

Current reviews of allergy and clinical immunology

(Supported by a grant from Glaxo Wellcome, Inc, Research Triangle Park, NC)

Series editor: Harold S. Nelson, MD

HIV: Clinical manifestations

Edina H. Moylett, MD, and William T. Shearer, MD, PhD *Houston, Tex*

HIV infection in the United States appeared early in the 1980s, when previously healthy homosexual men manifested opportunistic infections attributable to apparent underlying immunodeficiency. After these initial isolated reports, there appeared many other groups of patients at risk for development of this devastating disease. From these meager beginnings, the problem has escalated exponentially. HIV infection can affect every system in the human body. Since the era of highly active antiretroviral therapy, however, the prevalence of opportunistic infections and HIV-AIDS clinical manifestations has declined dramatically. In addition to antiretroviral therapy, management of HIV-infected persons requires knowledge of the extent of system involvement, as well as highly active antiretroviral therapy-related adverse effects, so as to recognize complications and initiate appropriate intervention. In the following review we will attempt to comprehensively summarize the clinical manifestations of HIV infection for both pediatric and adult populations. (*J Allergy Clin Immunol* 2002;110:3-16.)

Key words: HIV, AIDS, highly active antiretroviral therapy, opportunistic infections, clinical manifestations

ACUTE HIV INFECTION SYNDROME

As of the end of 2001, the Joint United Nations Programme on HIV-AIDS estimated that more than 40 million adults and children were living with HIV-AIDS, from a cumulative total of well over 60 million persons infected since the beginning of the epidemic (Fig 1). As the groups of persons at risk for AIDS expanded, clinicians noted an increasing spectrum of clinical manifestations of AIDS-associated immunodeficiency.

Primary HIV infection should be considered in any patient with possible HIV exposure who presents with fever of unknown cause. Unfortunately, the acute infection largely goes unrecognized because of nonspecific and occasionally mild symptoms. In an effort to estimate

Abbreviations used

ARL:	AIDS-related lymphoma
ART:	Antiretroviral therapy
CMV:	Cytomegalovirus
CNS:	Central nervous system
DILS:	Diffuse infiltrative lymphocytosis syndrome
GI:	Gastrointestinal
HAART:	Highly active antiretroviral therapy
HHV8:	Human herpes virus 8
HIV-AN:	HIV-associated nephropathy
HRPH:	HIV-related pulmonary hypertension
HSV:	Herpes simplex virus
KS:	Kaposi's sarcoma
KSHV:	Kaposi's sarcoma herpesvirus
LIP:	Lymphocytic interstitial pneumonitis
MAC:	<i>Mycobacterium avium</i> complex
NHL:	Non-Hodgkin's lymphoma
NIP:	Nonspecific interstitial pneumonitis
NRTI:	Nucleoside-analogue reverse transcriptase inhibitor
OI:	Opportunistic infection
PCP:	<i>Pneumocystis carinii</i> pneumonia
PI:	Protease inhibitor
VZV:	Varicella zoster virus

the frequency of symptomatic primary infection, Lavreys et al¹ prospectively followed a group of high-risk patients to monitor symptoms associated with seroconversion. Among 103 seroconverters, 81% developed 1 or more of 11 symptoms or signs. The acute viral syndrome generally develops 2 to 4 weeks after initial exposure to HIV, although incubation periods of 6 days to 6 weeks have been reported.²⁻⁵ The period of illness associated with acute infection is generally 10 days but might vary from 3 to 25 days. In a recent series of 46 patients, fever (94%) and myalgias (60%) were common, but fatigue (90%), pharyngitis (72%), weight loss (70%), and headache (55%) also were reported.⁶ The initial description of a mononucleosis-like illness^{2,7} might not always be evident, with only 15.6% of 218 patients in a study by Vanhems et al⁸ manifesting the typical mononucleosis-like syndrome of fever, pharyngitis, and adenopathy.

In addition to constitutional symptoms, acute HIV infection might be associated with a myriad of dermatologic manifestations. The typical rash is mononucleosis-like, nonpruritic, erythematous, and maculopapular and distributed on the face and trunk but might involve the palms and soles or be generalized.⁹ Additional reports

From the Department of Allergy and Immunology, Baylor College of Medicine, and Texas Children's Hospital, Houston.

Supported by Pediatric AIDS Clinical Trials Group (AI-27551), Women's and Infant's Transmission Study (HD-41983), Center for AIDS Research (AI-36211), General Clinical Research Center (RR-00188), and the Pediatric AIDS Fund of Texas Children's Hospital.

Received for publication April 19, 2002; revised April 29, 2002; accepted for publication May 1, 2002.

Reprint requests: Edina H. Moylett, MD, Texas Children's Hospital, Department of Allergy and Immunology, 6621 Fannin St, (MC-3291), Houston TX 77030.

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0091-6749/2002 \$35.00 + 0 1/10/125978

doi:10.1067/mai.2002.125978

Adults and children estimated to be living with HIV/AIDS as of end 2001



Total: 40 million

FIG 1. Graphic representation of the global distribution of HIV and AIDS. Figure adapted from the Joint United Nations Programme on HIV-AIDS. (UNAIDS. Global HIV/AIDS and STD Surveillance. Available at www.unaids.org.)

include desquamation of the palms and soles,² generalized urticaria,¹⁰ vesiculopustular rash,¹⁰ erythema multiforme,¹¹ or alopecia¹² as part of the presenting complex. Oral and genital mucocutaneous ulceration is also typically associated with acute HIV infection.^{7,13} Gastrointestinal (GI) manifestations might dominate the acute viral syndrome, with abdominal pain, vomiting, and diarrhea being the primary manifestations.^{1,6,13} Severe esophageal ulceration has also been reported.¹⁴ Headache and photophobia are frequently encountered complaints associated with the acute viral syndrome. More unusual nervous system manifestations include acute fulminating encephalopathy,¹⁵ brachial neuritis,¹⁶ myelopathy,¹⁷ peripheral neuropathy,¹⁷ facial nerve palsy,¹⁸ cauda equina syndrome,¹⁹ and Guillain-Barré syndrome.²⁰ Profound depression of the CD4⁺ T-cell count after acute infection might be associated with opportunistic infections (OIs), such as oral-esophageal candidiasis, *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV) colitis or encephalitis, cerebral toxoplasmosis, and tuberculosis.

METABOLIC MANIFESTATIONS

HIV infection is associated with a variety of disturbances in metabolic function, most notably hyperlipidemia, body fat redistribution lipodystrophy versus lipoatrophy, lactic acidosis, insulin resistance, and hyperglycemia. An increased rate of de novo lipid synthesis from the liver in HIV-infected individuals contributes to hypertriglyceridemia.²¹ In addition, protease inhibitors (PIs) have been shown to impair the conversion of retinoic acid to cis-9-retinoic acid either by binding to the binding protein region or by inhibiting cytochrome P450-3A isoforms that metabolize retinoic acid. PIs might also inhibit cleavage of fatty acids from circulating triglycerides, with reduced hepatic uptake of chylomicrons. The

resulting hyperlipidemia leads to fat redistribution to the abdomen, insulin resistance, and, in susceptible individuals, secondary Type II diabetes mellitus. Lipohypertrophy results in accumulation of fat in atypical locations, such as a buffalo hump, increased torso and abdominal girth, and increased breast size. The association between lipohypertrophy and PI therapy is variable.²²

On the other end of the scale is lipodystrophy. This is characterized by dramatic relocation of fat from the subcutaneous compartment, which atrophies, into the visceral compartment, where fat accumulation is noted. Highly active antiretroviral therapy (HAART), which contributes to altered lipid metabolism in addition to impaired mitochondrial function, contributes significantly to this syndrome.²³ A balance has been postulated between the lipodystrophy effects from nucleoside-analogue reverse transcriptase inhibitors (NRTI) and the hyperlipidemia related to PI therapy (Fig 2).²⁴ NRTI therapy, most notably stavudine, has also been associated with fatal lactic acidosis resulting from mitochondrial dysfunction.²⁵

ORAL MANIFESTATIONS

At least 90% of HIV-infected patients will have at least one oral manifestation at some time during the course of their disease.²⁶ Oral lesions might herald underlying immunodeficiency. Candidiasis involving the oral cavity is rare in immunocompetent patients; however, it is a common feature of HIV infection and occurs in as many as 75% of infected patients. Many studies have confirmed that the risk for oral complications increases as the level of immunodeficiency declines. Certain oral lesions are strongly associated with the degree of disease activity and might serve as a marker of degree of immunosuppression and viral burden.²⁷ Conversely, the implementation of HAART has resulted in a decline in the frequency of oral manifestations, as immune function is reconstituted.²⁸

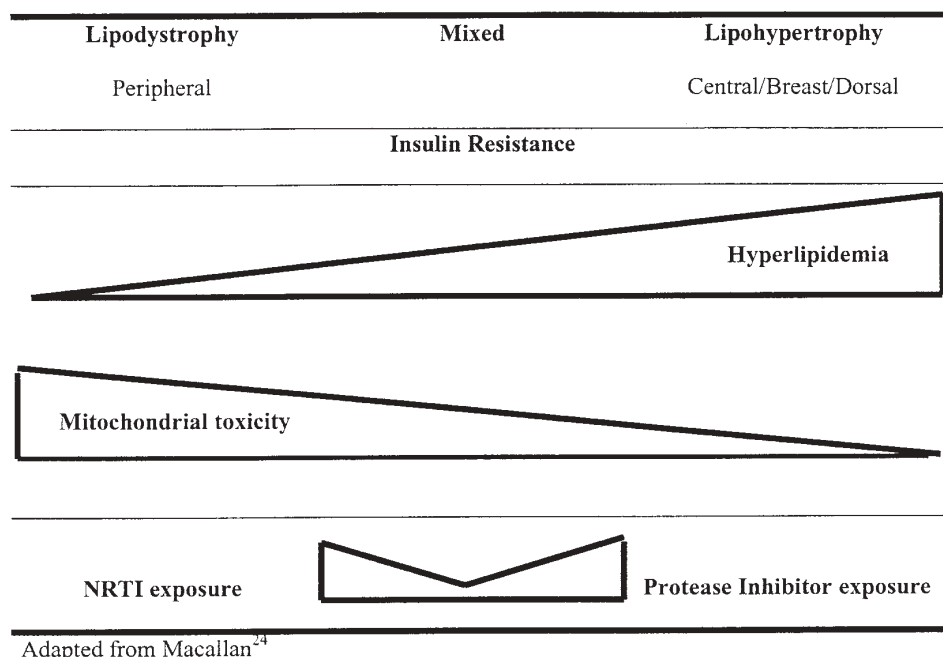


FIG 2. Proposed spectrum of clinical and biochemical abnormalities in HIV-associated fat-redistribution syndromes. PI exposure results in hyperlipidemia with primary lipohypertrophy. NRTI exposure results in significant mitochondrial toxicity and resultant lipodystrophy.

TABLE I. Occurrence of oral lesions depending on the level of immunosuppression

Oral manifestation	Frequency with primary infection	CD4 ⁺ T cells > 500 cells/mm ³	CD4 ⁺ T cells 200-500 cells/mm ³	CD4 ⁺ T cells < 200 cells/mm ³
Candidiasis	Common	Occasional	Common	Very common
Aphthous ulcers	Common	Occasional	Common	Very common
HSV	No	Occasional	Common	Common
Herpes zoster virus	No	Occasional	Occasional	Occasional
CMV	No	Rare	Rare	Occasional
Oral hairy leukoplakia	No	Occasional	Common	Very common
KS	No	Rare	Common	Very common
NHL	No	Rare	Rare	Occasional
Linear gingival erythema	No	Common	Common	Very common
Necrotizing gingivitis	No	Rare	Occasional	Common
Necrotizing periodontitis	No	Rare	Occasional	Common
Necrotizing stomatitis	No	No	Rare	Common
Salivary gland disease	No	Rare	Occasional	Occasional

Adapted from Weinert et al.²⁹

What then are the oral manifestations associated with HIV infection? Table I outlines the most commonly encountered oral lesions depending on the level of immunosuppression, as determined by means of CD4⁺ T-cell count.²⁹ Oral manifestations generally fall within 5 causative categories: fungal, bacterial, viral, neoplastic, and miscellaneous lesions. Oral candidiasis most commonly occurs as pseudomembranous candidiasis, also known as thrush, which involves the palate, buccal, and labial mucoase and dorsum of the tongue. Hyperplastic candidiasis, also referred to as leukoplakia, involves the buccal mucosa primarily and might be confused with oral hairy leukoplakia. The latter condition, which also

involves the lateral surface of the tongue, is believed to be related to reactivation of latent EBV and, in the absence of an alternative cause for immunosuppression, is diagnostic of HIV infection (Fig 3). Ulcerative lesions are noted in as many as 50% of patients and might be idiopathic (aphthous ulcers), drug related, or related to herpes virus infection (herpes simplex virus [HSV] 1 and 2, varicella zoster virus [VZV], and CMV). Oral HSV occurs in the general population, but recurrent HSV disease manifests as a more aggressive and protracted illness in HIV-infected patients. HSV ulcers generally occur on keratinized mucosa, whereas aphthous ulcers primarily affect nonkeratinized mucosal surfaces. VZV



FIG 3. Oral hairy leukoplakia in a young immigrant child with previously undiagnosed HIV infection. This is an unusual clinical manifestation in the pediatric population.

and CMV ulcers occur in a small percentage of HIV-infected patients. VZV tends to be unilateral and affects the oral mucosa along trigeminal nerve branches.

Periodontal disease is noted in up to 50% of HIV-infected patients. Four distinct phases exist: linear gingival erythema (profound erythema of the free gingival margin adjacent to the teeth); necrotizing gingivitis; necrotizing periodontitis (involvement of underlying alveolar bone); and necrotizing stomatitis (involvement of adjacent bone and soft tissue). Periodontal disease is likely related to mixed aerobic and anaerobic infection. Kaposi's sarcoma (KS), which is related to coinfection with human herpes virus 8 (HHV8), has been reported in 15% of patients with AIDS. Oral lesions might be the initial manifestation of KS in up to 50% of patients. Clinically, these lesions are macular, occurring on the hard palate or gingiva, and might progress to bulky tumors. Non-Hodgkin's lymphoma (NHL) affecting the oral cavity is a rare manifestation of HIV infection (Table I). The lesions occur at sites of lymphoid tissue (gingiva, tonsils, and palate) and are initially painless but progress to painful focal swelling.

Finally, parotid gland swelling, a condition more frequently encountered in children, is thought to be caused by lymphoid proliferation in response to HIV infection. It might present as unilateral or bilateral gland enlargement, with a prevalence rate of 0% to 58%.

OCULAR MANIFESTATIONS

Ocular diseases are extremely common manifestations of HIV disease, with a wide variety of causes, ranging from a benign HIV retinopathy to sight-threatening viral OIs. The most commonly encountered ocular manifestation is CMV retinitis, which affects up to 40% of adult patients but significantly fewer pediatric patients (approximately 5%). Table II outlines the more frequent ocular manifestations of HIV disease, along with a brief description of clinical presentation.³⁰

The clinical presentation and management of CMV retinitis in the era of HAART is changing. CMV retinitis

typically occurs when the CD4⁺ T-cell count decreases to less than $100 \times 10^6/L$.³¹ There has been a dramatic reduction in the incidence of CMV retinitis since the widespread implementation of HAART in developed countries. In addition, specific CMV therapy has been successfully discontinued in patients with AIDS receiving HAART (CD4⁺ T-cell count $>250 \times 10^6/L$), with follow-up periods of up to 90 weeks without documented relapse.³² However, immune reconstitution as a result of HAART results in a rejuvenated immune response, which might lead to intraocular inflammation.³³ Both a significant vitritis and retinal edema characterize this immune recovery uveitis.³³ The exact mechanism of immune recovery uveitis has not been delineated. Breakdown in the blood-ocular barrier might allow CMV antigen to leak out of the eye and give the antigen access to lymphoid organs. It is imperative that close follow-up is maintained of patients receiving HAART with a history of CMV retinitis in whom specific CMV therapy is discontinued.

CUTANEOUS MANIFESTATIONS

Cutaneous disorders occur very frequently in HIV-infected patients. Lesions are typically related to primary cutaneous disease or infection, which might disseminate to the viscera, or manifestations of primary systemic infection, such as fungal disease. The frequency and severity of cutaneous disorders increases as the disease progresses and immune function declines.³⁴ In addition, similar skin diseases might be observed in immunocompetent patients, but the frequency and severity is greater in HIV-infected patients and patients with AIDS. Generally speaking, cutaneous manifestations can be divided into 5 main categories (ie, infectious, infestation, papulosquamous, neoplasm, and inflammatory), as outlined in Table III. The acute HIV syndrome is classically associated with a rash, as described previously.

Herpes virus infections tend to be more frequent, atypical in presentation, and resistant to first-line therapy in HIV-infected individuals.^{35,36} The most commonly involved sites of HSV infection are the perianal, genital, orofacial, and digital areas. Characteristic lesions of herpes simplex appear first as painful erythematous papules; later, they vesiculate and ulcerate, and pustules might form. Giant perirectal ulcers and lesions at other sites that yield thymidine kinase-resistant strains of HSV-2 have occurred in patients who were previously treated with acyclovir. VZV typically reactivates as zoster in HIV-infected patients when the CD4⁺ T-cell count decreases to less than 200 to 500/mm³.^{36,37} Severe disease might be an early indicator of HIV infection.³⁴ Molluscum contagiosum, caused by a poxvirus, is commonly seen in HIV-infected individuals, most notably pediatric patients. Widespread molluscum in an apparently healthy child might indicate underlying immunocompromise. The umbilicated lesions can vary in size, and larger lesions might mimic cryptococcosis.

Cutaneous bacterial infections complicating HIV infection include *Staphylococcus aureus* (folliculitis,

TABLE II. Most frequently encountered ocular manifestations of HIV infection

Site	Condition	CD4 ⁺ T-cell count
Adnexal	HZV ophthalmicus: involves ophthalmic distribution of the trigeminal nerve; pain might be severe; affects 5% to 15% of HIV-infected patients	
	KS: highly vascularized mesenchymal tumor, which might mimic a chalazion or subconjunctival hemorrhage; 20% of HIV-infected patients with KS might have ocular lesions	<500 cells/mm ³
Anterior segment	Molluscum contagiosum: involvement of the eyelids occurs in 5% of HIV-infected patients; small, painless umbilicated lesions; highly contagious	
	Conjunctival microvasculopathy: asymptomatic conjunctival microvascular changes best seen with a slit lamp; cause unknown; no treatment indicated; affects up to 80% of HIV-infected patients	<100 cells/mm ³
	Keratoconjunctivitis sicca: affects up to 20% of HIV-infected patients at a later stage in the illness; cause probably related to HIV-mediated inflammation and destruction of primary and secondary lacrimal glands	<100 cells/mm ³
	Infectious keratitis: occurs in <5% of HIV-infected patients; VZV; HSV most commonly; might cause permanent vision loss; bacterial and fungal keratitis no more common in HIV-infected patients but more severe; ocular microsporidiosis is uncommon but might cause punctate superficial keratopathy	<100 cells/mm ³
Posterior segment	Iridocyclitis: mild disease might be associated with CMV-VZV; severe disease is rare and might be seen with toxoplasmosis-syphilis; drug-related disease (eg, rifabutin and cidofovir); endogenous autoimmune uveitis, such as Reiter's syndrome, more common in HIV-infected patients	
	Retinal microvasculopathy: also referred to as AIDS retinopathy; affects 50%-70% of HIV-infected patients; typical lesions include cotton-wool spots, intraretinal hemorrhage, and retinal microaneurysms; usually asymptomatic; frequency increases as CD4 ⁺ cell count decreases to	<100 cells/mm ³
	Infectious retinitis:	
	CMV retinitis: affects 30%-40% of HIV-infected individuals; patients usually report floaters or blurred vision; anterior chamber examination is typically unremarkable; fundus examination shows full-thickness retinal whitening; often with retinal hemorrhages	<100 cells/mm ³
	VZV retinitis: less frequent than CMV; affects 1%-4% of HIV-infected patients; similar clinical findings to CMV but with more rapid progression, multifocal lesions, and involvement of deep retinal layers	<100 cells/mm ³
	Toxoplasma retinochoroiditis: affects 1%-2% of HIV-infected patients; lesions typically involve the anterior chamber with vitreous inflammation; relative absence of retinal hemorrhage and pigmented chorioretinal scars; HIV-infected patients typically have more severe bilateral disease in contrast to immunocompetent patients	<250 cells/mm ³
	Bacterial-fungal retinitis: syphilis is the most common intraocular bacterial infection (1%-2%); <i>Pneumocystis carinii</i> choroiditis accounts for less than 1% of ocular disorders in HIV-infected patients	<100 cells/mm ³

HZV, Herpes zoster virus.

impetigo, and furuncles), group A β -hemolytic *Streptococcus* species (impetigo and lymphangitis), and *Pseudomonas aeruginosa* (folliculitis and ecthyma). Bacillary angiomatosis, caused by *Bartonella henselae* and *Bartonella quintana*, is characterized by a vascular disorder with red, occasionally hyperkeratotic papules and nodules. The disease is more frequent in adults and rarely seen in pediatric patients. Dissemination can occur with a fatal outcome if not treated. Primary *Mycobacterium tuberculosis* skin lesions are uncommon in HIV-infected patients. Most commonly reported atypical mycobacteria causing skin disease include *Mycobacterium fortuitum* (subcutaneous nodules in intravenous drug users) and *Mycobacterium haemophilum* (papules, ulcers, and cellulitis).

Fungal infections are most frequently attributable to *Candida albicans* infection (described elsewhere). Cryptococcosis (*Cryptococcus neoformans*) is the second most common fungal OI in the HIV-infected host. Cutaneous lesions are seen in 10% to 20% of patients with disseminated disease and include papules, nodules, molluscum-

like lesions, ulcers, and KS-like lesions. Coccidiomycosis and histoplasmosis might also manifest cutaneous lesions, typically pustules, nodules, and plaques; histoplasmosis lesions can also resemble acne vulgaris or folliculitis. Papulosquamous disease is the most common cutaneous manifestation of HIV infection (see Table III for more details).

PULMONARY MANIFESTATIONS

Pulmonary manifestations of HIV infection can be broadly divided into infectious, noninfectious, and malignant categories. Noninfectious complications will be discussed herein.

Lymphocytic interstitial pneumonitis (LIP) is primarily a disease of HIV-infected pediatric patients. Although believed to be related to a delayed immunologic response to EBV in the setting of HIV infection, the precise cause is unknown. Approximately 30% to 40% of perinatally infected children and 12% of transfusion-related HIV-infected children will have LIP. In a recent study the average age of onset was 2.3 years.³⁸ Clinically, children have

TABLE III. Cutaneous manifestations of HIV disease

Infectious	Bacterial	<i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes</i> , <i>Pseudomonas aeruginosa</i> , <i>Mycobacteria</i> species, <i>Bartonella henselae</i> and <i>Bartonella quintana</i>
	Viral	HSV I and II, EBV, VZV, CMV, human papilloma virus, poxvirus
	Fungal	<i>Candida albicans</i> , <i>Pityrosporum ovale</i> , <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i>
Infestation	Scabies	<i>Sarcoptes scabiei</i> : Patients with advanced HIV disease might have Norwegian or crusted scabies; patient is usually infected with thousands of mites
	Demodicidosis	<i>Demodex folliculorum</i> <i>Demodex brevis</i>
Papulosquamous disease	Seborrheic dermatitis	Might affect up to 80% of HIV-infected individuals; severity associated with advanced disease; most common cutaneous eruption
	Psoriasis	Not more frequent in HIV-infected patients, but lesions are more severe and worsen as the immune system deteriorates
	Reiter syndrome	Keratoderma blennorrhagicum is the most common cutaneous lesion seen in Reiter syndrome; usually involving the soles of the feet, dorsal surface of hands and feet, nails, scalp, and extensor aspects of the arms and legs
	Ichthyosis	Might be an association between HIV-infected IDU coinfecting with HTLV II and low CD4 counts
	Xerotic eczema	Extreme dryness with intense pruritis common in HIV-infected patients
	Folliculitis	Might occur in up to 25% of HIV-infected patients; eosinophilic folliculitis is more frequently encountered in HIV-infected patients; lesions distributed on the face, trunk, and proximal extremities; intensely pruritic
Neoplasms	KS	HHV-8: Initial lesions are often on the upper body but might be on mucous membranes or face; purple-red macules or papules might resemble benign lesions or macular, ecchymotic bruise-like lesions
	NHL	Skin lesions are rare; lesions are typically red-purple or plum-colored nodules or plaques
Inflammatory	Drug eruptions	Most commonly trimethoprim/sulfamethoxazole, aminopenicillins, antituberculosis medications, and phenytoin; frequently presents as morbilliform eruption of erythematous papules and macules on the trunk and extremities
	Photosensitivity reactions	Hypersensitivity to UV light might be a presentation of HIV disease; more commonly dark-skinned, characterized by pruritic, lichenoid, hyperpigmented, or violaceous plaques on sun-exposed skin

IDU, Intravenous drug users; HTLV, human T-cell lymphotropic virus.

an insidious onset of nonproductive cough associated with findings of generalized lymphadenopathy and digital clubbing. Auscultatory findings are usually unremarkable; however, radiographic findings consist of a diffuse, symmetric, reticulonodular or nodular pattern with or without hilar or mediastinal adenopathy. LIP might be associated with an increased frequency of bacterial pneumonia and resultant bronchiectasis. Cell-marker studies of bronchoalveolar fluid reveal a preponderance of CD8⁺ T cells, usually with a decline in peripheral CD4⁺ T cells. Because LIP supposedly represents an immune response to infection, the natural progression of the disease might alter with the advent of HAART.

Nonspecific interstitial pneumonitis (NIP) is more prevalent in the adult HIV-infected population. Clinically, NIP resembles PCP, but unlike PCP, NIP develops when the CD4⁺ T cells and total lymphocyte counts are still preserved. Histologic findings reveal a patchy lymphocytic infiltrate composed of B cells in focal aggregates, with T cells more extensively distributed.³⁹ Unlike LIP, the T-cell population is composed of a mixture of CD4⁺ and CD8⁺ T cells.³⁹ NIP does not lead directly to patient death but is associated with a downturn in the course of HIV infection.

With an increased time of survival and effective prophylactic treatment, noninfectious conditions associated with HIV infection are being recognized with increasing frequency. HIV-related pulmonary hypertension (HRPH) is one such condition.⁴⁰ HRPH occurs with a frequency of approximately 1 per 200 HIV-infected patients. The most dominant histopathologic finding in cases of HRPH is plexiform arteriopathy. Perivascular inflammation has been detected in cases of plexiform pulmonary hypertension, which suggests that different inflammatory mediators and growth factors derived from the inflammatory cells might play a role in the development of pulmonary hypertension. Genetic predisposition might also have a role in the development of HRPH because it is not related to the degree of immunosuppression and the CD4⁺ T-cell count and because only a minority of HIV-infected individuals have pulmonary hypertension. In support of genetic predisposition, an increased prevalence of HLA-DR6 and HLA-DR52 has been demonstrated in patients with pulmonary hypertension and HIV disease.⁴¹ Clinically, HRPH does not differ from typical primary pulmonary hypertension. Additionally, HRPH is a serious condition with significant associated mortality; the development of pulmonary hypertension in patients with

HIV has been shown to reduce the probability of survival by half. In some isolated case reports, HAART has been demonstrated to aggravate underlying HIV-associated pulmonary hypertension.⁴¹

CARDIAC MANIFESTATIONS

HIV infection is associated with cardiac abnormalities in almost 70% of infected patients.⁴² The incidence of cardiac disease increases as HIV-infected patients begin to have late-stage disease. Frequently, clinical signs are inadequate for the diagnosis of cardiac involvement, and a more direct assessment of cardiac function is required. Cardiac complications include pericardial effusion, myocarditis, endocarditis, dilated cardiomyopathy, pulmonary hypertension, and cardiac tumors. Small pericardial effusions occur in up to 20% of HIV-infected patients. The majority of pericardial effusions are idiopathic, but in some cases, the cause can be established. Infections, lymphoma, KS, myocardial infarction, fibrinous exudate, myocarditis, and endocarditis have been described as possible causes. Infectious endocarditis is most commonly associated with intravenous drug use. Right-sided heart valves are involved primarily, and *Staphylococcus aureus* and *Streptococcus viridans* are the most commonly isolated pathogens. Marantic or non-infectious endocarditis, affecting 3% to 5% of patients, is associated with hypercoagulable states, malignant neoplasms, and chronic wasting disease.

Lymphocytic myocarditis is a frequent complication of HIV infection. HIV or its proteins (p17, p24, and gp120/160) have been found in heart specimens from patients with AIDS in the presence and absence of cardiac disease.⁴³ Increased numbers of dendritic cells harboring HIV from endocardial biopsy specimens suggest that these might be involved in the development of cardiac dysfunction.⁴⁴ Lymphocytic myocarditis is often idiopathic, but in certain cases a pathogen is isolated, including CMV, *Cryptococcus neoformans*, *Candida* species, *Toxoplasma gondii*, sarcosporidium, *Histoplasma capsulatum*, *Mycobacterium tuberculosis*, Coxsackie virus, and *Aspergillus* species.

Dilated cardiomyopathy is one of the most common cardiac manifestations of HIV infection, with significant adverse effects on survival.⁴⁵ Most often noted in the late stages of infection, when CD4⁺ T-cell counts are low, it affects up to 40% of HIV-infected patients. Pathogenesis is unclear but presumably involves associated myocarditis and direct immune mechanisms related to HIV myocardial infection. One proposal involves enhanced TNF- α production with resultant increased nitric oxide production and a subsequent negative inotropic effect on cardiac contractility.⁴⁶ In a recent study by Lai et al (The prospective P2C2 HIV multicenter study),⁴⁷ aortic root dilatation was documented in vertically infected children at 2 to 9 years of age. Aortic root dilatation was associated with left ventricular dilatation, increased viral load, and lower CD4⁺ T-cell counts. In addition, a prospective study by Keesler et al⁴⁸ documents left ven-

tricular dysfunction and increased left ventricular mass in HIV-infected children. The latter findings are important indicators of survival for children infected with HIV.

Cardiac involvement with KS in an HIV-infected patient usually occurs as a part of disseminated KS. There is a predilection to involve the subepicardial tissue adjacent to a major coronary artery. Pericardial and myocardial involvement has also been reported. Primary NHL affecting cardiac tissue is extremely rare, but involvement as a result of dissemination occurs in approximately 15% of cases. Polypoid masses of the endocardium are noted most often. Patients might be asymptomatic initially but rapidly progress to pericardial effusion, tamponade, and heart failure.

Since the advent of HAART, there has been a change in the extent of cardiac manifestations. In a study by Pugliese et al,⁴⁹ cardiac involvement, including arrhythmia, pericarditis, ischemia, dilated cardiomyopathy, endocarditis, pulmonary hypertension, and myocarditis, were observed in 282 (52%) of 544 patients treated with NRTIs compared with 93 (18.6%) of 498 patients treated with HAART. Apart from the clinical benefit, HAART, in addition to other classes of medications to treat HIV-infected patients, is associated with cardiotoxicity.⁵⁰ Hyperlipidemia is strikingly associated with the use of PIs, although the clinical relevance is unknown at this time. In addition, PIs are potent inhibitors of CYP3A, which might precipitate an asymptomatic electrocardiographic abnormality into a dangerous arrhythmia.

NEUROLOGIC MANIFESTATIONS

The most prevalent and important neurologic complication related to HIV infection is subacute encephalitis, also referred to as AIDS encephalopathy or AIDS dementia complex. In addition, HIV infection might result in aseptic meningitis after acute infection, peripheral neuropathy, and vacuolar myelopathy. HIV-related central nervous system (CNS) malignancy and OIs will be discussed elsewhere. Neuropathy might also complicate antiretroviral therapy (ART). Approximately 10% of patients receiving stavudine or zalcitabine and 1% to 2% of didanosine recipients might have to discontinue therapy with these agents because of neuropathy. Drug-related neuropathy is typically sensory, bilateral, and peripheral and resolves on discontinuation of therapy. HIV infection predominantly results in peripheral neuropathy that is chronic, distal, symmetric, and predominantly sensory; symptoms of peripheral neuropathy are reported in approximately 50% of infected patients. HIV has been isolated from peripheral nerves.⁵¹ Less frequently, an inflammatory demyelinating polyneuropathy is noted, presenting with weakness, mild sensory deficits, and areflexia. Guillain-Barré-like syndrome, cranial nerve involvement, and mononeuropathy multiplex have also been documented. Vacuolar myelopathy causes a syndrome of progressive spastic paraparesis that evolves during a period of weeks to months. The lesion typically involves the posterior columns and clinically presents as

TABLE IV. Organisms associated with prostatitis in HIV-infected patients

Bacteria

Haemophilus parainfluenzae
Staphylococcus aureus
Escherichia coli
Klebsiella pneumoniae
Serratia marcescens
Pseudomonas aeruginosa
Mycobacterium avium-intracellulare
Salmonella typhi

Fungi

Histoplasma capsulatum
Cryptococcus neoformans

Viruses

HIV
 CMV

gait ataxia, leg weakness, upper motor neuron signs, incontinence, and posterior column deficits. Ninety percent of patients also have clinical evidence of dementia.

Before the advent of HAART, approximately one third of all adults and one half of all children with AIDS eventually showed neurologic symptoms directly caused by HIV-1 infection of the CNS.⁵² Since the widespread application of HAART, there has been little effect on the prevalence of HIV encephalopathy, whereas rates of other focal CNS lesions (lymphoma and toxoplasmosis) have drastically declined.⁵³ AIDS dementia initiates with cognitive impairment, loss of concentration, and slowness of thought, and motor dysfunction, behavioral symptoms, depression, and organic psychosis might also occur. Routine diagnostic studies generally show non-specific changes. Cerebrospinal fluid abnormalities are present in 85%, and computed tomographic scans show differing degrees of diffuse cerebral atrophy in 80% to 90% of patients, with significantly fewer patients demonstrating focal lesions. Pathologically, the characteristics of HIV encephalopathy consist of reactive astrocytosis, infiltration by circulating macrophages, resident microglia and multinucleated giant cells, and myelin pallor. Abnormalities are most prominent in the subcortical structures, with relative sparing of the cortex. HIV has been identified in the macrophages of HIV-infected patients with dementia.⁵⁴ Subsequently, peripherally derived monocytes have been shown to invade the CNS in patients with HIV dementia and serve as a reservoir of HIV infection.⁵⁵ It is proposed that CNS pathology is related in part to release of neurotoxins from infected macrophages. In addition, active replication of the virus results in release of large quantities of neurotoxic substances from macrophages (eicosanoids, free radicals, TNF- α , IL-1 β , and platelet-activating factor), contributing to neuronal damage.⁵⁶ There might be a relationship between HIV encephalopathy and cardiomyopathy. Cardiomyopathy appears more prevalent in pediatric patients with encephalopathy. HIV-infected adults with cardiomyopathy and concomitant encephalopathy have a poorer clinical course.

GENITOURINARY MANIFESTATIONS

In 1984, the first detailed report of a new pattern of sclerosing glomerulopathy in HIV-infected patients was reported.⁵⁷ Subsequently, HIV-associated nephropathy (HIV-AN) was noted to have significant racial predilection, with a black/white ratio of 12:1, and was documented more frequently in intravenous drug users. HIV-AN is the third leading cause of end-stage renal disease among African Americans aged 20 to 64 years, preceded only by diabetes and hypertension. HIV-AN usually occurs in patients with a low CD4⁺ T-cell count, but full-blown AIDS is certainly not a prerequisite. Clinical presentation varies from nephrotic-range proteinuria to subnephrotic proteinuria. The incidence of hypertension is variable, even in the face of significant renal insufficiency. The renal ultrasonographic findings in patients with HIV-AN show echogenic kidneys with preserved or enlarged size (average of >12 cm) in spite of the severe renal insufficiency. Although a number of patterns of glomerular damage have been seen in HIV-infected patients, the term HIV-AN is reserved for the characteristic pattern of focal segmental glomerulosclerosis with collapsing features and related mesangiopathies. Additional glomerulonephropathies noted in HIV-infected patients include immune complex type (mesangioproliferative), diffuse proliferative, membranous nephropathy, lupus-like nephropathy, and IgA nephropathy.⁵⁸ Immune complex glomerulonephritis is more prevalent in white patients. HIV-AN in the presence of advanced AIDS is associated with rapid-onset renal failure and death.

Infections of the renal tract in HIV-infected patients might be related to common urinary pathogens, as well as opportunistic pathogens. CMV infection involving the kidneys is generally related to systemic infection and is frequently associated with acute tubular necrosis. No direct evidence links renal CMV and HIV-AN. Prostatitis is more commonly seen in HIV-infected patients, with an increased frequency of abscess formation in patients with AIDS (Table IV). Symptoms of frequency and dysuria are commonly encountered in HIV-infected individuals. HIV and CMV might cause localized cystitis, and additionally, drug metabolite-induced urothelial damage might result in similar complaints. *Toxoplasma gondii* has been associated with bladder infection presenting as fever alone in an HIV-infected patient. Autopsy studies of patients with AIDS and systemic OIs have documented testicular involvement in 0% to 39%. A wide variety of pathogens have been identified, including HIV, CMV, *Toxoplasma gondii*, *Histoplasma capsulatum*, *Candida* species, and *Mycobacterium avium* complex (MAC). Documented OIs of the epididymis are more frequent in HIV-infected patients, and pathogens include *Candida* species, *Salmonella* species, MAC, and CMV.

Malignant lesions can affect any part of the urinary tract. Penile KS might be the presenting feature of HIV infection in up to 2% of patients.⁵⁹ An estimated 20% of patients with KS will have genital lesions.⁵⁹ The urethra might be the site for unusual malignancies, such as T- or

B-cell lymphoma. There is a greater risk of development of testicular tumors in HIV-infected patients; lesions develop in younger patients and are generally high grade. Testicular atrophy is commonly encountered in HIV-infected patients and might result from a number of insults, including prolonged fever, infection, drug toxicity, endocrine imbalance, and malnutrition.

RHEUMATOLOGIC MANIFESTATIONS

A seronegative arthritis believed to be distinct from spondyloarthropathy or rheumatoid arthritis that occurs in HIV-positive patients is well described. HIV-associated arthritis tends to be oligoarticular, affecting primarily the lower extremities. The arthritis is self-limited, and the exact cause is unclear. Homosexual men might have an increased risk for gonococcal arthritis or postinfectious reactive arthritis associated with genital or GI tract infections (Reiter's syndrome); however, data from population-based studies demonstrate that HIV-associated reactive arthritis (Reiter's syndrome) does not occur with increased frequency among HIV-infected persons.⁶⁰ Patients with this syndrome usually have human leukocyte antigen HLA-B27 and present with an asymmetric oligoarticular arthritis, primarily of the large joints of the lower extremities, and sacroiliitis. Urethritis, conjunctivitis, keratoderma blennorrhagicum, and circinate balanitis might also be present. HIV-infected patients are not at an increased risk for development of septic arthritis, the caveat being coexistent intravenous drug use, in which an increase in *Staphylococcus aureus* and *Pseudomonas* species infection might be observed. Bone and soft tissue infection caused by atypical pathogens, such as atypical mycobacteria, *Candida albicans*, and *Sporotrichosis schenckii*, is increased in the face of advanced HIV infection (CD4⁺ T-cell count <100/mm³).

Polymyositis is considered the most common of the HIV-associated myopathies. This condition is not typically associated with significant immunosuppression and might occur at any stage during the course of the disease. Typically, polymyositis presents with a subacute, progressive, proximal muscle weakness associated with an elevated creatine kinase level. The cause of HIV-associated polymyositis is unknown. Infectious pyomyositis is most frequently caused by *Staphylococcus aureus*, although other organisms have been identified, including *Salmonella enteritidis*, Microsporidia species, and *Toxoplasma gondii*. Infectious pyomyositis is rare in developed countries.

Zidovudine use was associated with myopathy within a year of its introduction.^{61,62} Zidovudine-induced myopathy is characterized by the insidious onset of myalgias, muscle tenderness, and proximal muscle weakness after a mean duration of 11 months of therapy. Symptoms tend to improve as the drug is discontinued. Creatine kinase levels return to normal within 4 weeks, and muscle strength returns within 8 weeks.

Most of the commonly described vasculitides occur in patients with HIV infection. Interestingly, a rapidly progressive focal necrotizing vasculitis of the aorta and large

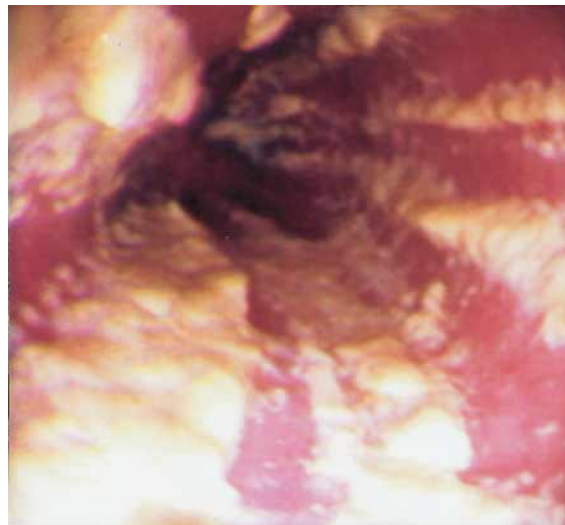


FIG 4. Severe *Candida* species esophagitis in an adolescent patient with advanced HIV-AIDS receiving HAART (poor compliance). HSV was also isolated from a biopsy sample on viral culture.

arteries with aneurysm formation and rupture resembling Takayasu arteritis has been described among Africans and North Americans with HIV infection.⁶³

Salivary gland enlargement and peripheral CD8⁺ T lymphocytosis characterize diffuse infiltrative lymphocytosis syndrome (DILS), which is often accompanied by sicca symptoms and extraglandular features in 60% of patients. Clinical presentation involves painless parotid enlargement, with a mean onset of 3 years from seropositivity to onset of symptoms. Extraglandular features include LIP, peripheral neuropathy, renal tubular acidosis, polymyositis, lymphocytic hepatitis, and lymphoma. DILS might occur in up to 8% of HIV-infected patients. Since the introduction of HAART, DILS occurs with less frequency.

GI MANIFESTATIONS

GI manifestations are common during the course of HIV infection. *Candida* species cause dysphagia or odynophagia (or both) and account for 60% to 75% of esophageal symptoms in patients with AIDS (Fig 4). Although oropharyngeal candidiasis is most commonly associated with *Candida* species esophagitis, it might also be associated with CMV or idiopathic esophageal ulcerations in the absence of *Candida* species esophagitis. In addition to *Candida* species, CMV, HIV, and HSV infection result in esophageal ulceration, albeit less frequently. CMV ulcers might be shallow or deep, single or multiple; diagnosis is confirmed by means of tissue biopsy. Esophageal ulcerations caused by HSV are usually multiple, deep, and erythematous, with overhanging edges. HIV infection might be associated with esophageal ulcers, ranging in size from 2 to 15 mm, causing odynophagia, dysphagia, and esophagospasm; symptoms and ulcers resolve spontaneously. Other infections reported to cause

TABLE V. Causes of diarrhea in patients with AIDS

Frequent	Less frequent	Unusual
Cytomegalovirus	Coccidian protozoa	Enteric protozoan
Coccidian protozoa	<i>Iso spor a belli</i>	<i>Entamoeba histolytica</i>
<i>Cryptosporidium parvum</i>	<i>Cyclo spor a cayetanensis</i>	Nematode
<i>Clostridium difficile</i>	Enterobacteriaceae	<i>Strongyloides stercoralis</i>
Enterobacteriaceae	<i>Shigella flexneri</i>	Enteroaggregative
<i>Salmonella</i> species	<i>Campylobacter jejuni</i>	<i>Escherichia coli</i>
<i>Mycobacterium avium</i> complex	Microsporidia	Gastrointestinal lymphoma
<i>Giardia lamblia</i>	<i>Enterocytozoon bienewisi</i>	Kaposi's sarcoma
Protease inhibitors (nelfinavir, zidovudine, zalcitabine, didanosine, zalcitabine)	<i>Septata intestinalis</i>	

esophageal disease in patients with AIDS include *Torulopsis glabrata*, *Cryptosporidium* species, and *Mycobacterium tuberculosis*.

The causes of abdominal pain in HIV-infected patients are diverse, and most are caused by OIs. Specific AIDS-related biliary tract disorders include acalculous cholecystitis and AIDS cholangiopathy. Acalculous cholecystitis is frequently attributable to a previous OI, such as CMV or *Cryptosporidium* species. Clinical presentation is similar to that of calculous cholecystitis and requires surgical intervention. AIDS cholangiopathy comprises a spectrum of biliary tract disorders, including papillary stenosis, sclerosing cholangitis, a combination of papillary stenosis and sclerosing cholangitis, and long extrahepatic bile duct strictures. Clinical presentation includes fever, right upper quadrant pain, diarrhea, and weight loss; the CD4⁺ T-cell count is frequently less than 200/mm³. The cause of this condition includes CMV, *Cryptosporidium* species, *Microsporidia* species, MAC, and chronic inflammation. The relative rarity of jaundice differentiates the cholangitis caused by AIDS from cholangitis of other causes. Pancreatitis was not a significant problem in HIV-infected patients until the introduction of dideoxyinosine.⁶⁴ Clinical presentation is similar to that seen in HIV-negative patients with pancreatitis, and causes include infection (CMV, MAC, and *Cryptosporidium*, *Cryptococcus*, and *Toxoplasma* species), medication (pentamidine, dideoxyinosine, dideoxycytidine, lamivudine, and trimethoprim-sulfamethoxazole), and malignancy. Hypertriglyceridemia, common in patients with AIDS, has also been associated with pancreatitis.

Diarrhea affects in excess of 50% of patients with AIDS during their illness, and the more frequently associated causes are listed in Table V. Protozoa, such as cryptosporidia and microsporidia, are most frequently the cause of diarrhea in HIV-seropositive individuals. The infection that is self-limited in immunocompetent patients might be life-threatening in patients with AIDS. *Blastocystis hominis*, another protozoan, might be isolated from stool samples of asymptomatic HIV-infected patients; most patients will either have spontaneous resolution of symptoms or successful identification of other infectious or noninfectious causes. CMV is an important cause of diarrhea and can frequently be isolated from the rectosigmoid area by means of intestinal biopsy. CMV can infect any portion of the GI tract. Pathogen-negative

diarrhea occurs in 10% to 20% of patients with AIDS, and proposed mechanisms include the presence of unidentified pathogens, abnormal motility, autonomic dysfunction, bacterial overgrowth, colonic inflammation, or HIV infection itself.

One of the well-documented side effects of PI therapy is diarrhea. Diarrhea occurs commonly with nelfinavir and zidovudine and is less common with zalcitabine. PI-induced diarrhea must be considered when patients fail to respond to therapy or when diarrhea relapses after successful treatment.

HEMATOLOGIC MANIFESTATIONS

As with any chronic disease state, HIV infection is typically associated with suppression of the bone marrow. Cytopenia is uncommon in the early stages of HIV infection, but the frequency and severity of cytopenia increase in the advanced stages of the disease. Anemia is the most common cytopenia, but frequently more than one cell line is involved.

Anemia of chronic disease is the most frequent cause of a reduced hematocrit level in HIV-infected patients; the red cells are normochromic and normocytic, frequently with anisocytosis. There is a decreased physiologic response to erythropoietin. Serum levels of TNF- α and, to a lesser extent, IL-1 β have been shown to be increased in HIV-infected patients with anemia, lymphopenia, or both.⁶⁵ Additionally, TNF- α , IL-1 β , and IFN- γ have all been shown to inhibit erythropoiesis in vitro, contributing directly to anemia of chronic disease.⁶⁶ Severe anemia might be an indicator of a coexistent OI: A hematocrit level of less than 26% has been reported to be present in 76% of patients with disseminated MAC disease. The presence of severe anemia, fever, and weight loss in a patient with advanced immunodeficiency should prompt an evaluation for MAC disease. Human parvovirus B19 infection might also result in a severe chronic anemia in HIV-infected patients. This syndrome is characterized by chronic anemia, reticulocytopenia, presence of giant pronormoblasts in the bone marrow, low levels or absence of IgG and IgM antibodies against parvovirus B19, and presence of high levels of parvovirus B19 DNA in the blood.

Anemia is frequently a complication of drug therapy in patients with AIDS. Zidovudine has been shown to sup-

press in vitro hematopoietic colony formation directly, particularly erythroid colony formation, in a dose-dependent manner. Macrocytosis develops within weeks in most patients treated with zidovudine and can be used as a marker of compliance with therapy. Erythropoietin has been demonstrated to be of clinical benefit in treating anemia caused by zidovudine therapy. Autoimmune hemolytic anemia is rare in patients with AIDS, except for those with an unusually high transfusion requirement. Reticulocytosis, which is characteristic of non-AIDS-related autoimmune hemolytic anemia, is often lacking in HIV-infected patients because of concomitant anemia of chronic disease. In addition, thrombotic thrombocytopenic purpura has been noted with increasing frequency in HIV-infected patients, with resultant fever, hemolytic anemia with the presence of schistocytes on the peripheral blood smear, and thrombocytopenia.

Thrombocytopenia might develop in HIV-infected patients and is more frequently associated with older age and lower CD4⁺ T-cell counts. An incidence of 5% was reported by Peltier et al⁶⁷ at baseline, with almost 20% of HIV-infected individuals having thrombocytopenia (platelet count <150 × 10⁹/L) during 30 subsequent months of observation. A retrospective study of 1004 patients attending an outpatient HIV clinic by Sloand et al⁶⁸ found thrombocytopenia in 21% of patients with symptomatic AIDS and 9% of asymptomatic HIV-seropositive patients. In the latter study the risk of bleeding was associated with a platelet count of less than 50 × 10⁹/L. There are 2 major components of the pathophysiology of HIV-associated thrombocytopenia: immune-mediated destruction of platelets and a defect in platelet production. In addition to HIV-associated thrombocytopenia, other secondary causes of thrombocytopenia should be considered in the differential diagnosis, including hypersplenism caused by coincident liver disease, marrow infiltration caused by OI or lymphoma, thrombotic thrombocytopenic purpura (see previously), or the myelosuppressive effects of drug therapy.

Neutropenia is frequently encountered in HIV-infected patients as a result of myelosuppressive drug therapy, and in patients with advanced AIDS, the virus has a directly suppressive effect on granulopoiesis. Rarely do antigranulocyte antibodies result in neutropenia in HIV-infected individuals. In addition to neutropenia impairment of neutrophil function, both killing and chemotaxis are encountered in these patients. Commonly used medications that are known to cause neutropenia in patients with AIDS include ganciclovir, zidovudine, trimethoprim-sulfamethoxazole, pentamidine, rifabutin, and antineoplastic chemotherapeutic agents. Neutropenia in symptomatic HIV-infected patients might respond to ART. In addition, colony-stimulating factors should be used in an attempt to reduce the incidence of OIs.

Hypergammaglobulinemia is frequently encountered in HIV-infected patients. An increase in immunoglobulin levels is caused by polyclonal B-cell proliferation and clinically associated with generalized lymphadenopathy. Typically, the increased plasma viscosity is not associat-

ed with hyperviscosity-related complications. Despite the increase in circulating immunoglobulin levels, humoral function is ordinarily suppressed in this population of patients.

HIV-RELATED MALIGNANCY

Before the widespread application of HAART, there was an estimated 310-fold increased risk for KS and a 113-fold increased risk for NHL among patients with AIDS compared with the general population.⁶⁹ Additional malignant conditions with temporal relationship to the AIDS era include angiosarcoma (37-fold), Hodgkin's disease (7.6-fold), multiple myeloma (4.5-fold), brain cancer (3.5-fold), and seminoma (2.9-fold).⁶⁹ Fortunately, there has been an impressive decline in the incidence of KS since the introduction of HAART. The United States Centers for Disease Control and Prevention reported a 50% reduction in KS with receipt of 3-drug ART, and moreover, the annual incidence of KS decreased from 4.1% to 0.7% over the study period.⁷⁰ By comparison, similar declines in the incidence of NHL, apart from

CNS lymphoma, have not been observed in the HAART era.⁷¹ Current data support a direct link between KS and infection with HHV8 or Kaposi's sarcoma herpesvirus (KSHV)⁷² related in part to the angiogenesis potential of HHV8. KS is primarily a disease of immunosuppression, most notably observed in adult patients; pediatric cases occur, albeit less frequently.⁷³ KS can be a presenting sign of HIV infection. Lesions are typically violaceous, nontender, macular, or papular, primarily involving the skin. Apart from cutaneous presentation, KS might involve lymphatic tissue, the oral cavity, the upper and lower respiratory tract, the GI tract, the abdominal viscera, and the genitalia. Lymph node and lymphatic vessel disease is frequently accompanied by significant edema local and distal to the involved site. Patients can present with disease limited to the skin, the viscera, or both. Cutaneous disease, although typical in presentation, should be differentiated from bacillary angiomatosis. Respiratory and GI tract involvement should be suspected in patients with AIDS with unexplained cough, hemoptysis, GI obstruction, perforation, or bleeding.

NHL, also referred to as AIDS-related lymphoma (ARL), is an AIDS-defining illness that is associated with advanced immunosuppression (CD4⁺ T-cell count <150 cells/mm³), whereas a CD4⁺ T-cell count approaching less than 50 cells/mm³ increases the risk for development of CNS lymphoma. The majority of ARL are of B-cell origin and high-to-intermediate grade, with an undifferentiated diffuse large cell, immunoblastic large cell, or small cell (Burkitt and Burkitt-like) histology. EBV and KSHV play a role in the pathogenesis of ARL. All primary CNS lymphomas are EBV related: 35% to 65% of systemic ARL is EBV related, whereas KSHV is associated with primary effusion lymphoma (lacking B-, T-, and hematopoietic-cell markers) and are exceedingly rare. The presenting symptoms of primary CNS lymphoma might be focal or nonfocal, including confusion,

TABLE VI. OIs in HIV-infected patients

Disease (CD4 ⁺ T cells/mm ³)	Description
PCP (<200)	Pneumocystosis in HIV-infected patients usually is a more subtle disease, with symptoms lasting from weeks to months; the organism burden is higher but lung damage is less severe.
Esophageal candidiasis (<200)	The most common symptoms of <i>Candida</i> species esophagitis include painful swallowing, a feeling of obstruction on swallowing, and substernal chest pain.
CMV disease and retinitis (<200)	The onset of CMV retinitis might be insidious or rapid. Patients complain of painless and progressive visual loss, blurring, and floaters.
Disseminated MAC (<100)	Fever, drenching night sweats, and weight loss are the hallmarks of disseminated disease in patients with AIDS.
Toxoplasmosis (<100)	Clinical manifestations of toxoplasmosis in patients with AIDS commonly reflect involvement of the brain, the lung, and the eye. Toxic encephalitis is the most common presentation of toxoplasmosis in patients with AIDS and is a frequent cause of focal CNS lesions in AIDS.
Cryptococcosis (<100)	Might present in CNS, the pulmonary tract, or skin, and acute manifestations are more common in immunosuppressed patients with AIDS.
KS (<50)	The skin is the most common first site of presentation. Other notable sites of disease include the tip of the nose, periorbital area, hard and soft palates, gingival areas of the mouth, external ear, conjunctiva, and penis.

memory loss, and lethargy. Computed tomographic imaging reveals multiple heterogeneous or ring-enhancing isodense to hyperdense lesions, with areas of low attenuation caused by necrosis. Lesions larger than 2 cm that cross the midline help differentiate ARL from CNS toxoplasmosis. Systemic ARL is characterized by extranodal involvement. Sites most commonly involved are the bone marrow (30%), the CNS (10%-20%), and the GI tract (10%-25%). Presenting symptoms can be highly variable because of the different sites of involvement; however, B symptoms are common. Primary effusion lymphoma, usually a complication of advanced HIV disease, typically presents with pericardial and pleural effusions or new-onset ascites, with negligible or absent lymphadenopathy. Hodgkin's disease is also noted with increased frequency among HIV-infected patients. The degree of immunosuppression associated with disease development is variable. Patients usually present late with advanced disease that involves extranodal sites, most often the bone marrow, and the tongue, rectum, skin, and lung might be the sites of involvement.

OPPORTUNISTIC INFECTIONS

Beginning in 1996, since the introduction of effective ART, there has been a dramatic decline in the incidence of OIs in HIV-infected patients. Consequently, OIs occur most frequently in the following clinical settings: previously undiagnosed patients, patients not taking ART, in the period after starting ART, and ineffective ART caused by viral resistance. Table VI outlines the most prevalent OIs in HIV-infected patients. Data from the Centers for Disease Control and Prevention's Adult and Adolescent Spectrum of Disease project outlines incidence trends for OIs from 1992 to 1998.⁷⁴ Briefly, PCP declined 21.5% per year from 1996 to 1998 compared with 3.4% per year from 1992 to 1995, MAC disease declined 39.9% per year from 1996 to 1998 compared with 4.7% per year from 1992 to 1995, and candidal esophagitis declined 16.7% per year from 1996 to 1998 compared with 0.2%

per year from 1992 to 1995. Ordinarily, there is an indirect correlation between the CD4⁺ T-cell count and risk for OI. Since the introduction of HAART, OIs continue to arise in patients with CD4⁺ T-cell counts less than the level for specific prophylaxis. PCP continues to be a problem in patients receiving HAART after a failure to maintain an undetectable viral load.

Deficits in the immune system caused by HIV infection increase the susceptibility to infection. Primarily, decline in CD4⁺ T cells, the pivotal cell in the immune system, results in defects in IL-2 and IFN- γ level and function. Subsequently, there is increased risk for infection from viral pathogens, as well as intracellular organisms. Apart from opportunistic pathogens, HIV-infected patients are also at increased risk for infection with bacterial pathogens. Abnormalities of B-cell function lead to reduced IgG2 production, leaving the host particularly susceptible to encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Systemic effects of immune reconstitution have become increasingly apparent in clinical practice.⁷⁵ In HIV-infected adults receiving HAART, the rapid decrease in plasma HIV RNA is characterized by a rapid, selective increase in memory CD4⁺ T lymphocytes,⁷⁶ and conversely, HIV-infected children demonstrate an increase in naive T cells in response to HAART.⁷⁷ This increase is associated with restoration of antigen-specific T-cell responses to CMV, tuberculin, and other antigens over the first 1 to 6 months of treatment, peaking at 3 months. Clinically, this manifests as worsening of certain OIs that previously were quiescent. CMV retinitis has been reported to develop with a preponderance of vitritis (unusual in CMV retinitis), without disease progression.⁷⁸ Additionally, there have been reports of patients having localized MAC infection characterized by an inflammatory response with fever and necrotizing lymphadenitis or skin lesions.⁷⁹ Similarly, the inflammatory response associated with pulmonary *Mycobacterium tuberculosis* infection might be worse after reconstitution of cellular immune function. Other opportunists, such as

Cryptosporidia parvum, might persist, despite adequate antimicrobial therapy, until reconstitution of immune function with HAART. Finally, such conditions as progressive multifocal leukoencephalopathy and KS, both associated with infectious agents (Jacob Creutzfeld virus and HHV8, respectively), have been reported to regress in association with immune reconstitution after effective HAART.^{80,81}

CONCLUSION

Before the HAART era, HIV-infected patients manifested a significant proportion of the clinical manifestations, as previously outlined. Fortunately, this is no longer the case. At-risk groups still remain; however, most important to consider are previously undiagnosed patients and noncompliant individuals. The latter group of patients is particularly prevalent among the adolescent population. Noncompliance leads to the rapid emergence of viral resistance and subsequent worsening of immune function, with the evolution of clinical manifestations. Compliance with difficult medical regimens is a major obstacle in patient management. In addition, reconstitution of immune function in patients with latent microbial infections will result in a variety of complications heretofore not seen in this immunocompromised patient population. Finally, interruptions in HAART therapy, as well as the discontinuation of prophylactic therapy, in the face of immune reconstitution will require extra vigilance by physicians caring for these complex patients.

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