Identifying the human immunodeficiency virus (HIV) at its various stages has important personal and public health implications. At the individual level, early recognition may offer patients a period of adjustment and an understanding of their diagnosis; an opportunity to address comorbidities such as viral hepatitis, substance abuse, and mental illness; and an opportunity to learn the value of medication adherence and the risks and benefits associated with antiretroviral therapy. At the community level, early recognition may facilitate patient education regarding HIV, sexually transmitted disease (STD), and risks of tuberculosis transmission and provide an opportunity to decrease transmission of resistant viruses. Patients identified earlier may have slower disease progression because of the restorative effect of highly active antiretroviral therapy (HAART) on immune function. A patient’s early presentation may facilitate better primary and preventive care, which may in turn decrease the effect of comorbid illnesses. Early HIV identification allows for the timely introduction of opportunistic infection prophylaxis, more effective vaccinations and education, and institution of preventive measures. Each of these may affect morbidity and survival. An earlier diagnosis allows clinicians to consider appropriate differential diagnoses when such patients become ill and to institute therapy for opportunistic infections. Identification of asymptomatic HIV-positive women during pregnancy and institution of antiviral therapy allow for a substantial reduction in maternal-fetal transmission of HIV. Despite all these advantages of early diagnosis, patients infected with HIV continue to present late in the course of the disease. A recent study from New York City suggested that even in the HAART era the median CD4 count at initial HIV diagnosis was only 152 cells/µL and that there was no difference in the likelihood of patients presenting ill in 1994 vs 1998.1 Several studies have highlighted missed opportunities for earlier diagnosis.1-3 How can clinicians identify such patients earlier? The goal of this article is to highlight opportunities for the clinical diagnosis of HIV throughout the spectrum of manifestations, from primary infection through late-stage disease.

CHANGING FACE OF THE HIV EPIDEMIC

The HIV epidemic has evolved from one principally affecting homosexual white men and recipients of blood products to that of heterosexual transmission affecting minorities and women.

The face of the epidemic of HIV varies geographically. In US urban centers and the rural southeast, minorities are affected disproportionately. Many of those affected are the medically underserved. Because of their limited access to medical care, HIV should be considered in these individuals at entry points to care such as walk-in clinics, emergency departments, public health clinics, STD clinics, and drug treatment programs. Another major demographic
change is the proportion of women affected by HIV. Women in the United States are the most rapidly growing group, from 7% of cases of acquired immunodeficiency syndrome (AIDS) in 1985 to 30% in 1999. In particular, the rate of HIV infection among African American women is 1 in 160 vs 1 in 3000 white women in the United States. Most of these women are from low-income groups and are of childbearing age. Because of this demographic shift and the ability of clinicians to provide interventions that may improve both maternal and fetal health, all pregnant women should be screened for HIV infection.

Conversely, despite overall declines in their infection rates, a new generation of men who have sex with men continue to engage in high-risk sexual behavior under the misconception that they may be protected by antiviral therapy. Of particular concern in this group is the transmission of multiply resistant strains of HIV because of prior antiviral drug experience. Some of these individuals may present immediately after exposure to HIV in search of “postexposure” prophylaxis. Thus, the initial step in recognizing HIV is to think about the disease in persons at risk.

SPECTRUM OF CLINICAL DISEASE ASSOCIATED WITH HIV INFECTION
Human immunodeficiency virus is a disorder of immune dysregulation that leads to a continuous spectrum of manifestations, ranging from an overactive and misdirected immune response to severe cellular immunodeficiency. Clinical manifestations vary depending on the stage of HIV. After primary infection, the stages of HIV are arbitrarily defined by the CD4 cell count: early (CD4 >500 cells/µL), intermediate-middle (CD4 200-500 cells/µL), advanced (CD4 100-200 cells/µL), and late-stage disease (CD4 <100 cells/µL). There is much individual variation in the clinical manifestations in the same disease stage and in the rate of progression through these stages.

PRIMARY HIV INFECTION
Clinical recognition of primary HIV infection is important for several reasons: early treatment may diminish the initial assault of HIV on the immune system, allowing preservation of HIV-specific immune responses; the initial burst of viremia may be more homogeneous, making treatment more effective at decreasing the latently infected viral reservoir and decreasing the role of resistant subpopulations; and a decrease in the extremely high initial viral load may diminish transmission during the period before seroconversion occurs.

Many patients experience an acute self-limited viral syndrome within weeks of primary HIV infection, which may persist for several weeks. The hallmarks of primary HIV infection are fever, rash, and myalgias, which mimic a mononucleosis syndrome. Other manifestations of primary HIV infection include fatigue, malaise, arthralgias, lymphadenopathy, splenomegaly, anorexia, nausea and vomiting, diarrhea, pharyngitis, headache, retro-orbital pain, meningitis and encephalitis, neuropsychopathy, myelopathy, maculopapular rash, and mucocutaneous ulceration. Lymphadenopathy typically occurs in the second week of the syndrome and may be generalized or may principally affect the occipital, axillary, and cervical nodes. In some cases, there may be profound but transient immunodeficiency with the development of oral and esophageal candidiasis, Pneumocystis carinii pneumonia, and other opportunistic infections. Even astute clinicians may miss the diagnosis at this earliest stage unless a thorough history is obtained to elicit the potential risk of acute HIV infection. These risks include unprotected sex with an infected partner, recent intravenous drug use, and exposure to contaminated blood products or bodily fluids from an infected person with a high HIV viral load. Early identification at this stage may be critical in allowing interventions that can alter the long-term host response to HIV. Once this phase has passed, most persons become clinically asymptomatic, and a window of opportunity for early diagnosis may be lost. Thus, the second step in recognizing HIV is an awareness of the acute HIV syndrome.

CHRONIC HIV INFECTION
A third opportunity for diagnosis occurs during the chronic but “clinically latent” phase. During this phase, patients may have minimal or no symptoms until late in the middle stage. However, there are ongoing immunologic, virologic, and clinical changes that are clues to the recognition of HIV. Many of these manifest cutaneously. As immunosuppression proceeds, patients may develop nonspecific symptoms such as fever, night sweats, weight loss, and decreased energy. These symptoms may be subtle and attributed to other causes. Also, during this phase, fever, lymphadenopathy, and malaise may be due to systemic infections such as tuberculosis, mycoses, or lymphoma. Many patients have painless stable lymphadenopathy, which may regress as HIV disease advances and destroys the architecture of lymphoid follicles. Frequently, the parotid glands enlarge or a lymphoepithelial cyst develops in the parotid region because of lymphoid hyperplasia. Anergy to skin testing becomes increasingly probable as the CD4+ count decreases below 400 cells/µL. Common episodic conditions during this stage include herpes zoster, thrush, seborrheic dermatitis, skin and nail infections (impetigo, folliculitis, fungal intertrigo, paronychia), and bacterial infections (pneumonias, bronchitis, sinusitis).

Mucosal Clues
The earliest physical signs of HIV infection tend to occur on mucosal surfaces of the mouth and vagina and on
the skin in asymptomatic patients. Oral manifestations range from oral candidiasis and hairy leukoplakia to ulcerative lesions and severe gingivitis. Pseudomembranous candidiasis (thrush) appears as white cottage cheese–like plaques anywhere in the mouth. Erythematous candidiasis appears as a flat red palatal lesion.

Hairy leukoplakia appears as white hairlike projections, usually on the lateral aspect of the tongue, and cannot be removed by swabbing. Gynecologic infections are the most common reason why HIV-infected women present for medical evaluation, and HIV counseling and testing can be offered at this visit. In women, recurrent and refractory vulvovaginal candidiasis may be a hallmark of HIV infection. Women also have an increased rate of cervical dysplasia and carcinoma in situ. For men or women who have been recipients of anal sexual intercourse, the anorectal examination should include evaluation for STDs such as papillomavirus infections, herpes simplex, gonorrhea, and chlamydia, and anal carcinoma. All patients presenting with STDs should be offered HIV testing.

**Dermatologic Clues**

Dermatologic manifestations include bacterial, fungal, viral, neoplastic, and other dermatitides. Staphylococcal infections present as persistent or recurrent folliculitis or superficial abscesses. Fungal rashes manifest as erythematous lesions, usually occurring in the axilla, inframammary areas, or groin. Herpes zoster is 17 times more common in HIV-infected persons than age-matched uninfected persons and is commonly seen early in the course of HIV infection, particularly in healthy-appearing individuals, before the onset of other symptoms. Finding zoster in a young adult indicates the need to test for HIV. The lesions in HIV-associated zoster may be bullous, hemorrhagic, necrotic, and painful and persist for 2 to 3 weeks. Dermatomal scarring should be sought when individuals at risk for HIV are being evaluated. Recurrent zoster is reported in about 20% of HIV-infected persons and is another clue to the presence of HIV.

Herpes simplex virus infection may occur as clustered vesicles around the mouth, genitals, or anus. Recurrent or severe cases should raise suspicion for immunocompromise. Another cutaneous viral infection associated with HIV is molluscum contagiosum, which presents as pearly white umbilicated papules usually on the face. The presence of multiple or widespread lesions should prompt consideration of HIV. When molluscum-like lesions are seen in association with fever or headache, a serum cryptococcal antigen test should be performed to evaluate for disseminated cryptococcosis.

The onset of psoriasis in an older adult, exacerbation of long-standing stable psoriasis, psoriatic erythroderma, or severe involvement of the axillae and groin should raise suspicion for HIV.

Severe pruritic or the development of recurrent pruritic papules should prompt the clinician to think of HIV. Pruritic papules may be due to a variety of causes, including bacterial folliculitis, eosinophilic folliculitis, *Demodex* mites, insect bite reactions, and granuloma annulare. A relapsing, intensely pruritic eruption of urticarial papules and pustules that appears in crops on the face and trunk of persons with HIV is eosinophilic folliculitis. This disorder typically occurs in HIV-infected persons with helper T-cell counts lower than 200 cells/µL and is an important cutaneous marker of the specific stage of HIV disease.

Seborrheic dermatitis is another common cutaneous manifestation that should raise suspicion for HIV. It occurs in 40% to 80% of patients with symptomatic HIV disease. The lesions are poorly defined faint pink scaly patches predominantly on the scalp, with frequent involvement of the eyebrows, eyelashes, nasolabial folds, and ears. More extensive involvement may occur on the center of the chest, groin, and axillae.

**Laboratory Clues**

Immune dysregulation in HIV may lead to polyclonal B-cell activation, decreased immune surveillance for malignancies, and autoantibody production. A variety of laboratory abnormalities that may precede or coincide with clinical manifestations of HIV are cytopenias, hypergammaglobulinemia, elevated partial thromboplastin time, false-positive rapid plasma reagin and antinuclear antibody test results, and antibodies directed at platelets leading to idiopathic thrombocytopenia (ITP).

Hematologic abnormalities are commonly recognized in most stages of HIV disease and may suggest the diagnosis of HIV. Anemia, common in patients with HIV infection, becomes more severe with advanced disease and is associated with a more rapid progression to AIDS and death in both men and women. In a study of patients receiving no myelosuppressive therapy, 8% to 18% of asymptomatic HIV-seropositive patients, 20% to 50% of those with symptomatic middle-stage HIV disease, and 71% to 75% of those with Centers for Disease Control and Prevention (CDC)-defined AIDS had anemia.

Thrombocytopenia is also encountered at various stages of HIV infection. In the Multicenter AIDS Cohort, 6.7% of participants had platelet counts lower than 150 × 10^9/L but did not have CDC-defined AIDS. In HIV-related ITP, production of antiplatelet antibodies results in the destruction of platelets. Often an early manifestation of HIV infection, ITP is seen in persons with CD4+ lymphocyte counts averaging between 300 and 600 cells/µL. Thus, patients presenting with ITP should be tested for HIV.
topenia is encountered in 13% of asymptomatic HIV patients and in 44% of those with CDC-defined AIDS, and HIV testing should be part of the evaluation for leukopenia.

Because of the decrease in immune surveillance and frequent infection with oncogenic viruses, hematologic malignancies are a common presenting syndrome. The most common malignancies associated with HIV disease are Kaposi sarcoma (KS) and non-Hodgkin lymphoma. There is a 60-fold increase in non-Hodgkin lymphoma among those infected with HIV, and this may be the presenting diagnosis in 4% of persons with AIDS. Human immunodeficiency virus–related KS occurs almost exclusively in HIV-infected homosexual men and is associated with human herpesvirus 8. Isolated KS lesions, as opposed to extensive and rapidly progressive KS, may appear extremely early in HIV disease (CD4+ cell counts >500 cells/µL). These early isolated KS lesions do not imply a poorer prognosis. Thus, the presence of these malignancies should prompt HIV testing.

PRESENTING ABNORMALITIES OF OTHER ORGAN SYSTEMS
Respiratory complications in mid-stage HIV are often overlooked because they occur commonly in all adults. These occur with increasing frequency as patients become more immunosuppressed. Persons with HIV are at increased risk for infection and bacteremia with encapsulated bacteria, especially Streptococcus pneumoniae. Also, HIV-infected persons have a 6-fold increased prevalence of pneumococcal pneumonia and a 100-fold increase in pneumococcal bacteremia compared with the general population. Tuberculosis is a common coinfection with HIV. Of persons with AIDS, 5% have active tuberculosis. In New York City, 20% to 70% of new cases of tuberculosis occur in HIV-infected minority populations (African Americans and Hispanics). Thus, persons presenting with recurrent sinopulmonary infections, pneumococcal pneumonia especially with bacteremia, and tuberculosis should be suspected of having HIV.

Another common manifestation of HIV in minority populations is renal disease. Almost 90% of these cases occur in Hispanics and African Americans. In 1999, HIV became the third leading cause of end-stage renal disease in African Americans aged 20 to 64 years. The most frequent presentation of HIV-associated nephropathy is marked proteinuria, usually without accompanying hypertension or edema.

Gastrointestinal disorders are one of the most common presentations of HIV. The earliest recognized manifestations of AIDS included marked wasting, “slim disease,” persistent diarrhea, and oral and esophageal candidiasis. Additionally, a host of diarrheal pathogens are commonly recognized at various stages of HIV disease. Before severe immunocompromise, salmonellosis and giardiasis may be common. With progressive immunodeficiency, Mycobacterium avium complex (MAC) and cryptosporidial and cytomegalovirus (CMV)-related diarrhea become more common. MAC frequently presents as a wasting syndrome manifested by fever, sweats, lymphadenopathy, weight loss, diarrhea, anemia, and elevated alkaline phosphatase levels. Some patients with these pathogens may present with a syndrome that mimics sclerosing cholangitis, known as HIV cholangiopathy. Patients presenting with weight loss and persistent diarrhea should be considered candidates for HIV testing.

Neuropathic manifestations, involving both the peripheral and central nervous system (CNS), are common throughout the spectrum of HIV infection. These may range from an acute aseptic meningoencephalitis in primary HIV infection to the development of opportunistic viral, fungal, and parasitic infections of the CNS. One of the most common neuropathic features of HIV is neuropathy. Four types of neuropathy are important to recognize as manifestations of HIV disease: distal symmetric polyneuropathy, mononeuropathy multiplex, inflammatory demyelinating polyneuropathy, and progressive lumbosacral polyradiculopathy. Distal symmetric polyneuropathy is by far the most common, occurring in 16% of asymptomatic HIV-seropositive patients and 35% of hospitalized persons with HIV.

LATE-STAGE HIV AND OPPORTUNISTIC INFECTIONS
As immunocompromise progresses, persons with HIV may present with the common cadre of opportunistic infections well known as AIDS. Thus, persons presenting with progressive pneumonia, odynophagia refractory to acid suppressive therapy, brain abscesses, chronic meningitis, dementia, and severe neuropathy should all be considered for HIV testing. Pneumocystis carinii is the most common presenting infection in late-stage disease. Systemic symptoms, including fever, fatigue, exertional dyspnea, and weight loss, are prominent, often without identifiable secondary causes. Cryptococcal meningitis may present with subtle findings of headache and fever or with progressive cognitive dysfunction. Dissemination of systemic mycoses, coccidiodomycosis, histoplasmosis, and cryptococcosis especially to the CNS should prompt HIV testing.

As the disease advances further and the CD4+ count decreases below 50 cells/µL, additional opportunistic infections as well as CNS non-Hodgkin lymphoma occur commonly, and, in homosexual men, existing KS may become extensive and cause disfigurement and clinically important edema. Visual loss may occur due to CMV ret-
initis. Central nervous system toxoplasmosis, cryptococcal meningitis, CMV disease, and progressive multifocal leukencephalopathy occur frequently. Infections due to MAC, CMV, Strongyloides stercoralis, herpes zoster, or tuberculosis, which normally are limited to an organ system or a local anatomical region, may invade tissue or disseminate widely. Simultaneous, clinically important infection by more than 1 pathogen is common. Secondary symptoms become increasingly problematic, including anorexia, nausea, vomiting, diarrhea, malabsorption, muscle wasting, and weakness. Without treatment, such patients die of HIV. However, in the past 6 years, with the introduction of HAART, many HIV-infected persons who initially presented at this late stage have had dramatic immunologic recovery with the development of a group of new syndromes associated with prolonged HIV survival.

PRESENTING SYNDROMES IN PATIENTS RECEIVING HAART

A final group of syndromes to recognize are those associated with HAART and prolonged HIV survival. Some, such as localized lymphadenitis and CMV immune recovery vitreitis, may be due to immune reconstitution, whereas others are due to adverse effects of medications. In recent years, a spectrum of changes in body habitus and metabolism has emerged among HIV-infected persons receiving HAART.19 These changes collectively called HIV-associated lipodystrophy include changes in both body fat distribution and disordered fat metabolism. Some patients experience a syndrome of lipoatrophy characterized by marked subcutaneous fat depletion that leads to facial and buttck wasting and the presence of varicosities of the arms and legs due to the subcutaneous fat loss. Another metabolic complication is central or visceral fat accumulation leading to truncal obesity, dorsocervical fat hump, and breast enlargement in both men and women. Insulin resistance, hyperglycemia, and hyperlipidemia are common. A metabolic disorder increasingly recognized as a consequence of HAART with nucleoside analogues is mitochondrial toxicity. This may lead to mitochondrial myopathy and neuropathy and is recognized as the cause of a syndrome of lactic acidosis and hepatic steatosis.

CONCLUSIONS

As we enter the third decade of the HIV epidemic in the United States, the presenting manifestations of this disease have evolved and expanded. It is important for practicing clinicians to recognize the increasing frequency of this disease in minority heterosexual populations in the United States, to recognize its protean manifestations, and to offer testing to those presenting with the syndromes described in this article.

REFERENCES

Questions About Presenting Syndromes of HIV

1. Which one of the following is not a hallmark of primary HIV infection?
   a. Fever
   b. Rash
   c. Oral thrush
   d. Myalgias
   e. High-titer viremia

2. Which one of the following groups is experiencing the most rapid growth of HIV?
   a. African American women
   b. Homosexual white men
   c. Elderly Latino men
   d. Intravenous drug users
   e. African American men

3. Which one of the following skin lesions is least likely to be found in early HIV disease?
   a. Seborrheic dermatitis
   b. Eosinophilic folliculitis
   c. Xerosis
   d. Psoriasis
   e. Staphylococcal folliculitis

4. Which one of the following is not a common presenting syndrome of HIV?
   a. Herpes zoster in a young adult
   b. ITP in a young man
   c. Recurrent vulvovaginal candidiasis in an African American woman
   d. Odynophagia and thrush in a former intravenous drug user
   e. Gram-negative bacteremia in a middle-aged woman

5. Which one of the following is not commonly seen in late-stage untreated HIV?
   a. Subcutaneous fat loss and central fat accumulation
   b. Pneumocystis carinii pneumonia
   c. Disseminated MAC
   d. Anemia
   e. Dementia

Correct answers:
   1. c, 2. a, 3. b, 4. e, 5. a