KEY POINTS

- The diagnosis of hospital-acquired and ventilator-associated pneumonia are suggested by a new lung infiltrate on imaging plus clinical findings, including new-onset fever, leukocytosis or leukopenia, purulent sputum, and decline in oxygenation.
- Empiric ventilator-associated pneumonia regimens should include coverage for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli; an agent active against methicillin-resistant *S. aureus* (MRSA) should be included for patients with MRSA risk factors or where MRSA prevalence exceeds 10% (or is unknown); similar regimens are recommended for empiric hospital-acquired pneumonia treatment.
- In patients receiving mechanical ventilation, the head of the bed should be elevated 30° to 45°; a supine position, particularly in patients receiving enteral nutrition, increases the risk for developing ventilator-associated pneumonia.

Hospital-Acquired Infections Caused by Multidrug-Resistant Organisms

Antimicrobial resistance has been noted in nearly all bacterial pathogens. Multidrug-resistant organisms (MDROs) are most prevalent in health care settings (highest incidence in long-term acute care hospitals) but are also observed in the community. Nearly half of *S. aureus* HCAIs in the United States are methicillin resistant, about 30% of enterococci are vancomycin resistant, 20.7% of Enterobacteriaceae produce ESBL and are resistant to all β-lactam antibiotics, 3.3% of Enterobacteriaceae are resistant to carbapenems, and 14.2% of *P. aeruginosa* and 43.1% of *Acinetobacter* species are multidrug resistant (some *Acinetobacter* are resistant to nearly all antibiotics).

Candida auris is an emerging drug-resistant pathogen shed from patients' skin into the environment, where it can survive for weeks and be transmitted to other patients. It causes severe invasive infections, particularly in immunocompromised patients. See Fungal Infections for additional information.

MDRO infections are difficult to treat, with mortality rates up to four times higher than infections caused by antibiotic-sensitive strains. Limiting transmission of MDROs in health care settings requires full adherence to hand hygiene protocols, contact precautions, and cleaning and disinfecting of the environment and patient care equipment. More than half of hospitalized patients receive antibiotics, a major risk for acquiring an antibiotic-resistant organism and *C. difficile* infection. Judicious use of antimicrobial agents is increasingly important to combat the rise of MDROs and emergence of untreatable infections.

KEY POINTS

- Multidrug-resistant organisms are most prevalent in health care settings (highest incidence in long-term acute care hospitals) but are also observed in the community.
- Limiting emergence and transmission of multidrug-resistant organisms in health care settings requires full adherence to hand hygiene protocols, contact precautions, cleaning and disinfecting of the environment and equipment, and judicious use of antimicrobial agents.

HVC

HIV/AIDS

HIV infection remains a significant global health concern despite being a treatable disease. Many persons living with HIV infection are not aware of their status because they have never been tested; others have been diagnosed but are not receiving care. This chapter will focus on HIV-1. Infection with HIV-2 primarily occurs in parts of Africa and remains rare in the United States; HIV-2 generally is a less progressive disease with less immunocompromise and lower risk of opportunistic infections. Testing for HIV infection detects HIV-1 and HIV-2 antibodies (see Screening and Diagnosis).

Prevention

HIV transmission occurs through sexual contact or exposure to other body fluids (**Table 60**). Reducing transmission can be accomplished by using barrier methods, such as condoms during sexual contact, and through clean syringe services programs (needle exchange programs) for persons who inject drugs. Universal blood donor testing has all but eliminated infection through blood transfusion in the United States, with current risk estimated to be one in 2 million.

Antiretroviral therapy (ART) has extraordinary potential to reduce new infections in addition to benefiting the treated person. Successful treatment is associated with significant reductions in HIV transmission. Although reducing viral load to an undetectable level in blood does not prove absence of virus in semen or vaginal fluid, the rate of transmission from a

TABLE 60. Risk of HIV-1 Transmission per Single Exposure

Exposure	Risk (%)
Occupational–needlestick	0.23
Occupational–mucous membrane	0.09
Needle-sharing injection drug use	0.63
Receptive anal intercourse	1.4
Receptive vaginal intercourse	0.08
Insertive anal intercourse	0.11
Insertive vaginal intercourse	0.04
Oral sex	0.01

sexual partner with undetectable blood viral load has been demonstrated to be close to zero, at a level the CDC called "effectively no risk" in a September 2017 statement; hence the slogan "Undetectable = Untransmissible" ("U=U"). Also termed "treatment as prevention" (TasP), maintaining an HIV RNA level less than 200 copies/mL (documented for ≥6 months) with ART prevents HIV transmission to sexual partners. In what is known as the "treatment cascade," medical care necessary to achieve successful viral suppression consists of testing and diagnosing infected persons, linking them to health care for counseling and treatment, keeping them in a treatment program, and ensuring antiretroviral and other treatment adherence. Each step along this continuum of care is a potential obstacle to successful HIV management on a personal and public health level. Even high-income countries have poor rates of retention in care and adherence to medication. The CDC estimates that the undiagnosed and not-in-care groups with HIV infection were responsible for 80% of HIV transmissions in the United States in 2016.

Postexposure prophylaxis has been used successfully for many years to prevent infection after occupational and nonoccupational HIV exposure. Prophylaxis should be started as soon as possible after exposure; it is not recommended if more than 72 hours have passed. A three-drug regimen is given for 4 weeks; the preferred regimen is tenofovir disoproxil fumarate (TDF) and emtricitabine plus either raltegravir or dolutegravir (see Management of Pregnant Patients for information on dolutegravir in pregnancy). The exposed person should undergo HIV testing at baseline and at 4 to 6 weeks, 3 months, and 6 months after exposure. **Figure 35** shows an algorithm for evaluation of possible HIV exposure.

The U.S. Preventive Services Task Force (USPSTF) and CDC recommend pre-exposure prophylaxis (PrEP) with ART to reduce the risk of infection for persons at high risk of HIV acquisition, including men who have sex with men, persons at risk through heterosexual contact, and persons who inject drugs (**Table 61**). A two-drug combination of TDF and emtricitabine, taken once daily, is FDA approved for HIV PrEP; with proven adherence, it has been shown to be more than 90% effective in reducing infection in those at high risk. Additionally, the FDA recently approved once-daily tenofovir alafenamide (TAF) and emtricitabine for HIV PrEP, excluding in persons who have receptive vaginal intercourse. Patients should also be counseled on the need to continue barrier precautions, on medication toxicity, and on continued risk for other sexually transmitted infections (STIs). Testing should be performed for HIV, hepatitis B virus (HBV), kidney function, and pregnancy before PrEP initiation; monitoring for HIV, other STIs, and pregnancy every 3 months and performing kidney function assessment every 6 months are also recommended during PrEP therapy. Persons taking PrEP who test positive for HIV should have a third drug (either

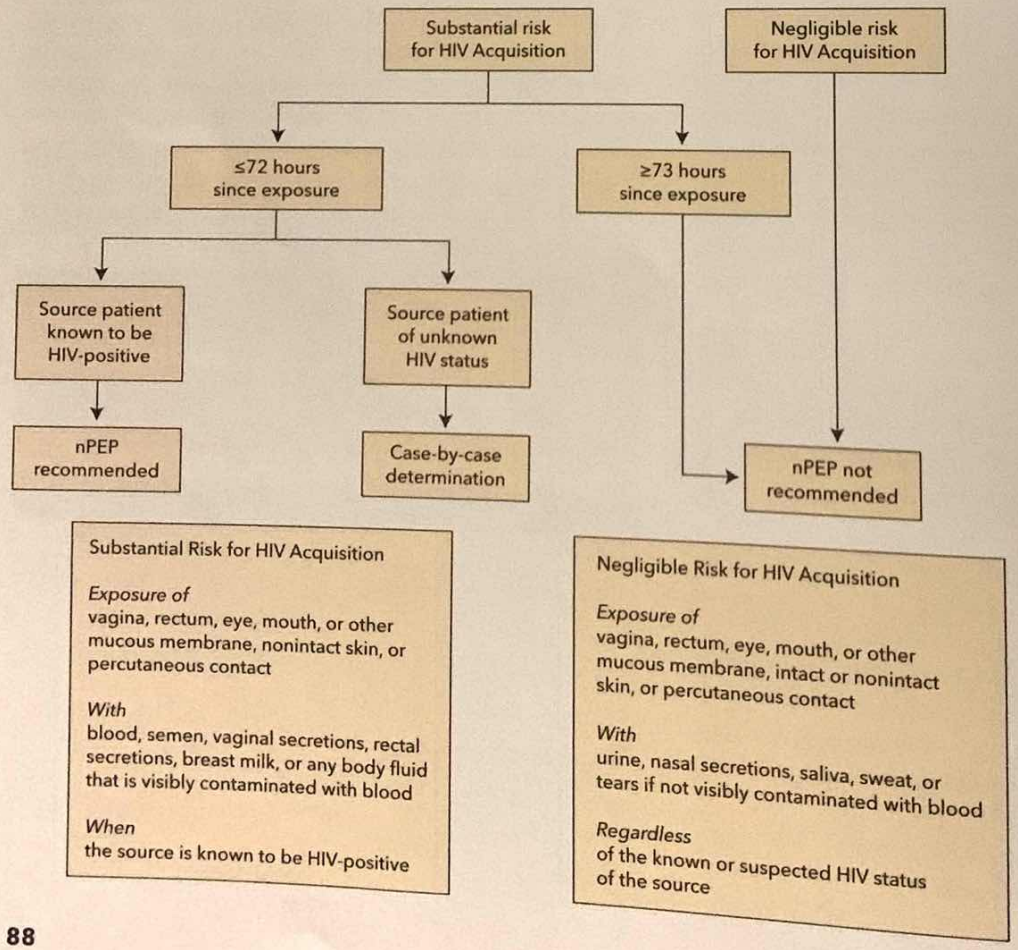

FIGURE 35. Algorithm for evaluation and treatment of possible HIV exposure. nPEP = nonoccupational postexposure prophylaxis.

Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. Available at https://stacks.cdc.gov/view/cdc/38856. Accessed January 29, 2018.

TABLE 61. Persons at High Risk of HIV Acquisition Who Should be Considered for PrEP[a]

Men Who Have Sex with Men	Heterosexual Men & Women	Persons Who Use Injection Drugs
Serodiscordant sexual partner	Serodiscordant sexual partner	Shared use of drug injection equipment
Inconsistent condom use during insertive or receptive anal sex	Inconsistent condom use with a partner whose HIV status is unknown or who is at high risk themselves	At risk of sexual acquisition of HIV as described for other risk groups
STI with chlamydia, gonorrhea, or syphilis within the previous 6 months	STI with syphilis or gonorrhea within the previous 6 months	

PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection.

[a]Each group is considered at high risk of HIV acquisition if they possess at least one of the listed characteristics. Additionally, persons who engage in transactional sex, persons who are trafficked for sex work, men who have sex with men and women, and transgender women and men who are sexually active can be at high risk of HIV infection and should be considered for PrEP based on the criteria outlined above. Transgender women are at especially high risk.

ritonavir-boosted darunavir or dolutegravir) added to the two-drug PrEP regimen pending results of HIV RNA and viral resistance testing. The evidence is conflicting concerning potentially increased high-risk behavior and incidence of other STIs in PrEP users during therapy. PrEP has also been calculated to have favorable cost effectiveness, well below that for other accepted preventive health measures.

KEY POINTS

- Reducing viral load to an undetectable level in blood reduces the rate of HIV transmission from a sexual partner to close to zero; "Undetectable = Untransmissible" ("U = U").
- Postexposure prophylaxis with a three-drug regimen (tenofovir disoproxil fumarate and emtricitabine plus either raltegravir or dolutegravir) should be started as soon as possible after HIV exposure; it is not recommended if more than 72 hours have passed.
- Pre-exposure prophylaxis with two antiretroviral medications (tenofovir disoproxil fumarate or tenofovir alafenamide, plus emtricitabine) is recommended in select persons at high risk for exposure to HIV to reduce the risk of infection.

Pathophysiology and Natural History

Most persons with acute HIV infection are symptomatic; however, because symptoms are nonspecific and self-limited, most acute infections are not diagnosed accurately. The frequency of signs and symptoms at presentation is shown in **Table 62.** During symptomatic acute infection, the fourth-generation antibody and p24 antigen testing may not yet be positive, and diagnosis depends on an HIV viral load test demonstrating HIV RNA.

TABLE 62. Signs and Symptoms of Acute HIV Infection (Acute Retroviral Syndrome)

Sign/Symptom	Frequency (%)
Fever	75
Fatigue	68
Myalgia	49
Rash	48
Headache	45
Pharyngitis	40
Lymphadenopathy	39
Arthralgia	30
Night sweats	28
Diarrhea	27

Patients with chronic HIV infection may present with opportunistic infections, especially when CD4 counts are less than 200/μL, meeting the definition for AIDS (see Opportunistic Infections). Even before progression to AIDS, patients with HIV infection may present with recurrent or severe episodes of infections that do not qualify as opportunistic. Other symptoms can result from chronic HIV infection itself, including lymphadenopathy, fever, night sweats, fatigue, weight loss, chronic diarrhea, and various oral and skin conditions (seborrheic dermatitis, eosinophilic folliculitis, xerosis, atopic dermatitis, and psoriasis). HIV should also be considered in patients with unexplained cytopenias or nephropathy.

KEY POINTS

- Most persons with acute HIV infection are symptomatic; however, because symptoms are nonspecific and self-limited, most acute infections are not diagnosed accurately.
- During symptomatic acute infection, the fourth-generation IgM and IgG antibody and p24 antigen may not yet be detectable, and diagnosis depends on an HIV viral load test demonstrating HIV RNA.

Screening and Diagnosis

Testing only symptomatic persons neglects numerous persons who are infected. Thus, the CDC, American College of Physicians, Infectious Diseases Society of America, and USPSTF recommend universal screening for HIV in all adults at least once. The CDC recommends those at higher risk undergo repeat HIV testing at least annually. In 2017, the CDC reaffirmed its support for this recommendation but noted that clinicians can consider the potential benefits of more frequent HIV screening (e.g., every 3 or 6 months) for some asymptomatic sexually active men who have sex with men based on

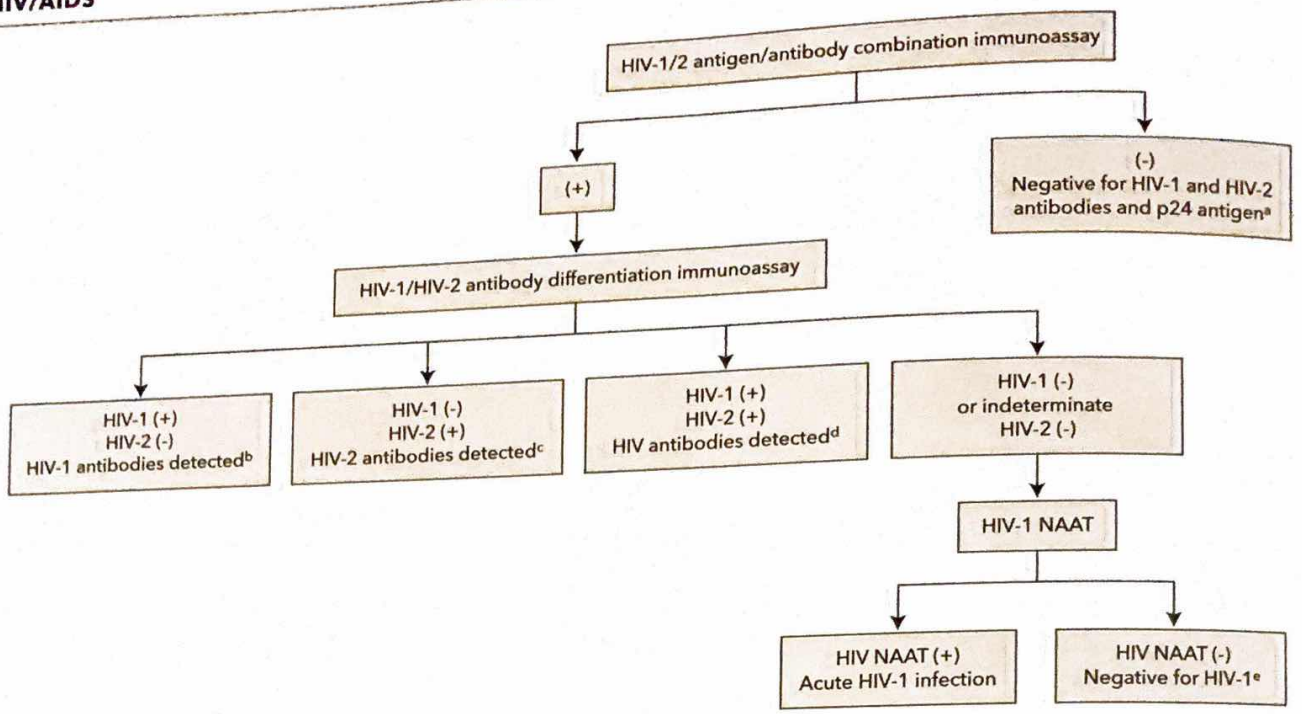

FIGURE 36. CDC-recommended algorithm for laboratory HIV testing. NAAT = nucleic acid amplification test. (+) indicates reactive test result. (−) indicates nonreactive test result.

[a]No evidence of HIV infection.

[b]HIV 1 infection.

[c]HIV 2 infection.

[d]HIV 1 and HIV 2 infection.

[e]HIV-1/2 antigen/antibody combination immunoassay result was a false positive.

Centers for Disease Control and Prevention; Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. January 2018. Available at https://stacks.cdc.gov/view/cdc/50872.

their individual risk factors, local HIV epidemiology, and local policies.

The fourth-generation HIV testing uses a combination assay for HIV antibody and HIV p24 antigen, which detects acute infection 15 to 20 days after the onset of infection. The testing algorithm is outlined in **Figure 36**. In chronic infection, the initial combination assay is nearly 100% sensitive and specific, but testing in low prevalence populations (such as general screening) can still result in false positives, so waiting for the results of the confirmatory antibody differentiation immunoassay or nucleic acid amplification testing is important for a definitive diagnosis.

KEY POINTS

- It is recommended that all adults be tested for HIV infection at least once.
- The fourth-generation HIV testing uses a combination assay for HIV antibody and HIV p24 antigen and is nearly 100% sensitive and specific for chronic HIV infection.

Initiation of Care

Initial Evaluation and Laboratory Testing

All persons who test positive for HIV should immediately be referred to a health care provider with HIV infection management expertise. Initial evaluation should include complete history (including social and sexual) and examination for signs and symptoms of opportunistic infection or other complications. Patient education and counseling should include information on transmission and prevention. Initial laboratory tests include baseline organ function and evaluation for other infections with higher prevalence in persons with HIV (**Table 63**). A baseline CD4 cell count guides opportunistic infection prophylaxis, and a baseline viral load supports monitoring ART effectiveness (see Management of HIV Infection).

Immunizations and Prophylaxis for Opportunistic Infections

Numerous immunizations are recommended for all persons with HIV, starting with the 13-valent pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines, respectively, at least 8 weeks apart; a 23-valent polysaccharide vaccine booster is also recommended after 5 years. Patients who are not already immune or infected with HBV should receive the hepatitis B vaccine series. Influenza, COVID-19, tetanus-diphtheria-pertussis, hepatitis A, and human papillomavirus vaccinations are indicated as for the general population. Measles-mumps-rubella, varicella, and recombinant zoster vaccines can be given as long as the CD4 cell count is greater

TABLE 63. Recommended Initial Laboratory Screening and Other Studies in Persons with HIV Infection

Test	Comments
HIV-specific tests for all persons with HIV	
HIV antigen/antibody testing	If written evidence of diagnosis not available or if viral load low or undetectable
CD4 cell count and percentage	Assess need for opportunistic infection prophylaxis
Plasma HIV RNA polymerase chain reaction (HIV viral load)	Establish baseline and monitor viral suppression
HIV resistance testing	Baseline genotype for protease inhibitor, nonnucleoside RTI, nucleoside/nucleotide RTI mutations for persons who have never initiated therapy, are reengaging in care and not receiving therapy, or with inconsistent access to therapy. INSTI genotype is recommended only if suspicion for INSTI mutation transmission.
Other laboratory tests	
Complete blood count with differential	Assess for anemia, neutropenia, thrombocytopenia
Alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase	Assess for evidence of liver damage, hepatitis, or systemic infection (e.g., elevated alkaline phosphatase level with some opportunistic infections)
Total protein and albumin levels	High total protein level common with untreated HIV infection because of increased immunoglobulin fraction secondary to B-cell hyperplasia; low albumin level may indicate nutritional deficiency or nephrotic syndrome
Electrolytes, blood urea nitrogen, creatinine	Assess kidney function; creatinine level for calculation of estimated glomerular filtration rate
Lipid profile and blood glucose; hemoglobin A_{1c}	Fasting not needed for initial lipid and glucose assessment; if abnormal, repeat fasting Hemoglobin A_{1c} measured before ART initiation but not used for diagnosis of diabetes in those taking ART
Urinalysis	Assess for evidence of proteinuria, hematuria
Screening for coinfections	
Cervical Pap test	21-29 years of age: annual Pap test; if three consecutive Pap tests are normal, follow-up screening in 3 years. ≥30 years of age: three consecutive normal Pap tests without an HPV test, follow-up Pap in 3 years; Pap with HPV testing are both negative, follow-up Pap in 3 years after combined test
Anal Pap test[a]	Anal Pap test for all persons with a history of receptive anal intercourse, genital warts, or abnormal cervical Pap result if access to appropriate referral for follow-up, including high-resolution anoscopy, is available
Gonorrhea, chlamydia	At least annual screening using nucleic acid amplification testing with sites based on exposure history (e.g., urine, vaginal, rectal, oropharyngeal; three-site testing preferred for all patients)
Trichomoniasis	Annual screening in all persons who have vaginal sex
Syphilis	At least annual screening using local protocol (either rapid plasma reagin or treponemal-specific antibody tests)
Latent *Mycobacterium tuberculosis*	TST or IGRA; IGRA preferred if history of BCG vaccination
Varicella-zoster virus	Anti-varicella IgG if no known history of chicken pox or shingles
Hepatitis A, B, and C virus	HBsAg, HBsAb, HBcAb, HCVAb; HAV total or IgG antibody. If HBsAg+ or HBcAb+, order HBV DNA level; if HCVAb+, order HCV RNA level and HCV genotype. Screen for hepatocellular carcinoma for all adult patients with cirrhosis and noncirrhotic patients with chronic HBV for an extended period.
Measles titer	Adequate evidence of immunity includes being born in the United States before 1957, written documentation of adequate vaccination, or serologic evidence of immunity. Persons born in the 1960s may have been vaccinated with a vaccine other than MMR and may have waning immunity. Patients may opt to receive a booster MMR vaccine rather than check serology.

ART = antiretroviral therapy; BCG = bacillus Calmette-Guérin; HAV = hepatitis A virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HCVAb = hepatitis C antibody; HPV = human papillomavirus; IGRA = interferon-γ release assay; INSTI = integrase strand transfer inhibitor; MMR = measles, mumps, rubella; RTI = reverse transcriptase inhibitor; TST = tuberculin skin test.

[a]At this time, no national guidelines are available for this intervention.

Adapted with permission from Thompson MA, Horberg MA, Agwu AL, et al. Primary Care Guidance for Persons With Human Immunodeficiency Virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2020 Nov 6:ciaa1391. Epub ahead of print. [PMID: 33225349] doi: 10.1093/cid/ciaa1391

TABLE 64. Prophylaxis against Opportunistic Infections in HIV/AIDS

Opportunistic Infection	Indication	Preferred Drug
Pneumocystis jirovecii	CD4 cell count <200/μL[a]	TMP-SMX, double-strength or single-strength tablet once daily[b]
Toxoplasmosis	CD4 cell count <100/μL and positive serologic results[a]	TMP-SMX, double-strength tablet once daily[c]
Mycobacterium avium complex	CD4 cell count <50/μL[d]	Azithromycin, 1200 mg once weekly or 600 mg twice weekly; clarithromycin, 500 mg twice daily
Latent tuberculosis	TST >5 mm or positive IGRA results	3 months of isoniazid plus rifapentine given once weekly
		3 months of isoniazid plus rifampin given daily[e]

IGRA = interferon-γ release assay; TMP-SMX = trimethoprim-sulfamethoxazole; TST = tuberculin skin test.

[a]Prophylaxis may be discontinued in patients with CD4 cell count ≥200/μL for ≥3 months; emerging evidence suggests prophylaxis may be discontinued in patients with CD4 cell count of 100-200/μL and a suppressed viral load for ≥3 months.

[b]Alternatives for *Pneumocystis jirovecii* prophylaxis may be found here: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/321/pneumocystis-pneumonia

[c]Alternatives for toxoplasmosis prophylaxis may be found here: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/322/toxoplasma-gondii

[d]Prophylaxis no longer recommended in patients who start antiretroviral therapy immediately.

[e]Drug interactions with first-line antiretroviral therapy regimens (including tenofovir alafenamide, integrase inhibitors) are common, and HIV or latent tuberculosis regimens may need to be modified. Daily pyridoxine is recommended in patients who will receive isoniazid because of the risk for peripheral neuropathy. See *Mycobacterium tuberculosis* Infection for dosing information. Other organizations may include additional recommended regimens. Recommendations from Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69:1-11. [PMID: 32053584] doi:10.15585/mmwr.rr6901a1

than 200/μL. The recombinant zoster vaccine should be given to individuals 50 years and older with CD4 cell count greater than 200/μL. All persons with HIV infection should be vaccinated for meningococcal disease with the quadrivalent meningococcal vaccine, including boosters every 5 years.

Prophylaxis for opportunistic infections depends on the patient's CD4 cell count (**Table 64**). Before beginning prophylaxis, active infection should be ruled out clinically and with any indicated testing to avoid undertreatment and selection for resistance, especially for tuberculosis and disseminated *Mycobacterium avium* complex.

KEY POINTS

- All persons with HIV should receive the 13-valent pneumococcal conjugate and 23-valent polysaccharide vaccines, hepatitis B vaccine series (in those not already infected or immune), and meningococcal vaccine; COVID-19, influenza, tetanus-diphtheria-pertussis, hepatitis A, and human papillomavirus vaccines are indicated as for the general population.
- Measles-mumps-rubella, varicella, and recombinant zoster vaccines can be given as long as the CD4 cell count is greater than 200/μL.

Complications of HIV Infection in the Antiretroviral Therapy Era

Metabolic, Kidney, and Liver Disorders

As HIV has become a treatable illness and persons with HIV age, metabolic disorders and specific organ diseases have become increasingly significant. HIV infection itself may be associated with manifestations of accelerated aging, and neurocognitive impairment can be exacerbated by HIV. Age-associated comorbidities and declines in kidney and liver function can also complicate management through drug interactions and increased toxicity.

HIV infection itself and some antiretrovirals affect lipids and can worsen hyperlipidemia; this is especially true for boosted protease inhibitor–based regimens, which can also worsen insulin resistance. Fasting glucose or hemoglobin A_{1c} and lipid levels should be checked at baseline and 3 months after initiating or changing antiretrovirals; hemoglobin A_{1c} should not be used for the diagnosis of diabetes in those taking ART.

Chronic kidney disease is increasingly common in HIV infection, although, with effective ART, it is less often attributed to HIV nephropathy. It is recommended that kidney function be assessed at least every 6 months in patients with HIV. Tenofovir, a very commonly used nucleoside analogue, is associated with risk for tubular nephrotoxicity, which usually manifests as proteinuria. Patients using a regimen containing tenofovir should undergo urinalysis or quantitative measurement of urine protein twice per year.

Bone mineral density is reduced in HIV, and tenofovir is also associated with possible worsening of bone density. Dual-energy x-ray absorptiometry scanning is recommended in men older than 50 years, postmenopausal women, patients with a history of fragility fracture, those with chronic glucocorticoid use, and those at high risk for falls. The newer prodrug of tenofovir, TAF, achieves high intracellular levels of active drug with much lower dosing and lower systemic levels compared with the older formulation, TDF. Compared with TDF, TAF has equal antiviral efficacy with reduced kidney and

bone toxicity and should be used preferentially over TDF in patients with or at risk for bone or kidney disease.

Liver disease is also increased in HIV infection, often because of coinfection with hepatitis B or C virus. All patients with HIV should be screened for hepatitis B and C viruses and immunized if they are HBV negative. If coinfected with HIV and HBV, patients should receive treatment with a TDF or TAF plus emtricitabine or lamivudine-based regimen, which treats both viruses. Patients coinfected with hepatitis C virus should be given a course of curative direct-acting antiviral treatment, although attention must be paid to drug interactions between the antiviral regimens (see MKSAP 19 Gastroenterology and Hepatology).

KEY POINTS

- Fasting glucose or hemoglobin A_{1c} and lipid levels should be checked at baseline and 3 months after initiating or changing antiretroviral therapy; hemoglobin A_{1c} should not be used for the diagnosis of diabetes in those taking antiretroviral therapy.
- Tenofovir disoproxil fumarate (TDF) is associated with increased risks of tubular nephrotoxicity and worsening of bone mineral density; tenofovir alafenamide should be used preferentially over TDF in patients with or at risk for bone or kidney disease.

Cardiovascular Disease

Rates of cardiovascular disease, including myocardial infarction and stroke, are higher in persons with HIV infection; this association remains after correction for increased risk factors such as smoking. Some of the increase may result from hyperlipidemia, but evidence indicates that the increase partially results from HIV infection being a chronic inflammatory state. It is clear that patients with untreated HIV infection have a higher risk of cardiovascular events compared with patients taking effective ART, regardless of any worsening of lipid levels from the ART. Attention to traditional risk factors such as smoking, lipid levels, and hypertension is crucial in patients with HIV, as is use of statin therapy (with attention to drug interactions between some statins and some antiretrovirals) based on current risk calculations. Guidelines from the American College of Cardiology/American Heart Association recommend patients with HIV infection and borderline risk for atherosclerotic cardiovascular disease (5% to <7.5%) should be engaged in risk discussion regarding initiating moderate-intensity statin therapy. An international multicenter trial is addressing whether patients with HIV should be treated with statins even with a 10-year risk less than 7.5%.

KEY POINT

- Rates of cardiovascular disease, including myocardial infarction and stroke, are higher in persons with HIV infection; control of cardiovascular risk factors (smoking, lipid levels, and hypertension) is essential, including statin therapy based on clinical risk calculations.

Neurocognitive Decline

Screening for neurologic complications, especially cognitive impairment, is important at entry into HIV care. Assessment should be repeated in older adults, especially if concerns arise regarding adherence to care and ART. As persons living with HIV age, neurocognitive impairment may be exacerbated by the effect of HIV infection on the brain. Classified as HIV-associated neurocognitive disorders (HAND), manifestations range from asymptomatic neurocognitive impairment to severe HIV-associated dementia (HAD). ART initiation and continuation is the main treatment for HAND, and it has a clear role in prevention and treatment of HAD.

KEY POINT

- Manifestations of HIV-associated neurocognitive disorders (HAND) range from asymptomatic neurocognitive impairment to severe HIV-associated dementia; if not already being provided, ART should be instituted immediately as part of prevention and treatment of HAND.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a disorder associated with worsening of a pre-existing infectious process (paradoxical IRIS) or with revelation of a previously unrecognized pre-existing infection (unmasking IRIS). It has also been reported with noninfectious complications, such as lymphoma. IRIS usually occurs within a few months of initiating effective ART in patients with low pretreatment CD4 cell counts (<100/μL). Management includes continuing ART while treating the opportunistic infection. In select patients, NSAIDs or glucocorticoids may be useful in mitigating inflammatory symptoms.

KEY POINT

- Immune reconstitution inflammatory syndrome is caused by an inflammatory response to a pre-existing infectious process; it usually occurs within a few months of initiating effective antiretroviral therapy and presents with a wide variety of infections and noninfectious complications.

Opportunistic Infections

Mucocutaneous *Candida* infections can occur in HIV-infected patients at relatively preserved CD4 cell counts. HIV-infected patients do not usually develop invasive *Candida* infection unless they have other risk factors. Oral candidiasis usually presents as thrush, with mucosal whitish plaques (**Figure 37**), and can be treated topically (e.g., with clotrimazole troches) or with a short course of oral fluconazole. Swallowing symptoms suggest esophageal disease, which requires systemic treatment, such as fluconazole, for a longer course; a lack of treatment response is an indication for endoscopy.

Reactivation of latent tuberculosis is also significantly increased in HIV infection, even without a decreased CD4 cell

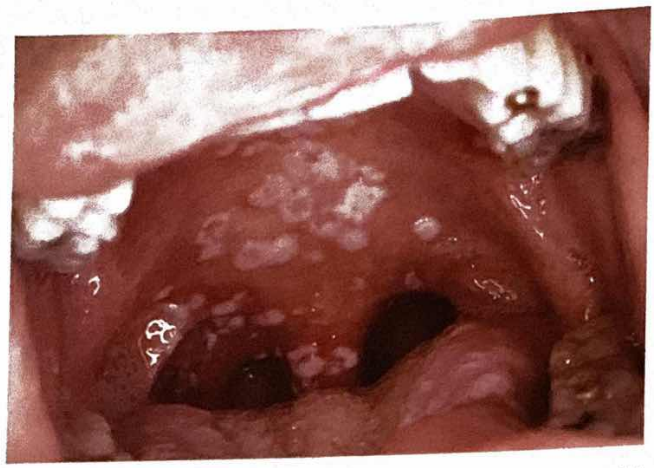

FIGURE 37. Secondary acute oral candidiasis presenting as white-to-red painful plaques in a patient with HIV/AIDS.

count. Tuberculosis is also more likely to present in extrapulmonary sites or with an atypical chest radiograph. Tuberculosis treatment in HIV must consider interactions of rifamycins with many antiretrovirals.

Infections with other opportunistic organisms usually occur at CD4 cell counts less than 200/μL. *Pneumocystis jirovecii* pneumonia usually presents as a subacute illness with fever, dyspnea, and dry cough in a patient with a CD4 cell count less than 200/μL who is not receiving prophylaxis. Chest radiographs most often show bilateral interstitial infiltrates; cavitation or pleural effusion is unusual and suggests another diagnosis. A normal chest radiograph does not exclude the diagnosis, and chest CT is more sensitive, demonstrating patchy "ground-glass" opacities. Normal lactate dehydrogenase levels and stable exercise oxygen saturation have a high negative predictive value, but elevated lactate dehydrogenase levels and oxygen desaturation with exercise are nonspecific. Diagnosis depends on demonstration of causative organisms and often requires bronchoscopy. The treatment of choice is high-dose trimethoprim-sulfamethoxazole; patients with hypoxia at presentation should be given adjunctive glucocorticoids to prevent worsening that may accompany treatment initiation.

Cryptococcus infection usually presents as subacute meningitis with headache, mental status changes, and fever. The diagnosis can be made most swiftly by antigen testing of cerebrospinal fluid and blood. Management includes antifungal therapy and attention to increased intracranial pressure, which is usually responsible for the morbidity and mortality associated with cryptococcal meningitis (see Fungal Infections).

Toxoplasma gondii infection in AIDS usually presents in patients with CD4 cell counts less than 100/μL. Because it is a reactivation disease, patients are usually serology positive. Clinical presentation includes headache, fever, and focal neurologic deficits. Imaging by CT or MRI (which is more sensitive) reveals multiple ring-enhancing lesions (**Figure 38**). The differential diagnosis includes primary central nervous system

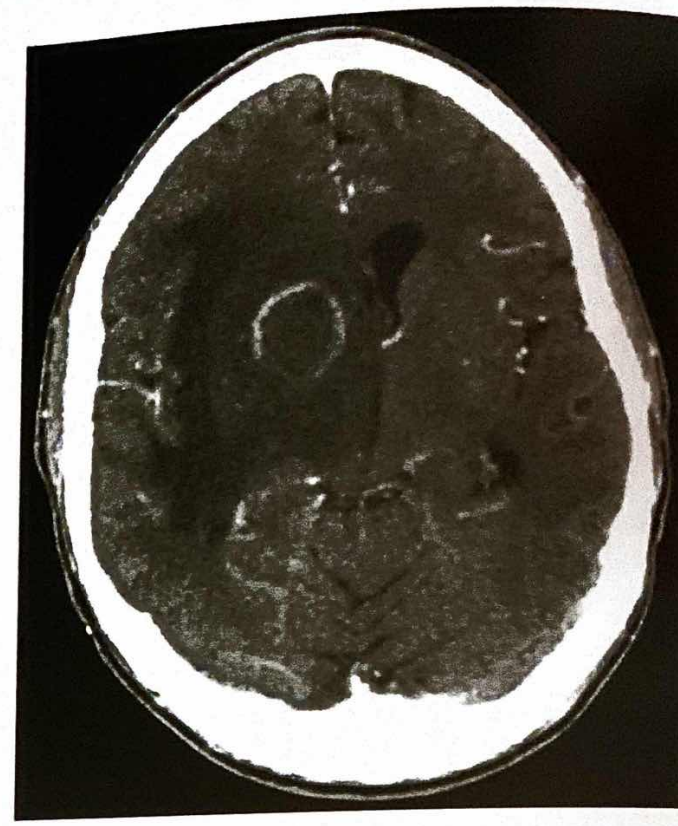

FIGURE 38. Cerebral toxoplasmosis characterized by a ring-enhancing brain lesion associated with edema and mass effect in a patient with AIDS. Although this patient has only a single apparent lesion, multiple lesions are more common.

(CNS) lymphoma, which most often appears as a single lesion on imaging, and progressive multifocal leukoencephalopathy, which is usually nonenhancing. Diagnosis of CNS toxoplasmosis is usually presumptive based on presentation, imaging, and response to empiric treatment.

Mycobacterium avium complex infection usually presents as disseminated disease in patients with CD4 cell counts less than 50/μL; symptoms and signs include fever, sweats, weight loss, hepatosplenomegaly, lymphadenopathy, and cytopenias. Blood cultures for acid-fast bacilli will usually grow *M. avium* complex, but it may also be found on lymph node or liver biopsy when necessary.

Cytomegalovirus most commonly presents with CD4 cell counts less than 50/μL. Cytomegalovirus retinitis, presenting with vision changes or floaters, is much more likely in AIDS than in other immunocompromised conditions, such as after transplantation. Gastrointestinal cytomegalovirus disease is also common, most often as esophagitis or colitis.

Patients with AIDS are also more likely to develop certain malignancies, especially those related to viruses. Non-Hodgkin lymphoma, especially primary CNS lymphoma related to Epstein-Barr virus, is significantly increased compared with age-matched controls. Kaposi sarcoma is caused by human herpes virus type 8 and presents as dark red, brown, or violaceous lesions of the skin or mucous membranes (**Figure 39**); human herpes virus type 8 can also cause primary effusion lymphoma and Castleman disease (giant lymph node

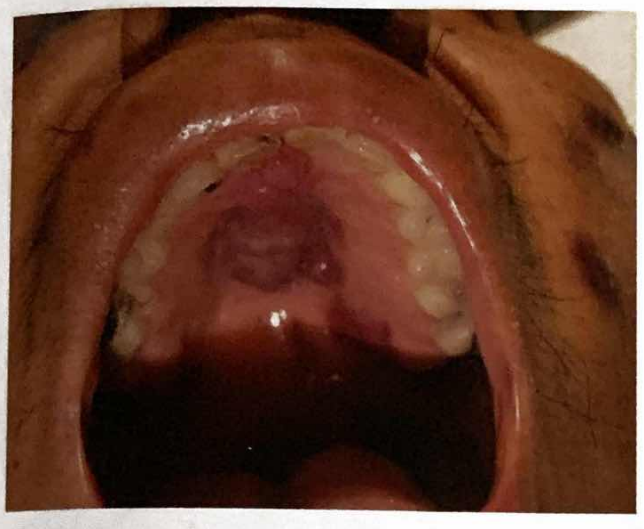

FIGURE 39. Kaposi sarcoma, presenting as firm purple nodules on the face and purple palatal nodules, is seen in a patient with AIDS.

hyperplasia). Human papillomavirus–related malignancies are significantly increased in HIV, including cervical and anal cancers, and regular guideline-based screening is important.

KEY POINTS

- *Pneumocystis jirovecii* pneumonia usually presents as a subacute illness with fever, dyspnea, and dry cough; although chest radiographs most often show bilateral interstitial infiltrates, a normal chest radiograph does not exclude the diagnosis.
- Successful management of *Cryptococcus* infection in patients with HIV includes antifungal therapy and attention to increased intracranial pressure, which is usually responsible for the morbidity and mortality associated with cryptococcal meningitis.
- MRI is more sensitive than CT in revealing the characteristic ring-enhancing lesions of *Toxoplasma gondii* infection in patients with HIV.

Management of HIV Infection

When to Initiate Treatment

All persons with HIV infection should begin ART as soon as they are ready, regardless of CD4 cell count. Rapid initiation of ART (on the day or within 2 weeks of initial diagnosis) has been shown to improve viral suppression and should be considered if no medical (symptoms suggesting opportunistic infections in which immediate ART is contraindicated) or structural (staffing and linkage to care service availability) barriers prevent doing so.

Antiretroviral Regimens

Antiretroviral agents used in the United States are shown in **Table 65**. Standards for effective antiretroviral regimens include use of three drugs from two different classes, preferably combining two nucleoside reverse transcriptase inhibitors with an integrase strand transfer inhibitor. Preferred regimens also feature a high barrier to resistance, good tolerability and safety, and combination pills with once-daily dosing to facilitate adherence (**Table 66**).

Patients with or at risk for reduced kidney function or osteopenia should not be given TDF. To reduce the risk of hypersensitivity, patients who are prescribed abacavir must first undergo HLA-B*57:01 testing to show they are negative. Many antiretrovirals interact with other drugs, and potential drug interactions must always be assessed when beginning HIV therapy or beginning any drug for someone already taking ART. Such assessment is especially necessary when pharmacokinetic boosters (ritonavir or cobicistat) are used specifically to inhibit drug metabolism and raise levels of antiretrovirals.

Viral load levels and CD4 cell counts are monitored to ensure effectiveness and to determine immune recovery. With optimal therapy, HIV RNA in blood should become and stay undetectable. CD4 cell counts will increase, although cell counts may take time to improve and may not show full recovery, especially in those who are older or who have other factors affecting lymphocytes. Patients taking ART who are stable with a CD4 cell count of 500/μL or more for more than 2 years can stop T-cell monitoring as long as viral load remains undetectable.

Resistance Testing

Viral resistance testing should be performed at baseline to ensure selection of a fully active regimen and should be repeated if the viral load increases during ART. The most common reason for breakthrough viremia is poor medication adherence. Plasma levels of HIV RNA must generally be greater than 500 copies/mL to provide enough virus for resistance testing. Viral resistance testing can be genotypic (looking for mutations associated with drug resistance) or phenotypic (assessing whether virus can replicate in the presence of the drug). Genotypic testing is faster, cheaper, and more commonly used. Resistance testing results are used to guide selection of a new regimen in the event resistant virus develops, but previous resistance testing results as well as previous regimens and responses must also be considered. Resistance testing may not be reliable if performed while the patient is not taking an antiretroviral regimen because resistance may not be detectable without the selective pressure of the antiretrovirals. Once selected for, previous mutations are generally archived in the viral population and may re-emerge even if resistance testing does not demonstrate the mutation. A regimen may also be switched because of adverse effects or to ease adherence or avoid drug interactions. Laboratory monitoring tests should be repeated 1 month after switching regimens to assess effectiveness and toxicity.

KEY POINTS

- All persons with HIV infection should begin antiretroviral therapy as soon as they are ready, regardless of CD4 cell count.

(Continued)

TABLE 65. Antiretroviral Agents Used in the United States to Treat HIV Infection

Class	Agent[a]	Adverse Effects
Nucleoside RTIs	Abacavir	Hypersensitivity[b] (exclude HLA-B*57:01 before prescribing)
	Emtricitabine	Minimal toxicity; has activity against HBV, and exacerbations have occurred with discontinuation of therapy
	Lamivudine	Minimal toxicity; has HBV activity, but dosing differs for HIV and HBV treatment
	TDF	Nausea, kidney disease, Fanconi syndrome, decreased bone density; has activity against HBV, and exacerbations have occurred with discontinuation of therapy
	TAF[c]	Nausea; more weight gain than TDF; less kidney and bone toxicity than TDF
	Zidovudine	Nausea, headache, anemia[b], leukopenia[b], lactic acidosis[b], lipodystrophy, myopathy[b]
Nonnucleoside RTIs	Efavirenz	Neuropsychiatric symptoms (dizziness, somnolence, sleep disturbance, vivid dreams, mood changes), rash, dyslipidemia
	Etravirine	Nausea, rash
	Nevirapine	Hypersensitivity[b], rash, hepatitis[b]
	Rilpivirine	Rash, headache, insomnia; requires food and gastric acid (no concomitant PPI use) for absorption
	Doravirine	Nausea, headache
Protease inhibitors	Atazanavir	Nausea, hyperbilirubinemia, nephrolithiasis, rash; requires food and gastric acid (no concomitant PPI use) for absorption
	Darunavir	Nausea, diarrhea, rash
	Lopinavir	Nausea, diarrhea, hyperlipidemia, insulin resistance
CCR5 antagonist	Maraviroc	Hypersensitivity, hepatitis[b]
Integrase inhibitors[d]	Dolutegravir[e]	Elevated creatinine level (decrease in tubular secretion, not GFR), insomnia, headache (generally well tolerated)
	Elvitegravir	Nausea, diarrhea (generally well tolerated)
	Raltegravir	Rash, myopathy (generally well tolerated)
	Bictegravir[f]	Elevated creatinine level (decrease in tubular secretion, not GFR), nausea, diarrhea, headache (generally well tolerated)
Pharmacokinetic boosters	Cobicistat	Elevated creatinine level (decrease in tubular creatinine secretion, not GFR), not recommended if CrCl <70 mL/min
	Ritonavir	Nausea, diarrhea, hyperlipidemia, insulin resistance, lipodystrophy, drug interactions[b]

CrCl = creatinine clearance; GFR = glomerular filtration rate; HBV = hepatitis B virus; PPI = proton pump inhibitor; RTIs = reverse transcriptase inhibitors; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a]Many agents are also available as components of combination medications.

[b]Black box warning. Note that all nucleoside analogues have a black box warning about possible lactic acidosis, although it is far more likely with stavudine, didanosine, and zidovudine than the other agents.

[c]TAF is not recommended in pregnant women because of insufficient safety data.

[d]Integrase inhibitors are associated with more weight gain than other antiretroviral classes.

[e]Dolutegravir may be used as an alternative antiretroviral drug for women of childbearing age who are sexually active and not using contraception; it may be used as a recommended option for those using effective contraception.

[f]Insufficient safety data exist regarding bictegravir around the time of conception or in pregnant women.

KEY POINTS *(continued)*

- Standards for effective antiretroviral regimens include use of three drugs from two different classes; preferred regimens combine two nucleoside reverse transcriptase inhibitors with an integrase strand transfer inhibitor.
- Viral resistance testing should be performed at baseline to ensure selection of a fully active regimen and should be repeated if the viral load increases during antiretroviral therapy.

Management of Pregnant Patients with HIV Infection

The management of pregnant women with HIV is similar to the management of nonpregnant women. Initiating ART is recommended as soon as possible in pregnant women with HIV who are not already being treated, and it is especially important that women already receiving HIV treatment who become pregnant continue treatment without interruption. ART in pregnancy benefits the woman and significantly reduces the risk of

TABLE 66. Recommended Regimens for Initial Treatment of Most Persons with HIV Infection[a]

ART can be initiated before drug resistance testing and HLA-B*57:01 test results are available. In this setting, one of the following antiretroviral therapy regimens is recommended:
Bictegravir/tenofovir alafenamide/emtricitabine
Dolutegravir with tenofovir[b] plus emtricitabine or lamivudine
Additional recommended regimens include:
Dolutegravir/abacavir/lamivudine[c]
Dolutegravir/lamivudine[d]
Raltegravir plus (emtricitabine or lamivudine) plus tenofovir[b]

[a]Revised based on the 2018 International Antiviral Society-USA Panel guidelines and the 2019 Department of Health and Human Services guideline update. A sample for genotypic testing should be sent before ART initiation. Before initiating treatment in a person of childbearing potential, a pregnancy test should be performed. Before prescribing ART to a person of childbearing potential, please refer to the guideline for information (https://clinicalinfo.hiv.gov/en/guidelines).

[b]Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

[c]Only for patients who are HLA-B*57:01 negative and without hepatitis B virus coinfection (AI).

[d]Except in those with a pretreatment HIV RNA level >500,000 copies/mL, chronic hepatitis B virus coinfection, or before results of HIV genotyping are available.

perinatal transmission of HIV to her baby. Recent data show no difference in birth defect rates with some antiretrovirals compared with the general population, including neural tube defects with efavirenz. Initial treatment regimen selection in pregnant women is similar to that for nonpregnant women; however, some antivirals are not recommended (see Table 65).

KEY POINTS

- Pregnant women should promptly initiate or continue receiving HIV treatment without interruption; efavirenz and tenofovir disoproxil fumarate can be safely used.
- In pregnant women with HIV, bictegravir and tenofovir alafenamide are not recommended.

Viral Infections

Influenza Viruses

Overview

Three types of influenza viruses primarily infect humans: A, B, and C. Influenza A viruses are divided into subtypes based on two surface proteins, hemagglutinin (H) and neuraminidase (N). Influenza A viruses can infect animals and humans and produce epidemics and pandemics. Influenza B viruses only affect humans and cause yearly epidemics but not pandemics. Influenza C causes mild illness and does not cause epidemics.

Minor changes in the H and N surface envelope glycoproteins (*antigenic drift*) of influenza A and B viruses cause yearly epidemics, and major changes (*antigenic shift*) in influenza A after genetic recombination from animals cause global pandemics. The last influenza pandemic occurred in 2009 and was caused by H1N1. Emerging subtypes of importance include H7N9, which circulates among poultry in China and can cause severe illness in humans; H5N1, which infects humans through close contact with infected poultry and can spread from person to person; and variants circulating in pigs that can sporadically infect humans.

Other respiratory viruses that may be documented in adults are outlined in **Table 67**.

Clinical Features and Evaluation

During the winter, influenza A causes a self-limiting illness with fever, cough, rhinorrhea, myalgia, and headache in most patients; influenza B causes a milder illness. Older adults (>65 years), young children, pregnant and postpartum women, immunocompromised patients, patients with chronic medical conditions (especially chronic lung disease), persons with obesity (BMI ≥40), persons with neuromuscular disease, and residents of extended-care facilities are at higher risk for

TABLE 67. Respiratory Viruses Causing Illness in Adults

Virus	Clinical Presentation	Populations at Risk	Treatment
Parainfluenza virus	Otitis media, pharyngitis, conjunctivitis, croup, tracheobronchitis, pneumonia, respiratory failure and death	Older adults; immunosuppressed persons, especially HSCT recipients; 50% mortality with pneumonia	Supportive Children with croup are treated with glucocorticoids
Respiratory syncytial virus	Upper and lower respiratory tract infection, including asthma and COPD exacerbation, pneumonia, and respiratory failure and death	Older adults; immunosuppressed persons, especially lung transplant and HSCT recipients; those with underlying cardiac and lung comorbidities	Aerosolized or oral ribavirin in HSCT and lung transplant Palivizumab for prophylaxis in children only
Human metapneumovirus	Upper and lower respiratory tract infection, including bronchiolitis, pneumonia, asthma, and COPD exacerbation	Older adults; immunosuppressed persons; those with underlying cardiac or respiratory comorbidities	Supportive

HSCT = hematopoietic stem cell transplantation.