H CONT. should be instituted for patients with VAP pending results of noninvasive sampling with semiquantitative cultures and based on local VAP antibiograms, if available.

Empiric VAP regimens should include coverage for *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli. An agent active against MRSA (vancomycin, linezolid) should be included for patients with MRSA risk factors or those in a unit with MRSA prevalence greater than 10% to 20% or unknown. Two antipseudomonal agents of different classes are recommended for empiric regimens only for patients with risk factors for resistance, with structural lung disease (bronchiectasis, cystic fibrosis), or in a unit with greater than 10% resistance to an agent being considered for monotherapy. Similar regimens are recommended for patients with HAP who are treated empirically. Antimicrobial coverage for oral anaerobes may be considered in patients with witnessed aspiration events or recent surgery. Cephalosporins should be avoided as monotherapy in settings where extended-spectrum β-lactamase (ESBL)–producing gram-negative organisms (such as *Klebsiella pneumoniae*) are prevalent; consider a carbapenem instead. VAP caused by gram-negative organisms sensitive only to aminoglycosides or colistin may be treated with a combination of systemic and aerosolized antibiotics.

Microbiologic results should be reviewed at 48 to 72 hours, and all patients should be re-evaluated for clinical improvement. Antimicrobial therapy should be de-escalated (to narrow-spectrum or oral therapy) based on microbiologic results and clinical stabilization or discontinued if the diagnosis of pneumonia is in doubt. Patients who do not improve within 72 hours of appropriate therapy should undergo investigation for infectious complications, an alternate diagnosis, or another site of infection. HAP and VAP should be treated for 7 days or less. H

KEY POINT

- 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.

H Prevention

Commonly used ventilator bundles include subglottic suctioning, peptic ulcer disease and deep venous thrombosis prophylaxis, and avoiding gastric overdistention. Use of ventilator bundles has been shown to decrease VAP rates by 71%. Additional interventions are listed in Table 61. H

KEY POINT

HVC
- 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 H

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. Seven of the 15 MDROs deemed urgent threats are predominantly health care associated. Nearly half of *S. aureus* HCAIs in the United States are methicillin resistant, 30% of enterococci are vancomycin resistant, 18% of Enterobacteriaceae produce ESBL and are resistant to all β-lactam antibiotics, 4% of Enterobacteriaceae are resistant to carbapenems, and 16% of *P. aeruginosa* and about half of *Acinetobacter* species are multidrug resistant. *Clostridium difficile* is not technically an MDRO, but it is a problematic pathogen in health care settings.

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. H

KEY POINTS

- 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.
- 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 is a retrovirus that infects CD4 lymphocytes, among other cell types. Depletion of CD4 T-helper cells results in impairment of cell-mediated immunity and increasing risk for opportunistic infections. 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. Current testing for HIV infection detects HIV-1 and HIV-2 antibodies (see Screening and Diagnosis).

Epidemiology and Prevention

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. Those with undiagnosed or untreated infection are responsible for most new infections. Diagnosis and successful treatment are crucial for personal and public health.

HIV transmission occurs through sexual contact or exposure to other body fluids (**Table 62**). 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 injection drug users. 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.

HIV treatment 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 sexual partner with undetectable blood viral load has been demonstrated to be close to zero, at a level the Centers for Disease Control and Prevention (CDC) called "effectively no risk" in a September 2017 statement, leading to the slogan "Undetectable = Untransmissable" ("U=U"). In what is known as the "treatment cascade," steps of medical care necessary to achieve successful viral suppression consist 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 management of HIV on a personal and public health level. Even high-income countries, such as the United States, have poor rates of retention in care and adherence to medication. One study estimated that the undiagnosed and not-in-care groups with HIV infection were responsible for 91.5% of HIV transmissions in the United States in 2009.

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched its "90-90-90" program of ambitious goals for reducing new HIV infection worldwide. These goals include that by 2020, 90% of HIV-infected persons will have been diagnosed, 90% of those diagnosed will be receiving treatment, and 90% of those receiving treatment will have successful viral suppression. Achieving such goals will require considerable resource commitment but, if achieved, will also dramatically reduce transmission and new HIV infections.

Postexposure prophylaxis antiretroviral therapy has been used successfully for many years in uninfected persons 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 and emtricitabine plus either raltegravir or dolutegravir. HIV testing of the exposed person should be conducted at baseline and at 4 to 6 weeks and 3 months after exposure. **Figure 22** shows an algorithm for evaluation of possible HIV exposure.

Pre-exposure prophylaxis (PrEP) with antiretroviral medication is recommended in select persons at high risk for exposure to HIV to reduce the risk of infection. A two-drug combination of tenofovir disoproxil fumarate and emtricitabine, taken once daily, is FDA approved for HIV PrEP; it has been shown to be effective in reducing infection in heterosexual couples, men who have sex with men, and injection drug users. Effectiveness is greater than 90% in those with proven adherence. 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 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.

TABLE 62. 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

KEY POINTS

- Although reducing viral load to an undetectable level in blood does not equal absence of virus in semen or vaginal fluid, the rate of transmission from a sexual partner with undetectable blood viral load is exceedingly low, with reductions in risk greater than 95%.
- 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.

(Continued)

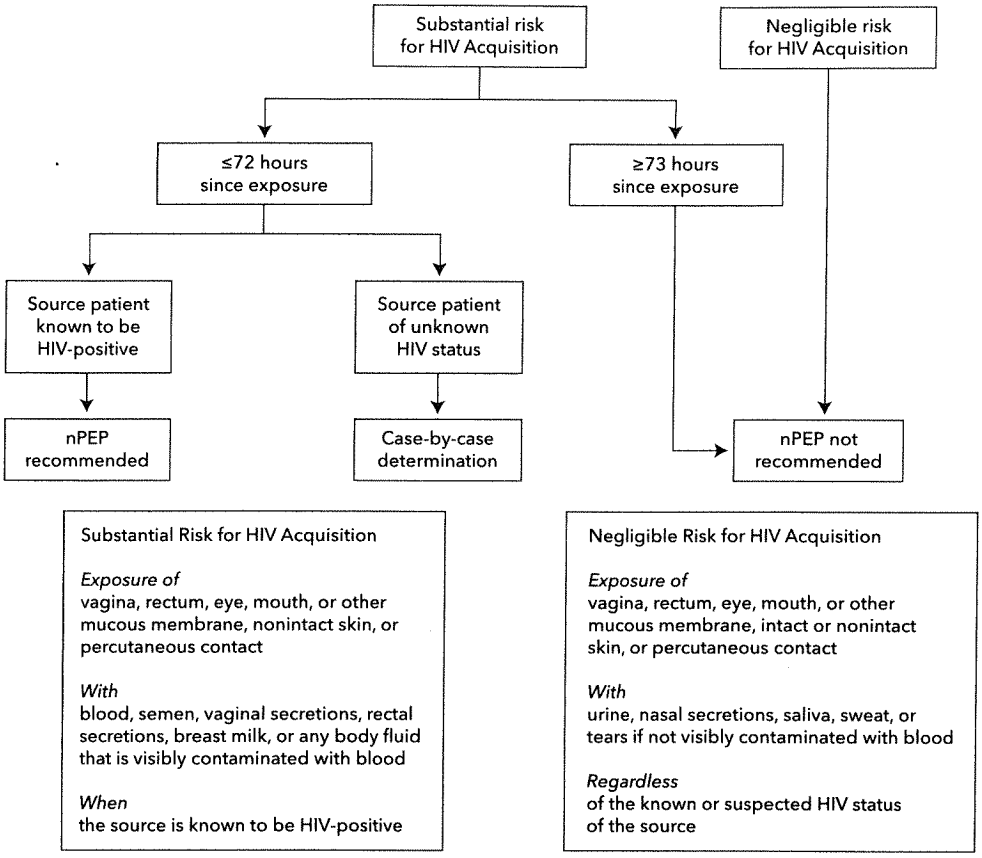

FIGURE 22. Algorithm for evaluation and treatment of possible HIV exposure. nPEP = nonoccupational postexposure prophylaxis.

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.

KEY POINTS *(continued)*

- Pre-exposure prophylaxis with two antiretroviral medications (tenofovir disoproxil fumarate and emtricitabine) is recommended in select persons at high risk for exposure to HIV to reduce the risk of infection.

Pathophysiology and Natural History

Acute Retroviral Syndrome

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 63**. The differential diagnosis includes Epstein-Barr virus infection, cytomegalovirus infection, and secondary syphilis. During symptomatic acute infection, HIV antibody may not yet be detectable, and diagnosis depends on demonstration of p24 antigen or HIV RNA. Currently recommended HIV testing includes p24 antigen testing as part of the initial evaluation (see Screening and Diagnosis). Persons with acute HIV infection should be immediately linked to care for prompt initiation of treatment.

TABLE 63. 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

KEY POINT

- Most persons with acute HIV infection are symptomatic; however, because symptoms are nonspecific and self-limited, most acute infections are not diagnosed accurately.

Chronic HIV Infection and AIDS

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, such as bacterial pneumonia, herpes zoster, herpes simplex virus, or vaginal candidiasis. 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 (see MKSAP 18 Dermatology). HIV should also be considered in patients with unexplained cytopenias or nephropathy.

KEY POINTS

- Before progression to AIDS, patients with chronic HIV infection may present with recurrent or severe episodes of infections that do not qualify as opportunistic, such as bacterial pneumonia, herpes zoster, herpes simplex virus, or vaginal candidiasis.
- Symptoms that can result from chronic HIV infection itself include lymphadenopathy, fever, night sweats, fatigue, weight loss, chronic diarrhea, and various oral and skin conditions.

Screening and Diagnosis

Although any of the presenting symptoms described previously should prompt HIV testing, testing only symptomatic persons neglects numerous persons who are infected. Thus, the CDC, American College of Physicians, Infectious Diseases Society of America, and U.S. Preventive Services Task Force (USPSTF) recommend universal screening for HIV in all adults at least once. The USPSTF suggests those at higher risk (injection drug users and their sexual partners, people who exchange sex for money or drugs, sexual partners of HIV-infected persons, and those with more than one sexual partner since their most recent HIV test) should 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 (for example, every 3 or 6 months) for some asymptomatic sexually active men who have sex with men based on their individual risk factors, local HIV epidemiology, and local policies.

Current (fourth generation) HIV testing uses a combination assay for HIV antibody and HIV p24 antigen, which detects acute infection at least 1 week earlier than older assays. A positive result on the combination assay leads to testing with an HIV-1/HIV-2 antibody differentiation immunoassay, which, if positive, confirms infection. Specimens that test positive on the initial combination assay but negative for HIV antibody are tested for HIV RNA by nucleic acid amplification testing; if positive, acute HIV infection is confirmed (**Figure 23**). Although the initial combination assay has a 99.6% specificity, 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 and 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.
- A combination assay for HIV antibody and HIV p24 antigen now detects acute infection at least 1 week earlier than older assays; a positive HIV-1/HIV-2 antibody immunoassay result confirms infection, or a positive HIV RNA nucleic acid amplification test result confirms acute HIV infection.

Initiation of Care

Initial Evaluation and Laboratory Testing

All persons who test positive for HIV should be immediately 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 64**). A baseline CD4 cell count guides opportunistic infection prophylaxis, and a baseline viral load supports monitoring antiretroviral therapy 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, tetanus-diphtheria-pertussis, hepatitis A, and human papillomavirus vaccinations are indicated as for the general population. Measles-mumps-rubella and varicella vaccines can be given as long as the CD4 cell count is greater than 200/μL. Although the recombinant zoster vaccine is considered safe in immunocompromised persons because it does not contain live virus, safety and efficacy data in patients with HIV are not yet available to inform recommendations. The Advisory Committee on Immunization Practices recommends that all persons with HIV infection 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 65**). Before beginning

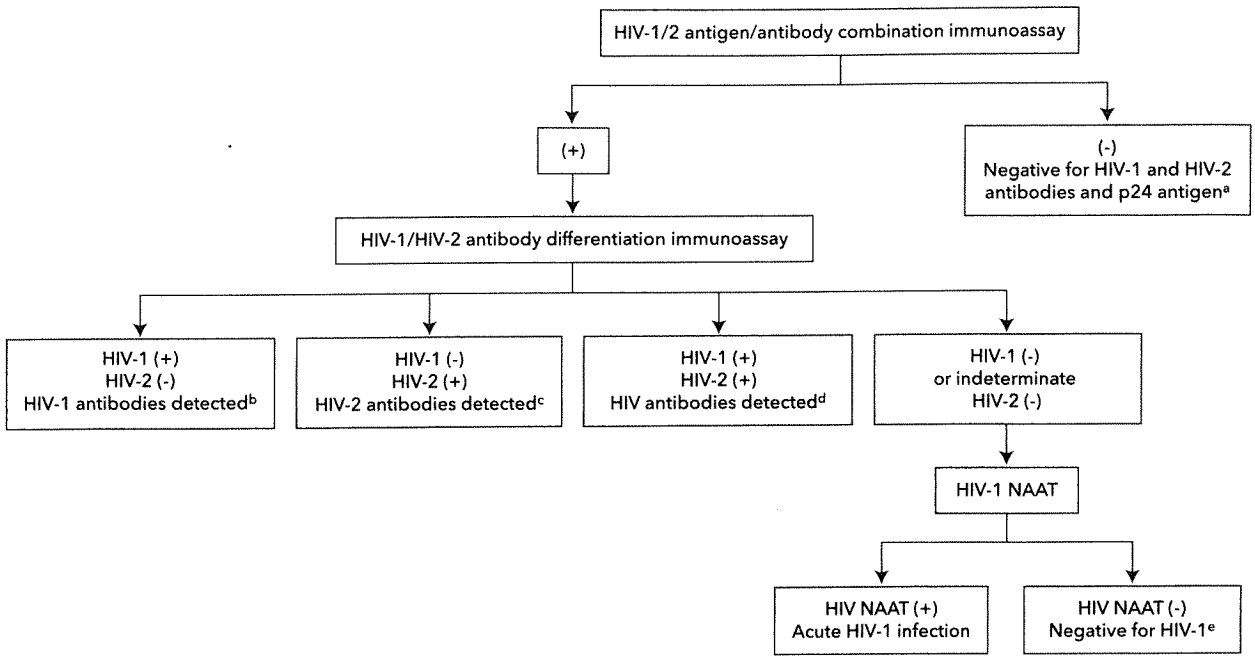

FIGURE 23. CDC-recommended algorithm for laboratory HIV testing. NAAT = nucleic acid amplification test. (+) indicates reactive test result. (−) indicates nonreactive test result.

[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.

TABLE 64. Laboratory Testing as Part of the Evaluation of HIV Infection

Repeat HIV antibody testing if no documentation
Viral resistance testing at baseline and for treatment failure
Quantitative HIV RNA assay (viral load)
T-cell subsets (CD4 cell count)
Complete blood count with differential
Chemistries, including kidney function studies and fasting plasma glucose level
Liver chemistry studies/liver enzyme levels
Fasting serum lipid profile
Urinalysis or quantitative measure of proteinuria
Tuberculin skin test or interferon-γ release assay
Serologic testing for hepatitis A, B, and C virus infection
Serologic testing for syphilis; testing for other sexually transmitted infections
Serologic testing for toxoplasmosis
Cervical Pap test

TABLE 65. 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
Toxoplasmosis	CD4 cell count <100/μL and positive serologic results[a]	TMP-SMX, double-strength tablet once daily
Mycobacterium avium complex	CD4 cell count <50/μL	Azithromycin, 1200 mg once weekly or 600 mg twice weekly; clarithromycin, 500 mg twice daily
Latent tuberculosis	TST >5 mm or positive IGRA results	Isoniazid, 300 mg once daily for 9 months or 900 mg twice weekly, both with pyridoxine, 25 mg once daily

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

[a]Prophylaxis may be discontinued in patients with suppressed viral load and CD4 cell count ≥200/μL for ≥3 months.

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; influenza, tetanus-diphtheria-pertussis, hepatitis A, and human papillomavirus vaccines are indicated as for the general population.
- Active infection should be ruled out before initiation of prophylaxis for opportunistic infections.

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.

Chronic kidney disease is increasingly common in HIV infection, although, with effective antiretroviral therapy, 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. A newer prodrug of tenofovir, tenofovir alafenamide (TAF), achieves high intracellular levels of active drug with much lower dosing and lower systemic levels compared with the older formulation, tenofovir disoproxil fumarate (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. Patients should be immunized if they are HBV negative. If coinfected with HIV and HBV, patients should receive treatment with a tenofovir (either 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 18 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.
- Tenofovir disoproxil fumarate (TDF), a very commonly used nucleoside analogue in HIV therapy, 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 antiretroviral therapy, regardless of any worsening of lipid levels from the antiretroviral therapy. 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. 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.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a disorder associated either 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 antiretroviral therapy in patients with low pretreatment CD4 cell counts (<100/μL). Management of IRIS includes continuing antiretroviral therapy 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, such as neutropenia. Oral candidiasis usually presents as thrush, with mucosal whitish plaques, and can be treated topically (for example, 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 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 who are hypoxic at presentation should be given adjunctive glucocorticoids to prevent the worsening that may accompany initiation of treatment.

Cryptococcus infection usually presents as subacute meningitis with headache, mental status changes, and fever. Because it often involves the basilar area, cranial nerve deficits may also be seen. 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. The differential diagnosis includes primary central nervous system lymphoma, which most often appears as a single lesion on imaging, and progressive multifocal leukoencephalopathy, which is usually nonenhancing. Diagnosis of central nervous system 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 *Mycobacterium 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 central nervous system 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 24**); human herpes virus type 8 can also cause primary effusion lymphoma and Castleman disease (giant lymph node 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.

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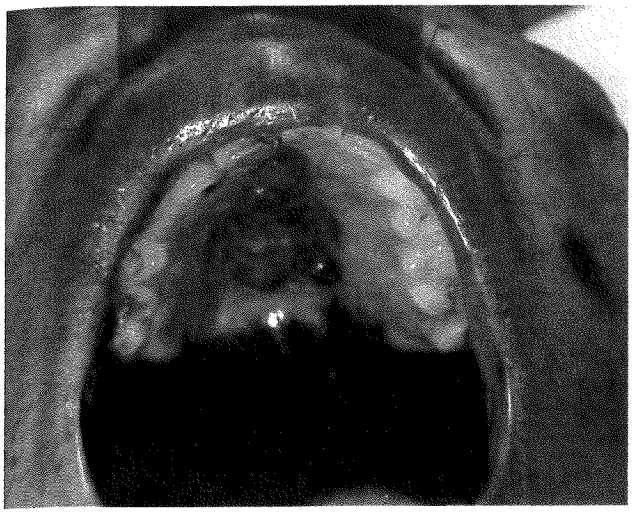

FIGURE 24. Kaposi sarcoma, presenting as firm purple nodules on the face and purple palatal nodules, is seen in a patient with AIDS.

KEY POINTS *(continued)*

- 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.
- *Toxoplasma gondii* infection in patients with HIV presents as multifocal central nervous system abscesses; MRI is more sensitive than CT in revealing characteristic ring-enhancing lesions.
- *Mycobacterium avium* complex and cytomegalovirus infections usually present in patients with HIV with CD4 cell counts less than 50/μL.
- Patients with AIDS are more likely to develop certain malignancies, including non-Hodgkin lymphoma, Kaposi sarcoma, and human papillomavirus-related malignancies (cervical and anal cancers).

Management of HIV Infection

When to Initiate Treatment

All persons with HIV infection should begin antiretroviral therapy as soon as they are ready, regardless of CD4 cell count. Previous controversy over whether to start antiretroviral treatment in asymptomatic patients with normal CD4 cell counts has been resolved with demonstration of clear clinical benefit in a large prospective, randomized clinical trial.

Antiretroviral Regimens

Antiretroviral agents used in the United States are shown in **Table 66**. 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 67**).

Patients with or at risk for reduced kidney function or osteopenia should not be given TDF. Patients who are prescribed abacavir must first undergo testing to show they are HLA-B*5701 negative to reduce the risk of hypersensitivity. Many antiretrovirals have interactions with other drugs, and potential drug interactions must always be assessed when beginning HIV therapy or beginning any drug for someone already taking antiretroviral therapy. 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 assess for 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 antiretroviral therapy 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 antiretroviral treatment. The most common reason for breakthrough viremia is poor medication adherence. In general, plasma levels of HIV RNA must 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 and cheaper, but phenotypic testing may be better in the presence of multiple mutations or for drugs such as protease inhibitors in which the correlation of specific mutations and resistance is less straightforward. 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.

TABLE 66. Antiretroviral Agents Used in the United States to Treat HIV Infection

Class	Agent[a]	Adverse Effects
Nucleoside RTIs	Abacavir	Hypersensitivity[b] (exclude HLA-B*5701 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	Nausea; 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
Protease inhibitors	Atazanavir	Nausea, hyperbilirubinemia, nephrolithiasis, rash; requires food and gastric acid (no concomitant PPI use) for absorption
	Darunavir	Nausea, diarrhea, rash
	Fosamprenavir	Nausea, diarrhea, rash
	Lopinavir	Nausea, diarrhea, hyperlipidemia, insulin resistance
	Saquinavir	Nausea, diarrhea, hyperlipidemia, QT prolongation
	Tipranavir	Nausea, diarrhea, hyperlipidemia, rash, hepatitis[b], intracranial hemorrhage[b]
CCR5 antagonist	Maraviroc	Hypersensitivity, hepatitis[b]
Integrase inhibitors	Dolutegravir	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	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 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.

TABLE 67. Preferred Regimens for Initial Treatment of HIV Infection[a]

Abacavir/lamivudine/dolutegravir
Tenofovir alafenamide/emtricitabine/dolutegravir
Tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir
Tenofovir alafenamide/emtricitabine/raltegravir
Tenofovir alafenamide/emtricitabine/bictegravir

[a]Endorsed by the 2016 International Antiviral Society-USA Panel guidelines and the 2018 Department of Health and Human Services guidelines.

KEY POINTS

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

Management of Pregnant Patients with HIV Infection

The management of pregnant women with HIV does not significantly differ from the management of nonpregnant women. Initiating antiretroviral therapy 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. Antiretroviral therapy in pregnancy benefits the woman and significantly reduces the risk of perinatal transmission of HIV to her baby. Previous concerns about teratogenicity of some antiretrovirals, including concerns about neural tube defects with efavirenz, have been allayed by data showing no difference in birth defect rates compared with the general population regardless of when therapy was started. Initial treatment regimen selection in pregnant women does not typically differ from nonpregnant women; however, elvitegravir-cobicistat is not recommended because levels are inadequate in the second and third trimesters, and bictegravir and TAF are not recommended until safety and pharmacokinetic data in pregnancy are available. Dolutegravir is not recommended in the first 8 weeks of pregnancy until more data are available regarding possible increased risk of neural tube defects.

KEY POINTS

- Pregnant women should promptly initiate or continue receiving HIV treatment without interruption; previous concerns about teratogenicity of efavirenz and tenofovir disoproxil fumarate have been allayed by data showing no difference in birth defect rates compared with the general population.
- In pregnant women with HIV, bictegravir and tenofovir alafenamide are not recommended until safety and pharmacokinetic data in pregnancy are available; dolutegravir should be avoided in the first 8 weeks of pregnancy until more safety data are available.

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.

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 women, and patients with chronic medical conditions (especially chronic lung disease) are at higher risk for severe primary influenza, complications such as superimposed bacterial pneumonia caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*, and death (see Community-Acquired Pneumonia). Less common but severe complications include asthma or chronic obstructive pulmonary disease exacerbations, myocarditis, encephalitis, rhabdomyolysis, myositis, sepsis, and multiorgan failure. Parotitis caused by influenza was reported during the 2015-2016 influenza season.

During the endemic season, patients can be diagnosed within 20 minutes using either rapid antigen tests or polymerase chain reaction (PCR) testing of nasopharyngeal swabs. Both tests are highly specific, but PCR has a sensitivity of nearly 100%; the rapid antigen tests have a sensitivity between 59% and 93%. Starting antiviral therapy following a negative antigen test result is reasonable if clinical suspicion is high. Serologic assays are not used clinically. Testing should be performed in patients at risk for complications (for example, those older than 65 years, patients with chronic medical conditions, immunocompromised patients, pregnant and postpartum women, those with a BMI of 40 or more, and persons with neuromuscular disease) and in health care workers, if the result will influence clinical management (decisions on initiation of antiviral treatment, impact on other diagnostic testing, antibiotic treatment decisions, and infection control practices).

KEY POINTS

- Older adults (>65 years), young children, pregnant women, and patients with chronic medical conditions (especially chronic lung disease) are at higher risk for severe primary influenza, superimposed bacterial pneumonia caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*, and death.
- Rapid antigen and polymerase chain reaction (PCR) tests of nasopharyngeal swabs are highly specific for influenza, but PCR has a higher sensitivity and can identify the virus subtype.

Management

Antiviral therapy should be started within 48 hours of symptom onset in patients with a positive PCR or rapid antigen test result to speed up recovery and decrease hospitalization rates and complications. Antiviral therapy should also be initiated