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Ocular Involvement in AIDS

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The acquired immunodeficiency syndrome (AIDS) is no longer a rare disease afflicting only a small segment of the world population. It has been recognised to occur in most countries of the world; and, as of October, 1987, there had been over 1000 cases reported in the United Kingdom.[1] Despite scientific determination of the causitive agent, better understanding of the pathogenesis of the clinical disease, and clarification of the risk factors involved, the epidemic continues to spread. As physicians, we are destined to have to deal with the ravages of AIDS increasingly in the future.

The first case reports of what became known as AIDS appeared in 1981.[2] Ophthalmic lesions were noted in the UCLA patients from the very beginning; they were reported by Holland and his associates in 1982.[3] Since then, clinical and autopsy studies have confirmed that clinically apparent ophthalmic disorders are common, occurring in 40% to 94% of surveyed patients with AIDS.[3–16] Often, they result in significant morbidity and may lead to severe visual impairment or blindness.

The ophthalmic complications of AIDS sort naturally into four categories: the lesions of a primary retinal microvascular disease of unknown cause; opportunistic infections of the eye; neoplasms of the eye and adnexa; and neuro ophthalmic abnormalities.

Retinal Vascular Disease

Retinal microvascular disease is the most common ophthalmic manifestation of AIDS.[15,17] The clinical features include: cotton–wool spots, retinal haemorrhages, microaneurysms, and intraretinal microvascular abnormalities. Autopsy studies of AIDS patients indicate that capillary changes in the retina are almost always present. These include swelling of endothelial cells, thickening of the basal lamina, degeneration and loss of pericytes, and narrowing of capillary lumens.[15] The pathogenetic mechanisms behind these changes are not known, however HIV has recently been shown to be present in retinal tissue.[18] Viral (HIV–1) antigen was found in the internal and external nuclear layers and the external plexiform layer as well as in the capillary endothelial cells. Possibly, the endothelial infection results in capillary alterations and occlusions. Another possibility is the deposition of circulating immune complexes, which have arisen from systemic infections, in the retinal capillaries.

Cotton–wool spots (CWS)

Having a similar ophthalmoscopic apppearance to those seen in other retinal capillary occlusive diseases, cotton–wool spots in AIDS patients are the result of obstruction of blood flow, ischaemia, and stasis of axoplasmic flow in the nerve fibre layer of the retina. The consequent accumulation of cellular organelles within the axon cause localised patches of swelling and opacification in the superficial retina which give the lesions their typical appearance (Fig. 1). They occur in the posterior pole, usually along the major vascular arcades, and they may be single or multiple. Their appearance is made even more striking by the absence of other extensive vascular changes or retinal abnormalities. The usual clinical course of CWP is to

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develop over a few days and then to regress over a period of 4 to 6 weeks. They are asymptomatic and, because of their transient nature, may only be found ophthalmoscopically with multiple examinations. Distinguishing CWP from early CMV retinopathy may be difficult. Serial observations, however, will clarify the diagnosis as CWP invariably will fade with time and CMV retinopathy will worsen.

Cotton–wool spots may also be seen in the AIDS related complex (ARC) and do not establish the diagnosis of AIDS in a patient with known HIV infection. Their prognostic significance is unclear at this time. Pathologically, CWP in AIDS patients are identical to those seen in other diseases such as diabetes or hypertension. Although one case report related cotton–wool spots to the prescence of *Pneumocystis carinii* cysts in the adjacent retina, the bulk of pathological and clinical evidence does not indicate that this organism plays a direct aetiologic role in the development of these lesions.[19,20]

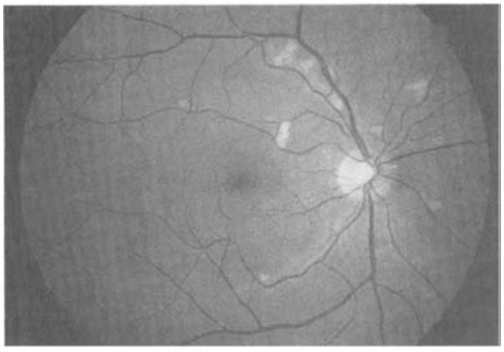

Fig. 1. *Cotton-wool patches in AIDS.*

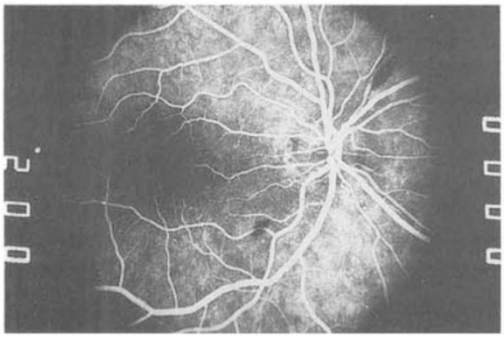

Fig. 2. *Fluorescein angiography demonstrating the retinal microvascular disease of AIDS. (Reprinted with permission).*

Other microvascular abnormalities.
Although less dramatic than the CWP, retinal haemorrhages, capillary microaneurysms, and intraretinal microvascular abnormalities (IRMA), are frequently seen ophthalmoscopically and on fluorescein angiography (Fig. 2). These changes are often subtle and less easily appreciated than CWP and have been reported in 15% to 40% of patients.[9,14,21] They are also located primarily in the posterior pole and are generally asymptomatic and without known prognostic implications.

Ischaemic maculopathy
Capillary occlusion may rarely involve the perifoveolar capillaries resulting in visual loss. This has been observed pathologically and clinically and is characterised by retinal oedema and exudates surrounding the fovea in association with multiple CWP.[15] We have observed one patient who developed perifoveal capillary occlusion and the formation of bilateral macular holes.

Opportunistic Ocular Infections
A number of organisms have been found to cause ocular infections which can involve the anterior segment, the posterior segment or the ocular adnexae.

Anterior Segment Infections
Virus Infections
Herpes simplex may produce corneal epithelial lesions which can be prolonged and severe. Response to topical antivirals is good, but recurrence is common as it is in most AIDS related infections. CMV may infect the conjunctiva, but it is probably not a cause of significant morbidity. HIV has not yet been implicated in any ocular disease.

Other infections.
Patients with corneas compromised by viral infection or adnexal problems may develop secondary bacterial infections. Corneal ulcers caused by *Candida albicans* and *Candida parapsilosis* have been reported.[22,23]

Posterior Segment Infections

Cytomegalovirus (CMV) retinopathy

By far the most commonest and most clinically significant opportunistic infection of the eye is that caused by CMV. CMV is a ubiquitous virus; nearly 80% of adults in the United States have complement–fixing antibody to it by the age of 40.[24] Other than in fetuses, it is not known to cause retinal infection in the immunocompetent host. Prior to the advent of AIDS, CMV retinopathy was seen only in immunocompromised patients and infants with cytomegalic inclusion disease. In contrast, the frequency of the retinal infection in AIDS patients has been reported to be as high as 46%.[15,17] One can expect that improvements in the general medical care of AIDS patients with extension of life–expectancy will lead to a greater at–risk period and higher liklihood of acquiring this complication. It has been suggested that the retinal microvasculopathy of AIDS may predispose patients to retinal infection with CMV.[14,15]

CMV retinopathy is characterised by single or multiple zones of yellowish–white retinal opacification with irregular, feathered borders (Fig. 3). Numerous, tiny white dots may be visible within the substance of the clouded regions giving it a mottled look. They are more evident at the edges of the lesions where the surrounding normal retina is transparent. Retinal haemorrhage usually accompanies the infection and may occur at the edges of the lesions or within their substance. Vascular sheathing may also be seen. Lesions may occur anywhere in the fundus from the ora serrata to the posterior pole, but the region of the vascular arcades is often where the infection is first noted. Typically, there is a centrifugal advance into the normal surrounding retina, leaving behind necrotic, thin tissue which has a stippled appearance and which is prone to develop retinal breaks. Unchecked, the lesions will spread to involve all of the retina. The rate of advance depends on the virulence of the organism and the resitance of the host. Diagnosis is rarely a problem because of the distinctive appearance of the lesions and their typical course.

Patients are often asymptomatic until the lesions affect the fovea or the optic nerve with direct infection or extension of oedema fluid. There is no pain associated with the infection and the anterior segment is usually quiet with the exception of minimal aqueous humour flare and cell reaction. Rarely, haemorrhage may extend into the vitreous and give rise to the sensation of "floaters". Retinal detatchment is attended with the usual symptom of visual field loss.

Pathologically, the retinal lesions are characterised by widespread, full–thickness necrosis.[9] There is remarkably little accompanying inflammation except for occasional lymphocytes and a few foci of acute inflammatory cells; hence, the preferred name for this entity is CMV retinopathy rather than retinitis. Scattered retinal haemorrhages may be noted and the adjacent vitreous humour is usually clear. The underlying choroid does not appear to be invaded by the infection although there may be a few foci of inflammatory cells there. Chronic lesions show marked replacement of the retina with a thin gliotic membrane.

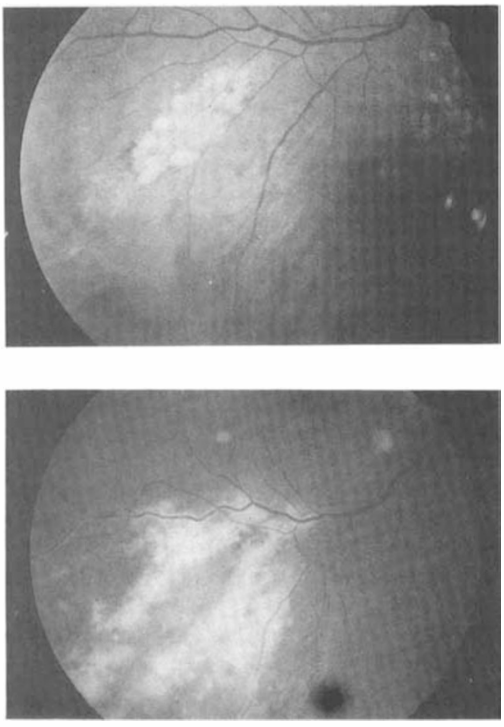

Fig. 3. *Cytomegalovirus retinopathy in AIDS. a. Initial lesion. b. Later, showing centrifugal enlargement.*

Treatment of CMV retinopathy is limited to immunomodulating drugs and to antiviral therapy. Ganciclovir, a recently introduced antiviral with activity against CMV, has been used with some success to halt progressive CMV retinopathy,[21,25–28] however it does not eradicate the virus and CMV can be recovered from the retina after treatment.[29] Because the disease will recur inevitably from the borders of the old lesions when the drug is withdrawn, it is necessary to keep patients on long–term, low dose, maintenance. This is complicated by the need for intravenous administration of ganciclovir and the tendency of the drug to further supress bone marrow function.[28] The commonest cause of theraputic failure with ganciclovir is drug induced, life-threatening neutropenia. Furthermore, some pateints continue to lose vision from progressive retinopathy despite continued low-dose maintenance. This is undoubtedly due to the persistance of live virus in the retina despite favourable clinical response to the initial treatment regimen.

Trisodium phosphonoformate hexahydrate is another antiviral drug with activity against CMV that is being investigated for the treatment of CMV retinopathy.[30] Its efficacy appears to be similar to that of ganciclovir and it also must be given as maintenance therapy to prevent reactivation of infection. Its major toxicity is renal.

Intravitreous injection of ganciclovir has been used in an attempt to achieve the theraputic benefit without the side effect of bone marrow suppression.[31] The pharmacokinetics of the drug administered in this fashion are poorly understood and the ideal dosage regimes and indications are under investigation. Our experience at UCLA has been limited to a small number of patients in which there was no other option to attempt to salvage vision. Our impression, at this time, is that progression of the disease can be slowed somewhat, but that morbidity of the treatment is considerable.

Rhegmatogenous retinal detachment is a severe complication of CMV retinopathy and other opportunistic necrotising retinopathies (Fig. 4).[32] Retinal breaks are likely to form in the regions of extreme retinal thinning even in the absence of vitreous traction. Untreated, blindness is the inevitable result of rhegmatogenous retinal detachment. Unfortunately, retinal detachment is often bilateral. In our series at UCLA, 81.5% of patients who developed retinal detachments had these in both eyes.[32] Even with successful surgical reattachment, the visual prognosis is poor because of the continuing infection and relentless retinal necrosis. Nevertheless, if the infection can be controlled by the use of antiviral medications and the retina is reatachable with modern vitreoretinal techniques, one should consider operating on those patients who would otherwise be blind without intervention. Limited, but useful vision may be salvagable in a few patients and provide some solace for the remaining months of their lives.

Rhegmatogenous retinal detachment in AIDS patients are unique in that there are usually large areas of retinal necrosis in which numerous retinal breaks may occur. Once these areas detach, they must be considered to be retinal breaks and be treated as such. Pneumatic retinopexy is rarely indicated because of this phenenomenon. Scleral buckling alone should be reserved for those patients in which the pathology is limited. Most often, vitrectomy, gas-fluid exchange, internal drainage of subretinal fluid, internal photocoagulation, and injection of long-lasting gas or silicone oil. is needed to have any chance of achieving enduring retinal reattachment. The late complications of silicone oil are less of a concern in these patients with limited life-expectancy.

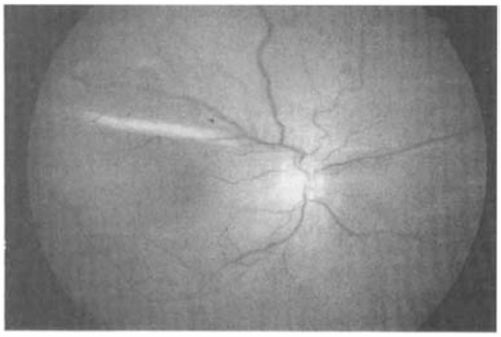

Fig. 4. *Rhegmatogenous retinal detachment following necrotising opportunistic retinopathy in AIDS.*

Other viral retinitides.
Herpes simplex also causes retinal infection in AIDS patients, but it occurs with much less frequency than CMV.[15,33] Herpes simplex virus has been found in the retina at autopsy and we have seen three patients with widespread necrotising retinitis which were presumed to be from this organism since the clinical picture was not similar to CMV retinopathy and the patients all suffered from cutaneous herpes simplex infections.[32]

The retinal lesions appeared suddenly as numerous grayish patches, 2 to 3 mm in diameter, located in the mid-periphery (Fig. 5). Over a span of 2 or 3 days these discontinous blotches coallesced rapidly into zones extending from the vascular arcades nearly to the ora serrata. Retinal haemorrhages were seen, but were not extensive until late in the course. The vitreous was clear. With time, the retinal lesions became more opaque and then began to thin and appear to dissolve. With this development, numerous retinal holes formed and the retina detached. The disease was bilateral in all patients. Treatment with acyclovir intravenously appeared to halt progression of the lesions acutely in one patient; however, as with CMV retinopathy, they would reactivate at their edges on cessation of intravenous therapy. In this individual, oral acyclovir seemed to inhibit spread of the infection slightly. Herpes zoster infection of the retina, producing a clinical appearance similar to the acute retinal necrosis syndrome, has been seen in a patient with AIDS.[34] It is likely that other viral infections of the retina will be discovered as our dealing with this disease increases.

Although HIV has been found to infect the retina, there has been no specific correlation with clinical retinitis or retinopathy. The role of this virus in initiating or facillitating other infections is yet to be clarified.

Ocular toxoplasmosis
Whereas toxoplasmosis is a common intracranial infection in AIDS patients, few reports of ocular involvement have appeared; they account for only 1-3% of ocular infection in patients with AIDS.[34] In contrast to toxoplasmic chorioretinitis occurring in an immunocompetent host, the retinitis is rarely associated with preexisting retinochoroidal scars, suggesting that is an acquired infection or is disseminated from a non-ocular site.

Retinal lesions present a variable clinical picture. They may be single, multiple, unilateral, bilateral, focal or diffuse. There may be little vitreous reaction or there may be severe vitritis and even anterior segment inflammation. It is unlikely that the lesions of toxoplasmosis would be confused with those of CMV. They lack the grainy appearance and associated haemorrhage and do not tend to spread in the characteristic "brush-fire" manner as do those of the viral infection. When ocular toxoplasmosis is suspected, patients should be evaluated for central nervous system involvement, especially if there are any neurological signs or change in mentation (Fig. 6).

Antiparasitic therapy may be effective in limiting visual loss and in treating the neurologic manifestations, but continued

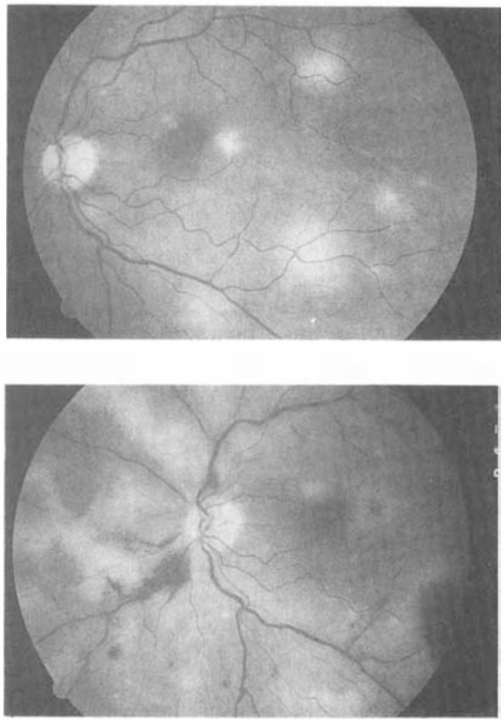

Fig. 5. *Herpes-associated retinopathy in AIDS. a. Initial lesion b. 48 hours later.*

treatment is necessary to prevent reactivation of the disease.

Candida Chorioretinitis

Although mucocutaneous candidiasis is very common in patients with HIV infection, candida chorioretinitis has been reported only rarely.[35,36] Apparently, it does not occur in the absence of other factors which favour endogenous spread of fungi to the eye, such as intravenous drug abuse or the presence of an indwelling intravenous catheter.

Syphilis

In AIDS patients Treponema pallidum can cause severe disease. Luetic retinitis and optic neuritis have been reported.[37,38] The retinal lesions are yellowish in colour and are located deeply within the tissue. They may be widespread and may result in significant retinal necrosis and ultimate retinal break formation and retinal detachment.[32] Resolution with penicilin therapy is the rule, but recurrence is common after treatment with doses felt to be adequate in the immunocompetent host.

Other infections

A number of infectious agents, including *Mycobacterium avium-intracellulare, Cryptococcus neoformans, Histoplasma capsulatum,* and *Pneumocystis carinii,* have been found in the eye at autopsy in patients with disseminated disease.[34] The clinical manefestations of these organisms have yet to be deliniated. Effective treatment with standard anti-microbial therapy may be limited to the extent of the infection and the severe immunosuppression of AIDS.

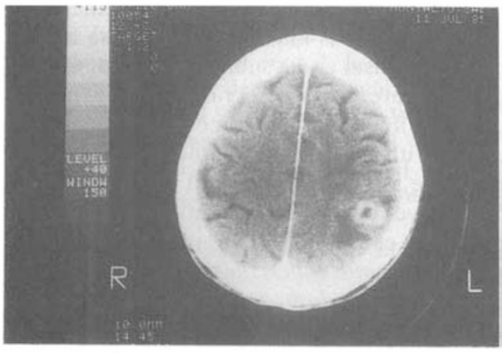

Fig. 6. *Computerised axial tomography revealing cerebal toxoplasmic necrotising granuloma in AIDS patient with toxoplasmic retinochoroiditis.*

Retinal vasculitis has been reported primarily in patients in Africa. Vitreous inflammation, without retinal lesions, has been seen.[3,9,11,39] The causes of these disorders are unknown, but it has been speculated that they are related to the presence of HIV in the intraocular tissues.

Adnexal infections

Herpes zoster ophthalmicus

Herpes zoster ophthalmicus occurs frequently in patients with HIV infection.[40,41] Although it alone does not establish the diagnosis of AIDS, it seems to be associated with an increasing incidence of development of the syndrome. Certainly, HIV infection should be suspected in any young individual with zoster ophthalmicus.

The skin lesions, keratitis, and anterior uveitis may be extremely severe and disseminated infections can occur.[5,6] Chronic dendriform keratitis, following skin envolement has been reported.[42]

Treatment should include systemic acyclovir to promote healing of the skin lesions and to limit the severity of the ocular lesions. Systemic steroids should be avoided because of their suppression of the immune system.

Other infections

Molluscum contagiosum may cause extensive cutaneous lesions of the eyelids and face. When severe, they may result in ocular surface irritation, trauma, or infection.[43]

Culture negative conjunctivitis and keratitis has been reported in up to 10% of patients in some series.[34] The cause is unknown.

Neoplasms

Kaposi sarcoma.

Kaposi sarcoma is a muticentric malignant neoplasm thought to be derived from endothelial cells.[9] It may involve the skin of the eyelids and lid margins, the conjunctiva, and rarely the orbit.[7,9,14,15,44,45] Conjunctival involvement has been reported in 16-18% of AIDS patients with Kaposi sarcoma.[9,15]

Conjunctival Kaposi sarcoma lesions appear as bright red subepithelial masses (Fig. 7) usually, they are located in the inferior *Cul-de-sac*, but palpebral and bulbar lesions may occur.[34] Small lesions may be mistaken for sub-conjunctival haemorrhages. Tumors may be overlooked unless the lids are everted during the ophthalmic examination. Since the conjunctiva may be the first site for development of the tumor, the conjunctiva should be inspected even in the absence of other known systemic sarcomas.

Rarely are the tumors symptomatic unless they ulcerate or become bulky and interfere with lid function. Since they are radiosensitive, treatment with irradiation will cause regression with little risk to the eye.

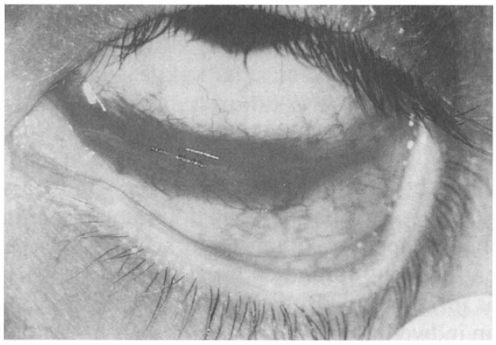

Fig. 7. *Sub-conjunctival Kaposi sarcoma. (reprinted with permission).*

Orbital lymphoma

Burkitt lympoma has been reported to occur in the orbit, manifestating as proptosis, lid swelling and motility disturbance.[46] This lesion may respond to irradiation or chemotherapy.

Neuro ophthalmologic Abnormalities.

A variety of neuro ophthalmologic signs and symptoms can result from manifestation of AIDS.[34] Often, the central nervous system is involved with primary HIV infection, opportunistic infections, and intracranial neoplasms. The frequency of neuro-ophthalmic findings in AIDS is unknown, however central nervous system disease may present in this manner and the clinician should be alert to the diagnostic possibilities.

Primary HIV infection

Primary HIV encephalopathy, characterised by progressive dementia, is the most common CNS illness associated with AIDS.[47] Visual disturbances, including gaze palsies and nystagmus, were found in 5% of patients in one series.[47] Hemianopsia has also been reported.[34]

Opportunistic infections

Opportunistic viral infections are represented mainly by JC virus, a papovavirus which causes progressive multifocal leukoencephalopathy, and the herpes viruses, which mainly cause encephalitis. Ocular findings, including visual field defects, papilledema, and cranial nerve palsies, have been reported with these entities.[47]

The main non-viral opportunistic infections of the brain are toxoplasmosis and cryptococcosis.[48] Cerebal toxoplasmic lesions in AIDS patients consist of necrotising granulomas. Headaches and alterations in conciousness are the commonest presenting symptoms; ocular findings may be seen depending on the location of the granulomas. Antibiotic therapy is often effective in controlling the infection, but recurrences off therapy are usual. In some series, cryptococcal meningitis is the commonest non-viral opportunistic infection of the CNS in AIDS patients.[48] In contrast to toxoplasmosis,which usually occurs in patients in whom AIDS has already been diagnosed, cryptococcal meningitis is often the initial opportunistic infection upon which the diagnosis of AIDS is made.[48] The disease has an insidious onset and a subacute course. Ocular findings are variable; cranial nerve palsies and papilloedema have been noted.[34] Treatment with antifungal medications may be effective, but the treatment of this disease has not yet been standardised.

Other causes of CNS infection include *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* various fungi including *Histoplasma capsulatum* and various bacteria.[42] Neuro-ophthalmic manifestations have not been characterised fully in these and other less common infections.

Intracranial neoplasms.
Intracranial neoplasms affecting AIDS patients include primary CNS lymphoma, metastatic Kaposi sarcoma, and systemic lymphoma with CNS involvement.[49] Neuro-ophthalmic findings depend on the nature and extent of the neoplastic involvement.

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