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## Fundus changes in AIDS

### Abstract

AIDS is a devastating disease that affects 28,000 people in the United States and has claimed over 16,000 lives. More than 270,000 persons are expected to contract the syndrome by 1991. Most AIDS patients are male homosexuals, intravenous drug users, of Haitian descent, or hemophiliacs. The causative agent in AIDS is the retrovirus HTLV-III/LAV. Infection with the AIDS virus causes a major collapse of the T-cell arm of the immune system, rendering the host vulnerable to a multitude of opportunistic infections and neoplasms. The most common fundus change observed in AIDS is cotton-wool spots. Cytomegalovirus (CMV) retinitis is the most damaging ocular finding since it may lead to total retinal atrophy. Retinal hemorrhages, Roth spots, and periphlebitis are manifestations of microvascular alterations that occur in AIDS. Opportunistic infections by *Toxoplasma* sp. and *Mycobacterium* sp. may also be manifest.

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# FUNDUS CHANGES IN AIDS

By: Anthony Lee Baumgartner

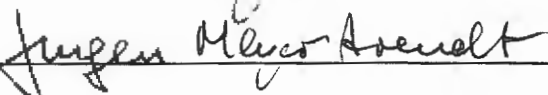
Advisor: Jurgen Meyer-Arendt, M.D.

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April 1987

**SIGNATURE PAGE**

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## BIOGRAPHICAL PAGE

A Montana native, the author obtained his bachelor's degree at Carroll College in Helena, Montana, in 1983. Graduating *Magna cum laude*, he earned a degree in biology with a minor in chemistry.

Following graduation from Pacific University College of Optometry, Dr. Baumgartner plans to pursue family practice optometry in his home state.

## Abstract

AIDS is a devastating disease that affects 28,000 people in the United States and has claimed over 16,000 lives. More than 270,000 persons are expected to contract the syndrome by 1991. Most AIDS patients are male homosexuals, intravenous drug users, of Haitian descent, or hemophiliacs. The causative agent in AIDS is the retrovirus HTLV-III/LAV. Infection with the AIDS virus causes a major collapse of the T-cell arm of the immune system, rendering the host vulnerable to a multitude of opportunistic infections and neoplasms.

The most common fundus change observed in AIDS is cotton-wool spots. Cytomegalovirus (CMV) retinitis is the most damaging ocular finding since it may lead to total retinal atrophy. Retinal hemorrhages, Roth spots, and periphlebitis are manifestations of microvascular alterations that occur in AIDS. Opportunistic infections by *Toxoplasma sp.* and *Mycobacterium sp.* may also be manifest.

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## INTRODUCTION

No epidemic in modern history has gained the notoriety of the acquired immunodeficiency syndrome (AIDS). Since its recognition as a public health problem in 1980, AIDS has claimed over 16,000 lives. As of December 8, 1986, over 28,000 cases of AIDS had been documented by the Center for Disease Control (CDC).<sup>1</sup> This figure represents a marked contrast to the 110 AIDS cases that had been reported by September of 1981. The AIDS crisis is expected to deepen in the future. Experts project that there will be nearly 270,000 cases of AIDS in the United States by 1991.<sup>2</sup>

Ninety-three percent of those infected with the AIDS virus are men. However, an increasing number of women and children are contracting the disease.<sup>1</sup> Most reported cases of the syndrome fall into four major risk groups. These groups include male homosexuals, intravenous drug users, persons of Haitian origin, and persons dependent upon donated blood products.<sup>3</sup> The majority of AIDS cases afflict homosexual or bisexual males.

The retrovirus that is believed to be the causative agent in acquired immunodeficiency syndrome was first isolated by F. Barre-Sinoussi and coworkers at the Pasteur Institute in 1983.<sup>4</sup> The French team labeled their isolate lymphadenopathy virus (LAV).

Shortly after the LAV isolation, Gallo and a group of researchers at the Cancer Institute reported the isolation of a similar virus which they

called human T-cell lymphotropic virus type III (HTLV-III).<sup>5</sup> It appears that LAV and HTLV-III represent the same virus. The transmission of either of the two viruses may cause AIDS.

Three modes of transmission are responsible for the vast majority of HTLV-III/LAV infections.<sup>6</sup> Exposure to infected semen during sexual contact accounts for most AIDS virus infections. Transmission of the virus also occurs via intravenous injections using contaminated needles. The administration of blood products can cause AIDS, especially factor VIII preparations for hemophiliacs.<sup>6</sup> Experts agree that the transmission of HTLV-III/LAV seems to be similar to that of the hepatitis B virus.<sup>7</sup>

The major clinical finding in a patient infected with AIDS is collapse of the body's immune system. A severe dysfunction of the T-cell arm of the system has been found to occur.<sup>8</sup> This dysfunction includes a decrease in the number of T-helper cells and a relative increase in the number of circulating T-suppressor cells. Humoral immune function appears to be intact in AIDS.<sup>8</sup>

Since the immune system is compromised, the AIDS patient is vulnerable to a host of opportunistic infections and neoplasms that are normally prevented. Systemic manifestations of AIDS include infections by *Pneumocystis carinii*, *Cytomegalovirus*(CMV), *Herpes simplex*, hepatitis B, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Candida albicans*, *Cryptococcus neoformans*, and toxoplasmosis.<sup>9</sup> The most common of these systemic afflictions is *Pneumocystis carinii* pneumonia, which affects 51 percent of AIDS patients.<sup>3</sup>

In addition to the multitude of systemic complications, 75 to 90 percent of AIDS patients have ocular signs attributable to the syndrome.<sup>10,11</sup> The AIDS virus has been isolated from nearly all ocular fluids and tissues. Fujikowa and coworkers reported the isolation of

HTLV-III from the tears of an AIDS patient.<sup>12</sup> Fujikowa has also noted the culture of the virus from the vitreous of one patient with the syndrome. Other teams of researchers have isolated the AIDS virus from the cornea and conjunctiva of patients with AIDS.<sup>13,14</sup> Recently, Tervo reported the recovery of HTLV-III from contact lenses that had been worn overnight by an AIDS patient.<sup>15</sup> The isolation of the virus from these media is indicative of the syndrome's affinity for the eye.

Ocular manifestations of AIDS include fundus changes, anterior segment opportunistic infections, neoplasms, and central nervous system involvement. Anterior segment infections include herpes simplex and herpes zoster. Conjunctival Kaposi's sarcoma is a common vascular lesion affecting AIDS patients. Central nervous system fungal infections may cause extraocular muscle paresis. The frequency of these ophthalmic manifestations indicates that many patients with AIDS will seek treatment from an eye doctor. Thus, the optometrist should be aware of the ocular conditions associated with the syndrome. This paper will focus on the fundus changes associated with the acquired immunodeficiency syndrome.

## FUNDUS CHANGES

**Cotton-wool spots.** The most common ophthalmoscopic finding in AIDS is cotton-wool spots (see Figure 1). Between 25 and 92 percent of persons with the syndrome present with these white opacities.<sup>17,18</sup> Retinal cotton-wool lesions associated with AIDS have an affinity for the posterior pole around the optic nerve head and vascular arcades.<sup>9,11</sup>

The precise etiology of cotton-wool spots in AIDS remains unclear.<sup>19</sup> The spots appear to be identical to those found in a number of systemic



Figure 1. Cotton-wool spots.

diseases including diabetes mellitus, hypertension, leukemia, and anemia.<sup>17</sup> Therefore, the presence of these conditions must be ruled out.

M<sup>C</sup>Leod describes the morphology of cotton-wool spots as the accumulation of cytoplasmic organelles in nerve fiber layer axons resulting from obstruction of axoplasmic transport.<sup>20</sup> This obstruction seems to occur at the border areas of retinal ischemia. Thus, the presence of cotton-wool spots seems to indicate a microvascular alteration in AIDS.<sup>10</sup>

Kwok postulates that the cotton-wool patches in AIDS occur as a direct result of *Pneumocystis carinii* infection of the retina.<sup>21</sup> Holland suggests that the lesions might result from a focal immune-complex vasculitis secondary to chronic cytomegalovirus infection.<sup>22</sup> However, neither of these postulates have been substantiated greatly in the

literature.

The appearance of cotton-wool patches in AIDS is often followed by spontaneous disappearance. In a prospective study, Freeman and associates reported that the appearance and disappearance of cotton-wool spots did not seem to be related to the general medical status of AIDS patients.<sup>23</sup> Cotton-wool spots were observed to appear in some patients as their clinical status improved and others when it deteriorated. This transient nature of cotton-wool patches serves as an important differential diagnostic factor. Cotton-wool lesions may be distinguished from early cytomegalovirus retinitis, another common retinal manifestation of AIDS, by lack of enlargement during serial observation.<sup>10</sup>

**Cytomegalovirus (CMV) retinitis.** The major cause of visual loss in AIDS is CMV retinitis.<sup>10</sup> CMV retinitis is often preceded by cotton-wool lesions, but a recent study suggests that CMV infection plays no role in the production of cotton-wool spots in AIDS.<sup>24</sup>

CMV retinitis results from an opportunistic infection that affects all layers of the retina. Early lesions of CMV appear as areas of dry, white, granular retinal opacifications adjacent to the major retinal vessels.<sup>16</sup> Initially, these manifestations may resemble cotton-wool spots, but are more grainy and dense in appearance and lie deeper than cotton-wool spots.<sup>18,23</sup> The lesions do not disappear spontaneously but may undergo periods of remission.

The early granular lesions eventually coalesce and spread. Histologically, these retinal lesions are characterized by coagulative necrosis of the retina.<sup>22</sup> Large cells containing inclusion bodies are found in the retinal layers. Retinal hemorrhage accompanies the necrosis and gives the disease its characteristic "brushfire" appearance.<sup>25</sup> The end-stage of CMV retinitis is total retinal atrophy. Once the retina is

totally atrophic, no CMV inclusions are demonstrable by electron microscopy.<sup>10</sup>

In addition to cotton-wool spots, differential diagnosis of CMV retinitis includes toxoplasmosis retinitis, acute retinal necrosis, and syphilis.<sup>11</sup> Toxoplasmosis usually occurs with a vitritis. Acute retinal necrosis is of sudden onset. Syphilis can mimic several neuroretinal diseases.

The accuracy of the diagnosis of CMV retinitis may be increased by the isolation of cytomegalovirus from the blood, urine, or eye.<sup>26</sup> However, active CMV retinitis cannot be excluded because of the absence of serologic or microbiologic evidence of CMV. Neuwirth described the diagnosis of CMV retinitis though he could not isolate the virus serologically or culture it from other organs.<sup>27</sup>

Treatment of cytomegalovirus retinitis has been frustrating. Conventional antiviral agents such as vidarabine and acyclovir have proven ineffective.<sup>11</sup> Recently, there have been encouraging reports concerning the effectiveness of other antiviral agents. Palestine noted chemotherapeutic success with dihydroxy propoxymethyl guanine.<sup>26</sup> In the study, CMV retinitis clinically responded to chemotherapy in 12 of 14 affected eyes. Palestine emphasizes that the agent merely suppresses but does not eliminate the virus.

The prognosis is very poor for the AIDS patient with CMV retinitis. One study reported that death occurred six weeks after the diagnosis of the condition.<sup>8</sup> Other authors cited mortality at four months after the diagnosis of CMV retinitis.<sup>18</sup> Hence, the "brushfire" appearance is of great concern when monitoring the AIDS patient.

**Retinal hemorrhages.** Another common ophthalmoscopic observation in AIDS is retinal hemorrhage. Up to 92 percent of AIDS

patients present with these vascular lesions.<sup>18</sup> The majority of hemorrhages found in AIDS are flame-shaped hemorrhages of the nerve fiber layer.<sup>18,28</sup> Deeper blot-type hemorrhages have also been observed in AIDS patients.<sup>18</sup> These hemorrhages may be isolated, or occur with cotton-wool spots. Like cotton-wool spots, hemorrhages often resolve spontaneously, and are not indicative of the patients' clinical status.<sup>16,23</sup>

When hemorrhages are observed in a suspected AIDS case, other systemic conditions known to cause retinal hemorrhage must be ruled out. These conditions include hypertension, collagen vascular disease, renal failure, and diabetes.

Fluorescein-angiographic study has demonstrated microvascular abnormalities in AIDS that are similar to the changes found in diabetes mellitus.<sup>18</sup> Microaneurysms, telangiectasias, focal areas of nonperfusion, and capillary loss have been documented in the retinas of AIDS patients. In one angiographic study, microvascular retinopathy was observed in all patients examined.<sup>18</sup>

**Roth spots.** Retinal hemorrhages in AIDS often have white central areas called Roth spots. In addition to AIDS, Roth spots occur with bacterial endocarditis, leukemia, anoxia, and anemia.<sup>29</sup>

Until recently, it was largely agreed that Roth spots represented a central accumulation of leukocytes in the hemorrhage. Contemporary literature suggests that these white central opacifications represent a fibrin thrombus.<sup>29</sup> When a patient presents with retinal hemorrhages and Roth spots, there may be few, if any, ocular symptoms.<sup>16</sup>

**Periphlebitis.** An additional vascular anomaly that has been described in AIDS is retinal periphlebitis.<sup>8,30</sup> This perivasculitis is characterized by dense white sheathing of the branches of the central retinal vein. Vessel sheathing extends to the peripheral retina and may

affect some retinal arterioles.

Retinal periphlebitis in AIDS is believed to be part of the noninfectious retinopathy of the syndrome.<sup>30</sup> Careful examinations of the peripheral retina in patients with AIDS could identify subtle perivascular sheathing as an early ocular finding.

**Toxoplasmosis.** Although profuse systemic toxoplasmosis is common in AIDS, ocular infection by *Toxoplasma gondii* is rare.<sup>31,32</sup> The pathogenesis of ocular toxoplasmosis in AIDS is different than that of typical ocular toxoplasmosis.<sup>32</sup>

Ocular toxoplasmosis typically presents as a focal necrotizing retinochoroiditis. The presentation of toxoplasmosis in AIDS is diffuse and resembles acute retinal necrosis. The presence of vitritis with ocular toxoplasmosis differentiates this condition from acute retinal necrosis.

**Choroidal granulomas.** Noncaseating granulomatous inflammation of the choroid has been described in AIDS.<sup>8,24</sup> These granulomas consisted of macrophages with intracellular acid-fast bacilli consistent with *Mycobacterium avium intracellulare*.

Nonreactive *Mycobacterium tuberculosis* has also been described in AIDS.<sup>33</sup> Croxatto and coworkers noted the presence of miliary tubercles in the choroid of a homosexual with AIDS.

## SUMMARY

Since early visual symptoms may be absent in AIDS, it is the role of the optometrist to recognize initial ocular signs of the disease. In addition to the fundus changes described, recognition of anterior segment manifestations of AIDS in young persons should alert the doctor. A thorough case history is essential when a patient presents with ocular



findings indicative of AIDS. Proper diagnosis is also necessary to avoid inappropriate corticosteroid therapy of opportunistic infections.

In March of 1987, the FDA approved the antiviral drug azidothymidine (AZT) for the treatment of AIDS patients. Successful clinical trials demonstrated the drug's ability to prolong the lives of patients with the syndrome. Consequently, the prevalence of ocular AIDS is expected to increase. Hence, the eye doctor should be aware of the ocular changes that are manifest in the disease.

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