risk for contracting HIV.
- Heterosexual transmission is the most common mode of transmission in sub-Saharan Africa and worldwide (~80% of cases).
- The risk of HIV transmission from sharing needles is approximately 0.67 per 100 episodes.
- Healthcare workers have a small risk of occupationally acquiring HIV, mostly through accidental injury, most often percutaneous needlestick injury. Mucocutaneous exposures (eg, tainted blood splash in eyes, mouth, or nose) carry a transmission risk of approximately 0.09%.
- Perinatal infection, or vertical transmission, is the most common cause of pediatric HIV infection. The risk of mother-to-child transmission is ~25% in the absence of antiretroviral therapy. Breast-feeding can also transmit HIV.

CLINICAL PRESENTATION

- The natural history of HIV infection exhibits three general phases: acute, chronic, and terminal (AIDS).
- Primary HIV infection also presents with high viral load (may exceed 1,000,000 copies/mL or 10^9/L) and a persistent decrease in CD4 lymphocytes.
- The most common signs and symptoms of primary HIV infection are fever, headache, sore throat, fatigue, GI upset (diarrhea, nausea, vomiting), weight loss, myalgia, morbilliform or maculopapular rash usually involving the trunk, lymphadenopathy, and night sweats. Less common signs and symptoms are aseptic meningitis, oral ulcers, and leukopenia.
- Clinical presentations of primary HIV infection vary, but patients often have a viral syndrome or mononucleosis-like illness with fever, pharyngitis, and adenopathy. Symptoms may last for 2 weeks.
- Most children born with HIV are asymptomatic. On physical examination, they often present with unexplained physical signs such as lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, weight loss or unexplained low birth weight, and fever of unknown origin. Laboratory findings include anemia, hypergammaglobulinemia, altered mononuclear cell function, and altered T-cell subset ratios. The normal range for CD4 cell counts in children is much different than for adults.
- The probability of progression to AIDS is related to RNA viral load; viral load is a major prognostic factor for disease progression, CD4 count decline, and death.
- The presence of HIV infection is screened with an enzyme-linked immunosorbent assay (ELISA), which detects antibodies against HIV-1. ELISA tests are generally highly sensitive (greater than 99%) and highly specific (greater than 99%), but rare false-positive results can occur particularly in those with autoimmune disorders. Positive screening tests are confirmed with another enzyme immunoassay to specify if the antibodies are to HIV-1 versus HIV-2. False-negative results also occur and may be attributed to the “window-period” before adequate production of antibodies or antigen.
- Once diagnosed, HIV disease is monitored primarily by two surrogate biomarkers, viral load and CD4 cell count. The viral load test quantifies viremia by measuring the amount of viral RNA. There are several methods used for determining the amount of HIV RNA: reverse transcriptase–coupled polymerase chain reaction, branched DNA, transcription-mediated amplification, and nucleic acid sequence–based assay.
- The number of CD4 lymphocytes in the blood is a surrogate marker of disease progression. The normal adult CD4 lymphocyte count ranges between 500 and 1600 cells/mm^3 (500 and 1600 × 10^6/L), or 40%–70% of all lymphocytes.

TREATMENT

- Goal of Treatment: The central goal of antiretroviral therapy is to decrease morbidity and mortality, improve quality of life, restore and preserve immune function, and prevent further transmission through maximum suppression of HIV replication (HIV RNA level that is less than the lower

limit of quantitation (ie, undetectable; usually less than 20 or 50 copies/mL [20×10^3 or 50×10^3/L]).

General Approach

- Contemporary combinations of three active antiretroviral agents from two pharmacologic classes potently inhibit HIV replication to undetectable plasma levels, prevent and reverse immune deficiency, and substantially decrease morbidity and mortality—constituting the modern ART era.
- Regular, periodic measurement of plasma HIV RNA levels and CD4 cell counts is necessary to determine the risk of disease progression in an HIV-infected individual and to determine when to initiate or modify antiretroviral treatment regimens.
- The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Maximum achievable suppression of HIV replication should be the goal of therapy.
- The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
- Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages. Combinations of three active antiretroviral agents from two pharmacologic classes profoundly inhibit HIV replication to undetectable plasma levels, prevent and reverse immune deficiency, and substantially decrease morbidity and mortality.
- Women should receive optimal antiretroviral therapy regardless of pregnancy status.
- The same principles of antiretroviral therapy apply to both HIV-infected children and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
- Persons with acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
- HIV-infected persons, even those with viral loads below detectable limits, should be considered infectious and should be counseled to avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infectious pathogens.
- An excellent source for information on treatment guidelines can be found at http://aidsinfo.nih.gov/.
- Untreated HIV is harmful even at high CD4 counts, and immediate ART confers individual- and population-level benefit compared with delayed ART. Major policy-makers now recommend immediate ART regardless of CD4 count.

Pharmacologic Therapy

Antiretroviral Agents

- Systemic delivery of antiretroviral agents for direct inhibition of viral replication has been the most clinically successful strategy for both treatment and prophylaxis.
- Inhibiting viral replication with a combination of potent antiretroviral therapy has been the most clinically successful strategy in the treatment of HIV infection. There have been four primary groups of drugs used: entry inhibitors, reverse transcriptase inhibitors, integrase strand transfer inhibitors (InSTIs), and HIV protease inhibitors (PIs) (**Table 41-2**).
- Significant drug interactions can occur with many antiretroviral agents. The latest information on drug interactions of antiretroviral drugs should be consulted. Many clinically significant antiretroviral-associated drug interactions involve CYP3A-mediated first-pass metabolism and clearance.

  ✔ **Ritonavir** and **cobicistat** are potent inhibitors of cytochrome P450 enzyme 3A and are now used exclusively at lower doses as pharmacokinetic enhancers of other HIV PI.

✔ **Rifampin**, a potent inducer of CYP3A metabolism and conjugation enzymes, is contraindicated with use of most HIV PIs, **etravirine**, **rilpivirine**, and **maraviroc** because concentrations are reduced substantially even with ritonavir enhancement.

TABLE 41-2

Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended in Antiretroviral-Naïve Persons

	Preferred Regimens[a]	Selected Limitations
InSTI-based	Bictegravir + tenofovir alafenamide fumarate + emtricitabine (coformulated) (AI)	Only if CrCl ≥30 mL/min (0.5 mL/sec); interactions with polyvalent antacids; bictegravir inhibits creatinine secretion increasing serum creatinine (distinguish vs. renal dysfunction)
	Raltegravir + tenofovir + emtricitabine (AI for tenofovir disoproxil fumarate; AII for tenofovir alafenamide fumarate)	Can be dosed once or twice daily; interactions with polyvalent antacids; creatine kinase increases
	Dolutegravir + abacavir + lamivudine (coformulated) (AI)	Only if HLA-B5701 negative; interactions with polyvalent antacids; possible increased risk of neural tube defects in infants if used at the time of conception; dolutegravir inhibits creatinine secretion increasing Scr—distinguish vs. renal dysfunction
	Dolutegravir + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (AI)	Same as above without HLA-B5701 negative requirement
Selected Alternative Regimens (Some Potential Disadvantages vs. Preferred Regimens)		
InSTI-based	Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine (coformulated) (AI)	Only if CrCl ≥70 mL/min (1.17 mL/sec); food requirement; interactions with polyvalent antacids; CYP3A4 drug interactions; cobicistat inhibits creatinine secretion increasing Scr— distinguish vs. renal dysfunction
	Elvitegravir + cobicistat + tenofovir alafenamide fumarate + emtricitabine (coformulated) (AI)	Only if CrCl ≥30 mL/min (0.5 mL/sec); same as above
	Raltegravir + abacavir + lamivudine (BI)	Only if HLA-B5701 negative and HIV RNA <100,000 copies/mL (100 × 10^6/L); can be dosed once or twice daily; interactions with polyvalent antacids; creatine kinase increases
HIV PI-based	Atazanavir + ritonavir (or cobicistat) + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (BI)	GI; food requirement; CYP3A4 drug interactions; hyperbilirubinemia leading to drug discontinuation, especially in those with Gilbert's; only for CrCl ≥70 mL/min (1.17 mL/sec) as cobicistat inhibits creatinine secretion increasing Scr—distinguish vs. renal dysfunction
	Atazanavir + ritonavir (or cobicistat) + abacavir + lamivudine (CI for ritonavir and CIII for cobicistat)	Only if HLA-B5701 negative; see issues above
	Darunavir + ritonavir (or cobicistat) + tenofovir disoproxil fumarate (or	Rash (darunavir has sulfonamide moiety); GI; food requirement; CYP3A4 drug interactions; only for CrCl ≥70 mL/min (1.17 mL/sec) as cobicistat

	tenofovir alafenamide fumarate) + emtricitabine (AI for ritonavir and AII for cobicistat)	inhibits creatinine secretion increasing serum creatinine (distinguish vs. renal dysfunction); see issues above
	Darunavir + ritonavir (or cobicistat) + abacavir + lamivudine (BII)	Only if HLA-B5701 negative; see issues above
NNRTI-based	Doravirine + tenofovir disoproxil fumarate + lamivudine (coformulated) (BI) Doravirine + tenofovir alafenamide + emtricitabine (BIII)	Only if CrCl ≥50 mL/min (0.83 mL/sec)
	Efavirenz + tenofovir disoproxil fumarate + emtricitabine (coformulated) (BI) Efavirenz + tenofovir alafenamide fumarate + emtricitabine (BII)	CNS side effects with efavirenz; CYP450 drug interactions; empty stomach dosing; teratogenic in nonhuman primates—controversial in humans—consider avoiding in women planning to conceive
	Rilpivirine + tenofovir disoproxil fumarate (or tenofovir alafenamide fumarate) + emtricitabine (coformulated) (BI)	Not recommended when HIV RNA >100,000 copies/mL (100×10^6/L) or CD4 <200 cells/μL (0.2×10^9/L); no proton pump inhibitors (rilpivirine); food requirement; antacid interactions
If abacavir and tenofovir cannot be used	Dolutegravir + lamivudine (CI)	Only if HIV RNA <500,000 copies/mL (500×10^6/L); possible increased risk of neural tube defects in infants if used at the time of conception
	Darunavir + ritonavir + raltegravir (CI)	Only if HIV RNA <100,000 copies/mL (100×10^6/L)and CD4 >200 cells/mm^3 (0.2×10^9/L); raltegravir must be dosed twice daily
	Darunavir + ritonavir + lamivudine (CI)	

Selected Regimens or Components that Should Not be Used at Any Time

Regimen or Component		Comment
Monotherapy with any single agent (AI)		Inferior virologic efficacy
Any NRTI regimen (AI)		Inferior virologic efficacy
Atazanavir + indinavir (AIII)		Additive adverse effects, including hyperbilirubinemia and jaundice
Didanosine + tenofovir (AII)		Inferior virologic efficacy, CD4 declines
Didanosine + stavudine (AII)		Toxicity including subcutaneous fat loss, peripheral neuropathy, and lactic acidosis
2 NNRTI combinations (AI)		Higher adverse events, drug interactions
Emtricitabine + lamivudine or zidovudine + stavudine (AIII, AII)		Analogs of same nucleobase, no additive benefit (or antagonistic)

Unboosted PIs (ie, darunavir, saquinavir, tipranavir) (AII)		Inadequate bioavailability
Etravirine + selected boosted PIs (AII)		Possible induction of PI metabolism, doses not established
Nevirapine in ARV naïve with higher CD4 counts (>250 cells/μL [0.25 × 10^9/L] for women, >400 cells/μL [0.4 × 10^9/L] for men) (BI)		High incidence of symptomatic hepatotoxicity

[a]Evidence-based rating definition. Rating strength of recommendation—A, strong recommendation; B, moderate recommendation; C, optional recommendation. Rating quality of evidence supporting the recommendation—I, evidence from at least one correctly randomized, controlled trial with clinical outcomes and/or validated laboratory; II, evidence from at least one well-designed clinical trial without randomization or observational cohorts with long-term clinical outcomes; III, expert opinion. Lamivudine and emtricitabine are considered interchangeable endpoints.

Treatment During Pregnancy

- Generally, pregnant women should be treated as would nonpregnant women, with the goal of maximally suppressing HIV RNA, with some exceptions. **Efavirenz** should be avoided in women planning to become pregnant or who are not using effective contraception as efavirenz has been associated with neural tube defects in the first trimester, in some but not all studies.
- **Dolutegravir** use at the time of conception was associated with neural tube defects in infants and until more is known, dolutegravir should be avoided if possible in women who are planning to become pregnant or are not using effective contraception.
- Intravenous (IV) **zidovudine** is recommended intrapartum depending on the mother's viral load, based on early studies demonstrating clear prophylactic effectiveness as well as extensive familiarity with the side-effect profile. Infants born to HIV-infected mothers should also receive zidovudine (±several doses of **nevirapine**) prophylaxis for 4–6 weeks after birth.

Chemoprophylaxis

- Post-exposure prophylaxis (PEP) with conventional ART regimens (eg, **tenofovir disoproxil fumarate–emtricitabine–rategravir**) should be initiated as soon as possible (ideally within 1–2 hours) after high-risk exposures to prevent HIV infection. The optimal duration of treatment is unknown, but at least 4 weeks of therapy is advocated.
- Preexposure prophylaxis (PrEP) involves daily tenofovir disoproxil fumarate–emtricitabine in HIV-negative persons at high risk of HIV acquisition to prevent infection should an HIV-exposure occur.

EVALUATION OF THERAPEUTIC OUTCOMES

- Following the initiation of therapy, patients are generally monitored at 3-month intervals until HIV RNA reaches undetectable levels. An assessment at 2–8 weeks is warranted to document early response. Monitoring may be increased to every 6 months in stabilized patients.
- There are two general indications to change therapy: significant toxicity and treatment failure.
- Specific criteria to indicate treatment failure have not been established through controlled clinical trials. As a general guide, the following events should prompt consideration for changing therapy: the inability to achieve less than 200 copies/mL (200 ×10^3/L) HIV RNA by 24 weeks of therapy initiation (repeat testing is suggested to confirm), or, after HIV RNA suppression, repeated detection of greater than 200 copies/mL (200 × 10^3/L) of HIV RNA.

Therapeutic Failure

- The most important measure of therapeutic failure is suboptimal suppression of viral replication.
- Therapeutic failure may be the result of factors such as pre-ART disease factors (eg, high viral load or preexisting drug resistance), nonadherence to medication, development of new drug resistance, intolerance to one or more medications, adverse drug–drug or drug–food interactions, or pharmacokinetic–pharmacodynamic variability.
- Drug resistance testing is recommended while the patient is undergoing the failing regimen or within 4 weeks after stopping the regimen as long as the HIV RNA count is greater than 500 copies/mL (500×10^3/L), which is the threshold for resistance assays (~500–1000 copies/mL [$\sim 500 \times 10^3$–1000×10^3/L]). Patients should be treated with at least two (preferably three) fully active antiretroviral drugs based on medication history and resistance tests. The goal of therapy is to suppress HIV RNA to undetectable levels. In cases when less than 50 copies/mL ($<50 \times 10^3$/L) cannot be attained, maintenance on the regimen is preferred over drug discontinuation so as to prevent rapid immunological and clinical decline.

INFECTIOUS COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS

- The probability of developing specific opportunistic infections (OIs) is closely related to CD4 count thresholds. The principle in the management of OIs is treating HIV infection to enable CD4 cells to recover and be maintained above protective levels. Other important principles are:
  - ✔ Preventing exposure to opportunistic pathogens
  - ✔ Using vaccinations to prevent first-episode of disease (consult HIV-specific guidelines)
  - ✔ Use primary chemoprophylaxis at certain CD4 thresholds to prevent first-episode of disease
  - ✔ Treating emergent OIs
  - ✔ Use secondary chemoprophylaxis to prevent disease recurrence
  - ✔ Discontinuing prophylaxis with sustained immune recovery
- The spectrum of infectious diseases observed in HIV-infected individuals and recommended first-line therapies are shown in **Table 41-3**.

TABLE 41-3

Selected Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals

Clinical Disease	Preferred Initial Therapies for Acute Infection in Adults (Strength of Recommendation in Parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
Fungi		
Candidiasis, oral	Fluconazole 100 mg orally for 7–14 days (AI)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting
	or	
	Nystatin 500,000 units oral swish (~5 mL) four times daily for 7–14 days (BII)	Taste, patient acceptance
Candidiasis, esophageal	Fluconazole 100–400 mg orally or IV daily for 14–21 days (AI)	Same as above

	or	
	Itraconazole 200 mg/day orally for 14–21 days (AI)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting
Pneumocystis jirovecii pneumonia	*Moderate-to-severe episodes* Trimethoprim–sulfamethoxazole IV or orally 15–20 mg/kg/day as trimethoprim component in three to four divided doses for 21 days[a] (AI) moderate or severe therapy should be started IV	Skin rash, fever, leucopenia, thrombocytopenia
	Mild-to-moderate episodes Trimethoprim–sulfamethoxazole 15–20 mg/kg/day as trimethoprim component orally in three divided doses or trimethoprim–sulfamethoxazole double strength tablets, two tablets three times daily	
Cryptococcal meningitis	Liposomal amphotericin B 3–4 mg/kg/day IV with flucytosine 100 mg/kg/day orally in four divided doses for a minimum of 2 weeks (AI) *followed by*	Nephrotoxicity, hypokalemia, anemia, fever, chills
		Bone marrow suppression
	Fluconazole 400 mg/day, orally for 8 weeks or until CSF cultures are negative (AI)[a]	Same as above
Histoplasmosis	Liposomal amphotericin B 3 mg/kg/day IV for 2 weeks (AI) *followed by*	Same as above
	Itraconazole 200 mg orally thrice daily for 3 days then twice daily, for 12 months (AII)[a]	
Coccidioidomycosis	Liposomal amphotericin B 3–5 mg/kg/day IV until clinical improvement (usually after 500–1000 mg) then switch to azole (AIII)[a]	Same as above
	or	
	Fluconazole 400–800 mg once daily (meningeal disease) (AII)[a]	Same as above
Protozoa		
Toxoplasmic encephalitis	Pyrimethamine 200 mg orally once, then 50–75 mg/day	Bone marrow suppression
	plus	
	Sulfadiazine 1–1.5 g orally four times daily	Rash, drug fever
	and	
	Leucovorin 10–25 mg orally daily for 6 weeks (AI)[a]	
Isosporiasis	Trimethoprim and sulfamethoxazole: 160 mg trimethoprim and 800 mg sulfamethoxazole orally or IV four times daily for 10 days (AII)[a]	Same as above

Bacteria		
Mycobacterium avium complex	Clarithromycin 500 mg orally twice daily, *plus* ethambutol 15 mg/kg/day orally (AI) for at least 12 months	GI intolerance, optic neuritis, peripheral neuritis, elevated liver tests
Salmonella enterocolitis or bacteremia	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 14 days (longer duration for bacteremia or advanced HIV) (AIII)	GI intolerance, headache, dizziness
Campylobacter enterocolitis (mild-to-moderate)	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 7–10 days (or longer with bacteremia) (BIII)	Same as above
Shigella enterocolitis	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 7–10 days (or 14 days for bacteremia) (AIII)	Same as above
Viruses		
Mucocutaneous herpes simplex	Acyclovir 5 mg/kg IV every 8 hours until lesions regress, then acyclovir 400 mg orally three times daily until complete healing (famciclovir or valacyclovir is alternative) (AIII)	GI intolerance, crystalluria
Primary varicella-zoster	Acyclovir 10–15 mg/kg every 8 hours IV for 7–10 days (severe cases), then switch to oral valacyclovir 1 g three times daily after defervescence (famciclovir or acyclovir is alternative) (AIII)	Obstructive nephropathy, CNS symptoms
Cytomegalovirus (retinitis)	Intravitreal ganciclovir (2 mg) or foscarnet (2.4 mg) for 1–4 doses over 7–10 days (for sight threatening lesions) ***plus*** valganciclovir 900 mg twice daily for 14–21 days then once daily until immune recovery from ART (AIII)[a]	Neutropenia, thrombocytopenia
Cytomegalovirus esophagitis or colitis	Ganciclovir 5 mg/kg IV every 12 hours for 21–42 days; may switch to valganciclovir 900 mg orally every 12 hours when oral therapy can be tolerated (BI)	Same as above

[a]Maintenance therapy is recommended.

ART, antiretroviral therapy; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

See **Table 41-3** for levels of evidence-based recommendations.

Pneumocystis jirovecii Pneumonia

- *P. jirovecii* pneumonia (PCP) is the most common life-threatening OI in patients with AIDS. The taxonomy of the organism is unclear, having been classified as both protozoan and fungal.

Clinical Presentation

- Characteristic symptoms include fever and dyspnea. Clinical signs are tachypnea with or without rales or rhonchi and a nonproductive or mildly productive cough occurring over a period of weeks, although more fulminant presentations can occur. Chest radiographs may show florid or subtle infiltrates or may occasionally be normal, although infiltrates are usually interstitial and bilateral. Arterial blood gases may show minimal hypoxia (partial pressure of oxygen [PaO_2] 80–95 mm Hg [10.6–12.6 kPa]) but in more advanced disease may be markedly abnormal.

- The onset of PCP is often insidious, occurring over a period of weeks. Clinical signs are tachypnea with or without rales or rhonchi and a nonproductive or mildly productive cough occurring over a period of weeks, although more fulminant presentations can occur. The diagnosis of PCP usually is made by identification of the organism in induced sputum or in specimens obtained from bronchoalveolar lavage.

Treatment

- The treatment of choice is **trimethoprim–sulfamethoxazole,** which is associated with a 60%–100% response rate.
- Trimethoprim–sulfamethoxazole is given in doses of 15–20 mg/kg/day (based on the trimethoprim component) as three or four divided doses for the treatment of PCP. Treatment duration is typically 21 days but must be based on clinical response.
- Trimethoprim–sulfamethoxazole is usually initiated by the IV route, although oral therapy (as oral absorption is high) may suffice in mildly ill and reliable patients or to complete a course of therapy after a response has been achieved with IV administration.
- The more common adverse reactions seen with trimethoprim–sulfamethoxazole are rash (including Stevens–Johnson syndrome), fever, leukopenia, elevated serum transaminases, and thrombocytopenia. The incidence of these adverse reactions is higher in HIV-infected individuals than in those not infected with HIV. Mild rashes should be watched closely for progression to more severe reactions but are not an absolute contraindication to continuing therapy.
- For pentamidine, side effects include hypotension, tachycardia, nausea, vomiting, severe hypoglycemia or hyperglycemia, pancreatitis, irreversible diabetes mellitus, elevated transaminases, nephrotoxicity, leukopenia, and cardiac arrhythmias.

Prophylaxis

- Primary prophylaxis of PCP is recommended for any HIV-infected person who has a CD4 lymphocyte count less than 200 cells/mm^3 (200 $\times 10^6$/L) (or CD4 percentage of total lymphocytes <14%) or a history of oropharyngeal candidiasis. Secondary prophylaxis is recommended for all HIV-infected individuals who have had a previous episode.
- Trimethoprim–sulfamethoxazole is the preferred therapy for both primary and secondary prophylaxis of PCP in adults and adolescents. The recommended dose in adults and adolescents is one double-strength tablet daily.

See Chapter 143, Human Immunodeficiency Virus Infection, authored by Peter L. Anderson, Jenna Yager, and Courtney V. Fletcher, for a more detailed discussion of this topic.