

FERRIS STATE UNIVERSITY  
COLLEGE OF OPTOMETRY

THE CLASSIFICATION SYSTEM OF HIV INFECTION  
FOR THE OPTOMETRIST: WHEN TO EXPECT  
OCULAR MANIFESTATIONS IN YOUR PATIENT

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## The Classification System

Ocular involvement occurs in an estimated 70 percent of patients with the acquired immunodeficiency syndrome (AIDS).<sup>1</sup> The Centers for Disease Control and Prevention projects that one million people in the United States are infected with the human immunodeficiency virus (HIV), the retrovirus responsible for AIDS.<sup>2</sup> It is inevitable that the optometrist of today will be providing eyecare to patients who are HIV positive. In order to provide this patient population with the most appropriate care, it is important to understand the staging of the disease. With each progressive stage of HIV infection comes the possibility of an array of ocular manifestations. By knowing the most common ophthalmic disorders found in each stage, the optometrist can make a better differential diagnosis and initiate the proper treatment.

In 1993, the Centers for Disease Control revised the classification system for HIV infection based on the clinical importance of the CD4+ T-lymphocyte count in the categorization of HIV-related clinical conditions.<sup>3</sup> The T-lymphocyte is one of the principal cells of the immune system and helps to destroy foreign organisms. The human immunodeficiency retrovirus has a high affinity for the CD4 molecule found on the surface of T-lymphocytes. The uptake of HIV nucleoprotein into the T-cell allows productive replication of the virus to occur. This

replication is lytic to these infected cells and leads to a gradual decrease in CD4+ T-lymphocyte counts.<sup>4</sup> Progressive impairment of the immune system leaves the host immunocompromised thus allowing opportunistic infections to occur.<sup>5</sup>

The new CDC classification system uses CD4+ T-cell counts per microliter of blood combined with clinical conditions associated with HIV infection to form mutually exclusive subgroups. CD4+ T-lymphocyte blood counts are broken down into three categories:

- \*Category 1: greater than or equal to 500 cells/mm<sup>3</sup>
- \*Category 2: 200-499 cells/mm<sup>3</sup>
- \*Category 3: less than 200 cells/mm<sup>3</sup>

HIV infection is based on several criterion. A person is considered HIV positive if the virus is identified in host tissue, if HIV antigen is detected, or if the person tests positive on specific licensed tests for HIV antibodies. The criteria for HIV infection help to define the three clinical categories.

Category A consists of patients who have asymptomatic HIV infection, persistent generalized lymphadenopathy (PGL), or acute primary HIV infection with accompanying illness or history of acute HIV infection. Conditions defining Category B and C must not have occurred.

Category B consists of patients who have symptomatic conditions of HIV infection not included in Category C. These conditions must be attributed to HIV infection or are considered by physicians to have a clinical course or management complicated by HIV infection (see Table for conditions).

Category C includes clinical conditions listed in the AIDS surveillance case definition (see Table 1 for conditions). Once a Category C condition has occurred, the person remains in Category C.<sup>3</sup>

The AIDS surveillance case definition was developed by the CDC in 1981 and is used to diagnose AIDS cases.<sup>2</sup> The surveillance case definition has been expanded over the years and now consists of all HIV-infected persons with a CD4+ T-lymphocyte count of less than 200 cells/mm<sup>3</sup> and 23 clinical conditions (see Table 1) including, more recently, pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer.<sup>3</sup>

The matrix formed by the three ranges of CD4+ T-cells and the three clinical categories help to simplify the classification of HIV infection (see Table 1). Optometrists with an understanding of this matrix and medical records that include the stage of HIV infection can better predict ophthalmic conditions.

### The Ophthalmic Conditions

Ophthalmic disorders found in AIDS patients belong in four major categories: lesions associated with disease of the microvasculature; opportunistic infections; neoplasms; and neuro-ophthalmic disorders associated with intracranial infection and neoplasms.<sup>6</sup> At least 20 percent of AIDS patients are at risk for severe visual loss from these disorders so early and accurate diagnosis is critical.<sup>2</sup>

In Stage 1 HIV infection, ophthalmic conditions are rare. With a CD4+ T-cell count of greater than 500/mm<sup>3</sup>, the infected individual is generally healthy enough to ward off most opportunistic infections.

In Stage 2 HIV infection, neoplasms of the eye may develop. Kaposi's sarcoma, a hallmark of HIV disease, occurs in up to 24 percent of HIV infected patients and 20 percent of these may involve the eyelids, conjunctiva, and rarely, the orbit.<sup>5</sup> Kaposi's sarcoma may make its first appearance on or around the eye, with the inferior fornix being the most common site of involvement.<sup>2</sup> Lesions on the lid are more purple in appearance and may be flat or raised, while those located on the bulbar or tarsal tissue present as bright red.<sup>7</sup>

Another neoplasm, B cell lymphoma, is a growing problem among patients with AIDS. Intraocular lymphomas may be

manifested as a cellular reaction in the vitreous fluid or as an ill-defined subretinal mass.<sup>2</sup> Patients may present with anterior, nontender orbital masses or proptosis and complain of diplopia, ptosis, conjunctival edema or hemorrhage.<sup>8</sup> These space-occupying lesions frequently cause neurologic complications, primarily visual field changes.<sup>7</sup>

Herpes zoster ophthalmicus is ordinarily a disease of older or debilitated patients but is also seen in younger patients with immunodeficiency.<sup>1</sup> This disorder can develop relatively early in the course of a patient's illness, and is believed to be a poor prognostic sign for the eventual development of the full AIDS illness.<sup>6</sup> Characterized by a vesiculobullous rash over the ophthalmic branch of the trigeminal nerve, it may be an initial manifestation of HIV infection.<sup>5</sup> All levels of the visual system can be affected, giving rise to dermatitis, conjunctivitis, keratitis, iritis or uveitis, vitritis, retinitis, optic neuritis, and encephalitis.<sup>1</sup>

Varicella-zoster is the most frequently implicated virus in acute retinal necrosis (ARN).<sup>5</sup> This rapidly progressive viral uveitis is probably the second most common infection of the retina in HIV-infected patients. Multifocal, deep retinal opaque lesions throughout the peripheral retina coalesce and progress to necrosis within a few days. Retinal detachments occur early in the course of the infection and most patients have no light perception in either eye by the time they die.<sup>2</sup>

The majority of ocular manifestations do not occur until Stage 3 HIV infection has occurred. When the CD4+ T-lymphocyte

count falls below 200 cells/mm<sup>3</sup>, the patient is diagnosed as having AIDS. It is at this point that HIV-infected individuals are at a high risk of developing an extensive array of opportunistic infections and malignancies.

The most common retinal manifestation of HIV disease is AIDS retinopathy, appearing in about 70 percent of persons with advanced HIV disease. It is a noninfectious microvascular disorder characterized by the presence of cotton-wool spots, microaneurysms, retinal hemorrhages, telangiectatic vascular changes, and areas of capillary nonperfusion.

Cotton-wool spots occur in approximately 50 percent of patients and are the most consistent finding in HIV retinopathy.<sup>5</sup> These lesions of the nerve fiber layer develop in response to retinal ischemia associated with a diffuse retinal microvasculopathy.<sup>6</sup> They are fluffy, white painless lesions and are indistinguishable from those seen in diabetes, hypertension, anemia, or collagen vascular diseases.<sup>8</sup> Cotton-wool spots are most common at the posterior pole of the eye and tend to disappear over several months without any subjective vision impairment.<sup>7</sup>

Hemorrhages occur in about 20 percent of patients and are probably associated with microvascular damage.<sup>5,6</sup> Telangiectatic vascular changes associated with microaneurysms and retinal vein and artery occlusions have also been observed in patients with HIV disease.<sup>5</sup>

Of the opportunistic retinal infections found in Stage 3, toxoplasmosis is one of the most common. Patients with HIV

retinochoroidal scar, suggesting that this is an acquired infection.<sup>5</sup> Ocular toxoplasmosis associated with AIDS is frequently bilateral, and is characterized by considerable vitreous inflammation.<sup>7</sup> In toxoplasmic retinochoroiditis, the retina appears to have a thick, wet, and "indurated" appearance with sharply demarcated borders.<sup>2</sup>

Like HIV, *Treponema pallidum* is transmitted sexually. Therefore, syphilitic involvement of the posterior pole in HIV infection has been well documented.<sup>5</sup> Syphilitic retinal disease can take a variety of forms. They may be patchy infiltrates with or without retinal necrosis or a large, nonelevated, subretinal, plaque-like mass with distinctly yellow borders.<sup>2</sup> Ocular involvement may be unilateral or bilateral and is associated with evidence of CNS infection in up to 85 percent of patients.<sup>5</sup> Most patients with ocular symptoms harbor neurosyphilis as well.<sup>1</sup>

The most common systemic infection in HIV patients, *Pneumocystis pneumonia*, occurs as the initial manifestation in 63 percent of patients.<sup>5</sup> Ocular involvement, although rare, can occur in patients undergoing prophylactic therapy with aerosolized pentamidine.<sup>7</sup> Multiple, pale yellow-white choroidal lesions, usually bilateral, characterize *Pneumocystis* choroiditis. They are round or ovoid, and may coalesce to form large regions of confluent involvement with resultant choroidal necrosis.<sup>5</sup> Histologically, lesions are collections of organisms with few or no inflammatory cells and rarely reduce vision.<sup>2</sup>



Cryptococcal meningitis is a common neurologic infection in AIDS patients with visual system involvement in 40 percent of cases.<sup>1</sup> Lesions of the choroid and retina appear as multiple, discrete yellowish spots in varying sizes.<sup>5</sup> Neuro-ophthalmic problems caused by *Cryptococcus neoformans* include external ophthalmoplegia, nystagmus, papilledema, and cortical blindness.<sup>7</sup>

Cytomegalovirus (CMV) retinitis is the most common retinal opportunistic infection in patients with HIV disease. It occurs in 15 to 40 percent of patients with advanced HIV disease and is a CDC AIDS-defining illness.<sup>5</sup> The risk of CMV retinopathy is inversely related to the level of CD4+ T-lymphocytes; it is uncommon to find CMV retinitis in patients with a CD4 count of more than 40 mm<sup>3</sup>.<sup>2</sup>

CMV is a species-specific DNA virus that invades the retinal cells with resultant retinal necrosis.<sup>5</sup> CMV retinitis is essentially painless with minimal vitreous and anterior chamber inflammatory reactions.<sup>2</sup> Lesions appear in the retina as multiple granular white dots with varying amount of hemorrhage.<sup>5</sup> All lesions will have an irregular, dry-appearing granular border, which is the most clinically diagnostic feature of CMV retinopathy.<sup>2</sup> Small satellite lesions are often seen beyond the leading edge.<sup>8</sup> The lesions slowly enlarge and coalesce and appear to follow the vascular arcades.<sup>5</sup>

The location of lesions has important implications for vision. Those in the macula and around the optic nerve head are considered to be immediately vision threatening, and are

considered to be in "zone 1" of the retina. Those outside the major vascular arcade (zones 2 and 3) are not immediately threatening to central vision.<sup>2</sup>

The majority of patients have unilateral disease and 80 percent will develop bilateral disease if antiviral therapy is not initiated and maintained.<sup>7</sup> CMV retinitis demands aggressive intervention to prevent severe loss of vision; without it, lesions continue to progress and the entire retina is destroyed over several months.<sup>1</sup> There are currently two drugs available for treatment of CMV retinopathy: ganciclovir and foscarnet. With the availability of these drugs, it is now rare for patients with AIDS to die without any vision as a result of CMV retinopathy.<sup>2</sup>

Rhegmatogenous retinal detachments occur in at least 20 percent of patients with CMV retinopathy. It is generally a late complication of the disease, and the risk appears to increase with the duration of infection.<sup>2</sup> Detachments can be repaired, but final visual acuity is often poor.<sup>7</sup> Surgery should be considered in all patients with bilateral CMV retinitis since the eye with the retinal detachment may ultimately be the better seeing eye.<sup>5</sup>

The number one reason for suicide among HIV-infected individuals is said to be the fear of blindness.<sup>2</sup> Therefore, the challenge for eyecare professionals is to reduce the risk of vision loss by properly diagnosing and treating HIV-related eye disorders. By helping to maintain vision in HIV-infected patients, optometrists play a major role in preserving their quality of life.

**Table 1. AIDS Surveillance Case Definition for Adolescents and Adults: 1993 (MMWR 41:1-9, 1992)**

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, PGL, or Acute HIV Infection	B Symptomatic (not A or C) <sup>b</sup>	C <sup>a</sup> AIDS Indicator Condition (1987)
1. >500/mm <sup>3</sup> (≥29%)	A 1	B 1	C 1
2. 200-499/mm <sup>3</sup> (14-28%)	A 2	B 2	C 2
3. <200/mm <sup>3</sup> (<14%)	A 3	B 3	C 3

<sup>a</sup>All patients in categories A3, B3, C1-C3 are reported as AIDS based on prior AIDS-indicator conditions (see below) and/or a CD4 cell count of <200/mm<sup>3</sup>. AIDS indicator conditions include three new entries added to the 1987 case definition (MMWR 36:15, 1987): recurrent bacterial pneumonia, invasive cervical cancer, and pulmonary tuberculosis.

<sup>b</sup>Symptomatic conditions not included in category C that (a) are attributed to HIV infection or indicate a defect in cell-mediated immunity or (b) conditions are considered to have a clinical course or to require management that is complicated by HIV infection. Examples of B conditions include but are not limited to bacillary angiomatosis; thrush; vulvovaginal candidiasis that is persistent, frequent, or poorly responsive to therapy; cervical dysplasia (moderate or severe); cervical carcinoma in situ; constitutional symptoms such as fever (38.5°C) or diarrhea for >1 month; oral hairy leukoplakia; herpes zoster involving two episodes or >1 dermatome; ITP; listeriosis; PID (especially if complicated by a tubo-ovarian abscess); peripheral neuropathy.

#### Indicator Conditions in Case Definition of AIDS (1987-1992, Adults)

Candidiasis of esophagus, trachea, bronchi, or lungs  
 Cervical cancer, invasive<sup>c,d</sup>  
 Coccidioidomycosis, extrapulmonary<sup>c</sup>  
 Cryptococcosis, extrapulmonary  
 Cryptosporidiosis with diarrhea for >1 mo  
 Cytomegalovirus of any organ other than liver, spleen, or lymph nodes  
 Herpes simplex with mucocutaneous ulcer for >1 mo or bronchitis, pneumonitis, esophagitis  
 Histoplasmosis, extrapulmonary<sup>c</sup>  
 HIV-associated dementia<sup>a</sup>: disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living  
 HIV-associated wasting<sup>c</sup>: involuntary weight loss of >10% of baseline plus chronic diarrhea (≥2 loose stools/day for ≥30 days) or chronic weakness and documented enigmatic fever for ≥30 days  
 Isosporosis with diarrhea for >1 month<sup>c</sup>  
 Kaposi's sarcoma in patient younger than 60 (or older than 60<sup>c</sup>)  
 Lymphoma of brain in patient younger than 60 (or older than 60<sup>c</sup>)  
 Lymphoma, non-Hodgkin's of B cell or unknown immunologic phenotype and histology showing small, noncleaved lymphoma or immunoblastic sarcoma  
*Mycobacterium avium* or *M. kansasii*, disseminated  
*Mycobacterium tuberculosis*, disseminated<sup>c</sup>  
*Mycobacterium tuberculosis*, pulmonary<sup>c,d</sup>  
 Nocardiosis<sup>c</sup>  
*Pneumocystis carinii* pneumonia  
 Pneumonia, recurrent-bacterial<sup>c,d</sup>  
 Progressive multifocal leukoencephalopathy  
*Salmonella* septicemia (nontyphoid), recurrent<sup>c</sup>  
 Strongyloidosis, extraintestinal  
 Toxoplasmosis of internal organ

<sup>a</sup>Requires positive HIV serology.

<sup>d</sup>Added in the revised case definition 1993.

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