OPHTHALMIC COMPLICATIONS OF HIV INFECTION

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More than 50% of patients with acquired immunodeficiency syndrome (AIDS) have ophthalmic changes associated with human immunodeficiency virus (HIV) infection. Microvascular abnormalities and opportunistic infections cause the majority of ophthalmic lesions seen in HIV-infected individuals. As a consequence of the chronic loss of T lymphocytes, infections generally occur with minimal reactive inflammation and require prolonged medical therapy to prevent disease recurrence. Certain ocular infections, such as herpes simplex keratitis, do not appear to occur any more frequently in patients with AIDS than in immunocompetent age-matched patients but can be more severe and atypical. Others, such as cytomegalovirus (CMV) retinitis, occur almost exclusively in patients with AIDS. The ocular manifestations of HIV infection can be grouped into five general categories: (1) a noninfectious microangiopathy, often referred to as HIV retinopathy; (2) opportunistic ocular infections; (3) neoplasms of the ocular adnexa; (4) neuro-ophthalmic lesions; and (5) drug-induced manifestations (Table 1).

HIV RETINOPATHY

HIV retinopathy is the most common ophthalmic lesion seen in patients with AIDS and is characterized by the presence of cotton-wool spots and less

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Table 1. OCULAR MANIFESTATIONS OF AIDS

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Microangiopathy</td>
<td></td>
</tr>
<tr>
<td>HIV retinopathy</td>
<td>50%–65%</td>
</tr>
<tr>
<td>Opportunistic ocular infections</td>
<td></td>
</tr>
<tr>
<td>Anterior segment</td>
<td></td>
</tr>
<tr>
<td>Microsporidial keratoconjunctivitis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Herpes zoster ophthalmicus</td>
<td>4%</td>
</tr>
<tr>
<td>Posterior segment</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus retinitis</td>
<td>Up to 40%</td>
</tr>
<tr>
<td>Varicella zoster retinitis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Toxoplasmic retinitis</td>
<td>1–2%</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> choroiditis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ocular neoplasms</td>
<td></td>
</tr>
<tr>
<td>Kaposi's sarcoma (eyelid)</td>
<td>1%–2%</td>
</tr>
<tr>
<td>Kaposi's sarcoma (conjunctiva)</td>
<td>1%–2%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Neuro-ophthalmic lesions</td>
<td>10%</td>
</tr>
<tr>
<td>Drug-induced lesions</td>
<td></td>
</tr>
<tr>
<td>Didanosine (children)</td>
<td>7%</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Unknown</td>
</tr>
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</table>

Frequently intraretinal hemorrhages, microaneurysms, and telangiectatic vessels (Fig. 1). The presence of retinopathy correlates well with the degree of immunodeficiency. In a series of HIV-infected patients, the presence of retinopathy was noted in 66% of patients with category C disease, 40% of patients in category B, 1% of patients in category A, and 0% in HIV-negative homosexual men.\(^7\) These findings concurred with the study by Freeman and colleagues,\(^4\) who reported that HIV retinopathy was associated with lower CD4+ T cell counts.

**Figure 1.** HIV retinopathy, with cotton-wool spots and intraretinal hemorrhages.
Cotton-wool spots have been reported to occur in 28% to 92% of patients with AIDS, with most series reporting a frequency of greater than 40%.

Previously known as soft exudates, cotton-wool spots are microinfarcts of the nerve fiber layer of the retina. Cotton-wool spots occur as a result of ischemic disruption of axonal transport with subsequent swelling and are seen clinically as white fluffy lesions with feathery borders. They resolve in 4 to 6 weeks, usually without any scarring and visual sequelae. Intraretinal hemorrhages occur less commonly, with most series reporting a frequency of less than 20%. Rarely, perivascular sheathing in the absence of concurrent infectious retinitis is seen, reported to occur in less than 1% of patients with AIDS or the AIDS-related complex (ARC) in the United States. Perivascular sheathing is more common in Africa, however, occurring in 15% of pediatric patients with AIDS and 60% of pediatric patients with ARC. Reasons for these regional differences in frequency are unknown.

The pathogenesis of HIV retinopathy is probably multifactorial, most likely a combination of immune complex deposition, HIV infection of the retinal vascular endothelium, local release of cytotoxic factors, or rheologic abnormalities. Ultrastructural studies using immunohistochemical stains have shown retinal arterioles with narrowed lumens, swollen endothelial cells, thickened basal lamina, and loss of pericytes. Immunoglobulins and complement were found within vessel walls. HIV has been isolated from the retinas of patients with AIDS, and HIV antigens were demonstrated within the retinal vascular endothelium. Faber and co-workers reported, however, that HIV infection of retinal endothelial cells does not occur frequently enough to account for the high incidence of cotton-wool spots in patients with AIDS. They suggested that the local release of cytokines or proteolytic enzymes plays a greater role in the pathogenesis of HIV retinopathy. Abnormal rheologic factors, such as red cell aggregation, elevated fibrinogen levels, circulating immune complexes, and plasma viscosity, have been reported to correlate with the occurrence of ocular microangiopathy, including abnormal conjunctival vessels. It is likely that these same abnormalities also contribute to the occasional large vessel disease seen in HIV-infected patients: central or branch retinal vein occlusions. The subtle, often subclinical, and less often appreciated abnormalities of color vision and contrast sensitivity noted in patients with AIDS may be the result of diffuse loss of axons in the optic nerves, demonstrated by histologic morphometric studies. It has been suggested that these changes may be due to the cumulative effects of a diffuse microvascular disease or to direct effects of HIV infection.

The clinical picture of HIV retinopathy is similar to that caused by diabetes mellitus, malignant hypertension, and collagen vascular diseases. Differentiation of HIV retinopathy from other causes can usually be made with a careful history and physical examination. Occasionally, early CMV retinitis lesions may resemble cotton-wool spots. In such cases, close observation over several weeks reveals the diagnosis because CMV retinitis enlarges, whereas cotton-wool spots fade.

OPPORTUNISTIC OCULAR INFECTIONS

Cytomegalovirus Retinitis

CMV, a ubiquitous double-stranded DNA virus, is a herpesvirus. Highly species specific, it shares with other herpesviruses the unique ability to remain latent in tissues after an acute infection in the immunocompetent host.
setting of progressive immunosuppression, however, CMV may reactivate and cause significant morbidity and mortality.

The prevalence of antibody to CMV in the general population ranges from 40% to 100%, depending on the age and population studied. In the United States, serologic surveys indicate a 53% prevalence in adults between the ages 18 and 25 years, increasing to 81% for adults over 35 years. In healthy American homosexual men, seroprevalence rates are usually greater than 90%, and in individuals with AIDS, this figure approaches 100%. CMV has been isolated from urine, semen, and throat specimens; it has been documented that CMV can be transmitted sexually and by blood transfusions.

The advent of effective prophylaxis for and treatment of opportunistic infections has led to increased survival for patients with AIDS. This increased survival, in turn, has resulted in a rise in the frequency of CMV disease, with an estimated 45% of patients with AIDS developing this disease sometime after the diagnosis of AIDS. CMV retinitis is the most common CMV disease seen. In one study, CMV retinitis accounted for 85% of cases of CMV disease; CMV esophagitis accounted for 9%; CMV colitis accounted for 7%; and pneumonitis, gastritis, hepatitis, and encephalitis the rest.

CMV retinitis generally occurs in the late stage of HIV disease when CD4+ counts are less than 50 cells/µL. In the study by Gallant and associates, 10% of patients with CD4+ counts less than 100 cells/µL developed CMV retinitis within 1 year. No differences in frequencies were noted for patients with counts between 50 and 100 and for those with less than 50 cells/µL. In contrast, Pertel and colleagues reported that a CD4+ count less than 50 cells/µL was associated with a greater risk of developing CMV retinitis than one of 50 to 100 cells/µL. They reported that 42% of patients with CD4+ counts less than 50 cells/µL developed CMV retinitis within a 27-month period. The relative risk of CMV retinitis for a CD4+ count less than 50 cells/µL was 4.62 and for a CD4+ count of 50 to 100 cells/µL was 2.47 when compared to those patients with a CD4+ count of greater than 100 cells/µL. Patients developing CMV retinitis with CD4+ counts of greater than 100 cells/µL have been reported, but these cases are unusual.

CMV retinitis does not cause a red painful eye. Patients generally complain of deteriorating vision, seeing moving spots of different shapes and sizes (floaters), flashing lights (photopsias), and patches of blind spots (scotomata). If the lesion is small or peripheral, however, the patient is asymptomatic. In one cross-sectional study, 54% of patients with CMV retinitis were asymptomatic. Not knowing the significance of the aforementioned symptoms, size, location, and unilaterality of lesions all account for this underrecognition.

CMV retinitis may be asymptomatic, especially when only the peripheral retina is affected. Two reports have estimated the prevalence of undiagnosed CMV retinitis in patients with CD4+ T cell counts 50 cells/µL or less at 13% to 16%. Because most patients with CMV retinitis have CD4+ T cell counts of 50 cells/µL or less, several investigators have suggested that patients with CD4+ T cells 50 cells/µL or less be screened by an ophthalmologist every 3 to 4 months. The occurrence of visual symptoms is a clear indication for referral for ophthalmologic evaluation; other possible indications include a rapidly falling CD4+ T cell and evidence of visceral CMV disease.

Several studies have suggested that CMV viremia and viruria are important risk factors for CMV disease. Patients may be viremic or viruric with CMV, however, without clinically apparent end-organ disease. Given the variability of the reported relative risks, the predictive value, sensitivity, and specificity of a positive culture remain to be determined. With the increasing
use of polymerase chain reaction detection of CMV DNA in blood and serum, however, high-risk patients may be better identified.

The diagnosis of CMV retinitis is almost always made clinically. The characteristic lesion is an edematous, yellowish white area of retinal necrosis, with or without hemorrhages, often occurring in the posterior pole (Fig. 2). These lesions are also described as fulminant. The more peripherally located lesions tend to be less edematous, more granular, and usually without hemorrhages. These have been described as indolent or granular. Less commonly, there may be prominent vascular sheathing, or there may be macula edema associated with an area of retinitis distant from the macula. Untreated, CMV retinitis is a progressive, blinding disease. There is total destruction of the retinal architecture in affected areas, and as the lesion spreads, the central area is replaced by a thin gliotic scar, and the borders remain active and edematous. This progression of borders has been termed a brush-fire lesion. In some patients, the atrophic retina develops holes resulting in a retinal detachment.

As of December 1, 1995, two drugs had been approved by the US Food and Drug Administration (FDA) for the treatment of CMV retinitis: ganciclovir and foscarnet. Both drugs are approved as an intravenous formulation for induction and maintenance, and ganciclovir is also approved as an oral formulation for maintenance therapy. In addition, local intravitreal therapy with ganciclovir and foscarnet has been used for the treatment of CMV retinitis.

Ganciclovir is a nucleoside analogue similar to acyclovir; foscarnet is a pyrophosphate analogue, which inhibits both the herpetic DNA polymerase and the HIV reverse transcriptase. Multiple studies have reported that both drugs given intravenously are effective in slowing the progression of CMV retinitis, with favorable responses reported in 87% to 97% of patients. Stabilization of lesions (decreased border opacification and failure of borders to advance) is usually evident within 2 weeks of institution of treatment, and most lesions become inactive scars 2 to 3 weeks later. Because both drugs are virostatic, discontinuation of therapy results in a recurrence, which occurs on
average within 28 days. Therefore, indefinite (maintenance) therapy is necessary. Despite the use of maintenance therapy, however, patients with CMV retinitis often relapse, a phenomenon sometimes referred to as breakthrough retinitis. Although clinical estimates of the rate of relapse while on maintenance therapy have varied from 18% to 50%, the current impression is that, given enough time, nearly all patients relapse, with a median time to relapse by clinical funduscopic visualization of 3 months. Fundus photographic reading centers are more sensitive and give shorter times to progression, generally on the order of 2 months.

The most commonly used intravenous treatment regimen involves an induction period of 2 to 3 weeks when the drug is given twice daily, followed by a once-daily maintenance therapy, which lasts indefinitely. Ganciclovir is given at a dose of 5 mg/kg twice daily during induction therapy and 5 mg/kg once daily during maintenance therapy. Foscarnet is given at a dose of 60 mg/kg three times daily or 90 mg/kg twice daily during induction therapy and 90 to 120 mg/kg once daily during maintenance therapy. These doses must be adjusted according to the patient's renal function. The Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial (FGCRT), a multicenter, randomized, controlled clinical trial comparing foscarnet and ganciclovir as initial treatments for CMV retinitis, demonstrated that foscarnet and ganciclovir were equivalent for controlling the retinitis. Therefore, the choice of initial therapy depends on other systemic and social factors. Ganciclovir and foscarnet have different side-effect profiles. The primary side effect of ganciclovir is bone marrow suppression; granulocytopenia (defined as an absolute neutrophil count [ANC] <500 cells/µL) develops in approximately one third of patients, and often the fall in ANC occurs near or just after the completion of induction therapy.141, 143 Ganciclovir-induced granulocytopenia is reversible with discontinuation of the drug and usually can be treated with filgrastim (granulocyte-colony stimulating factor [G-CSF]) or sargramostim (granulocyte-macrophage-colony stimulating factor [GM-CSF]). Thrombocytopenia, which occurs in about 5% of patients, may occasionally limit the dose of ganciclovir tolerated.

The major side effect of foscarnet is nephrotoxicity, which develops in an estimated 14% of patients on foscarnet over a 6-month period. Because of the potential for nephrotoxicity, foscarnet is administered in conjunction with saline hydration. As such, the infusion of foscarnet takes longer (3 hours versus 1 hour for ganciclovir) and is more inconvenient to administer. Serum creatinine should be measured and an estimated creatinine clearance rate calculated twice weekly during induction therapy and weekly thereafter. Although nephrotoxicity because of foscarnet is reversible with discontinuation of the drug, the time to reversal is generally over a period of days to weeks, requiring a change to ganciclovir therapy to prevent relapse of the retinitis.

Foscarnet is also associated with metabolic abnormalities, including hypocalcemia, hypomagnesemia, and hypokalemia. Monitoring of serum electrolytes plus oral supplementation as needed is required. Seizures, previously thought to be associated with foscarnet therapy, were not associated with foscarnet in FGCRT. In this trial, the rate of seizures was similar in the foscarnet and ganciclovir groups. Other reported side effects from foscarnet include infusion-related nausea, dysuria, and, rarely, genital ulcers. Infusion-related nausea may be minimized by slowing down the infusion rate or the administration of antiemetics. The FGCRT also reported that foscarnet was less well tolerated than ganciclovir and had a greater discontinuation rate for side effects than did ganciclovir. Despite the greater difficulties in its administration, foscarnet had one benefit over ganciclovir. In the FGCRT, ganciclovir was associated with
a 50% greater mortality rate than was foscarnet. Analysis of concomitant antiretroviral therapy suggested that the difference in mortality was not due to antiretroviral therapy. The likely explanation was that foscarnet, which has a modest anti-HIV activity, behaved as an antiretroviral drug in this trial. The survival benefit with foscarnet therapy was also independently reported in one other study.

Hence, the decision as to which drug to start depends on the patient's medical condition and the patient's preference, particularly in the areas of quality of life and convenience. For those patients with renal disease, with cardiac disease, or on nephrotoxic drugs, ganciclovir is a better first choice. For those patients in whom granulocytopenia or aplasia presents a problem (e.g., on chemotherapy for cancer), foscarnet appears to offer advantages. For patients who are employed and for whom the additional infusion time required for foscarnet represents an imposition, ganciclovir may be preferred. Finally, for those patients who can tolerate the drug, the additional infusion time, and additional expense, initial therapy with foscarnet appears to offer a survival advantage.

Because central venous catheters (CVC) are necessary to deliver the daily intravenous medications for CMV retinitis, CVC-associated bacterial infections have been a cause of substantial morbidity and sometimes mortality in patients with AIDS. Infection rates vary from 0.20 to 0.47 infections per 100 days of catheter use. The risk of serious catheter-related infections is no different for patients treated with foscarnet or ganciclovir. A lower risk of serious infections was seen in patients with tunneled CVC placement compared with those CVCs placed percutaneously.

The FDA has approved the use of oral ganciclovir for maintenance therapy; the dosage generally used is 1 g three times daily. Comparative studies with intravenous ganciclovir suggest that oral ganciclovir may be less effective than intravenous ganciclovir as maintenance therapy. Although time to progression using fundus photographs in the two published comparative studies was similar between oral ganciclovir and intravenous ganciclovir, the clinicians' evaluation using funduscopy was markedly different, with oral ganciclovir having a shorter time to progression. Reasons for this discrepancy remain uncertain, but there remains a clinical impression that oral ganciclovir may be less effective than intravenous ganciclovir as maintenance therapy. Nevertheless, eliminating the central venous catheter for long-term daily infusions has made oral ganciclovir an attractive alternative for maintenance therapy. Because it may be less effective than intravenous therapy for prevention of relapse, oral ganciclovir might be less appropriate for those patients with immediately vision-threatening lesions (i.e., lesions adjacent to the optic nerve or fovea). For those patients with peripheral lesions, in whom an episode of relapse can be tolerated, oral ganciclovir may be a reasonable alternative for maintenance therapy.

Relapse of CMV retinitis invariably occurs despite long-term maintenance therapy. Furthermore, once relapse has occurred, subsequent relapses occur at an ever-accelerating rate. A whitening of the borders of a lesion as well as advancement of the borders is often a sign of relapse; development of a new lesion occurs less frequently. Persistent border opacification that does not advance does not require reinduction therapy. Calcium or lipid deposits should also not be mistaken for active disease. Relapses generally have been treated by reinduction for 2 weeks followed by resumption of maintenance therapy. Alternative strategies have included the use of induction levels of ganciclovir for maintenance therapy, switching to the alternate drug, or the use of combination therapy with both ganciclovir and foscarnet. The reasons for relapse
are unclear but probably include the failing immune system in patients with AIDS and CMV retinitis, the inadequate intraocular penetration of systemically administered anti-CMV agents, or the development of resistance. Resistance is generally associated with long-term therapy. In one study, 38% of patients who received maintenance ganciclovir for more than 3 months and had positive urine cultures developed resistance to ganciclovir. Overall, approximately 10% of patients developed resistance. Mutations in the CMV gene region UL97 have been found to confer viral resistance to ganciclovir. UL97 encodes a viral phosphotransferase that is necessary for the initial phosphorylation of ganciclovir. Foscarnet resistance has also been reported. The magnitude of the problem of CMV resistance and its impact on control of the ocular and extraocular disease remain poorly characterized. It is clear, however, that in patients with frequent relapses of CMV retinitis, resistant virus can be isolated from either blood or urine. In this situation, switching to an alternative drug regimen is often tried. The use of combination ganciclovir and foscarnet in those patients who are frequently relapsing and not responding to either drug alone has been reported to be efficacious in controlling the retinitis. Because combination therapy requires two daily infusions, it has a greater impact on the quality of life. The CMV Retinitis Treatment Trial is a multicenter clinical trial comparing high-dose ganciclovir, high-dose foscarnet, and combination therapy as treatments for retinitis that has relapsed. This study has shown that combination therapy with ganciclovir and foscarnet is more effective for controlling retinitis than monotherapy with either drug alone.

Toxicity, cost, and central venous line complications have led to the use of intravitreal therapy in some patients. This form of local treatment requires 2 to 3 weeks of induction with twice-weekly to thrice-weekly intravitreal injections, followed by once-weekly injections as maintenance therapy. Intravitreal injections with either ganciclovir or foscarnet have been reported to be effective in controlling CMV retinitis. The logistic problems of weekly injections, however, have generated interest in alternative methods of delivery of intravitreal drug, such as the sustained-release ganciclovir intraocular device. This device achieves drug levels in the vitreous that are sustained at high levels and avoids the peaks and troughs of intravenous therapy. Although designed to release ganciclovir for 8 months, the device generally lasts 6 to 7 months. A surgical procedure is required, but the incidence of ocular complications, such as endophthalmitis or vitreous hemorrhage, appears to be low. The device has been reported to be highly effective when used as initial therapy for controlling CMV retinitis. Patients who receive the implant bilaterally should be forewarned that there is a transient period of blurred vision secondary to a changing refractive error while the eye heals and that their corrected visual acuity recovers to the preoperative level over a period of 3 to 4 weeks.

Although effective locally, intraocular administration does not protect the contralateral eye or the viscera from CMV disease. The National Eye Institute (NEI) intramural study of the ganciclovir intraocular device reported that by 6 months, 50% of patients with unilateral CMV retinitis treated with the device alone developed CMV retinitis in the contralateral eye and that 31% of patients developed visceral CMV disease, requiring intravenous therapy. Limited autopsy data suggested that the rate of unrecognized systemic disease might be even higher. One potential regimen for the treatment of CMV retinitis might be the ganciclovir intraocular device for control of the ocular disease and oral ganciclovir to prevent the development of contralateral ocular or visceral disease. The device was approved by the FDA in 1996.

The role of intravitreal injection therapy, as most often used in the United
States, is as an adjunct to systemic therapy for those patients who have suffered multiple relapses or are intolerant of systemic therapy. Some clinicians, however, especially in Australia, are offering intravitreal injections as primary therapy.154 A further complication of CMV retinitis is the development of retinal detachments. Case studies suggest that 17% to 34% of patients with CMV retinitis develop retinal detachments.31, 43, 45, 47, 69, 105, 119, 134 One retrospective study suggested that the cumulative frequency of retinal detachments at 1 year would be 50%,69 and a similar rate was reported in the FGCR, a prospective study.142 Detachments appear to occur most often in those patients with large lesions extending into the periphery, especially when the ora serrata is involved. The presence of active retinitis also increases the risk of retinal detachments.43, 69 These detachments are often complicated, but modern vitrectomy surgery using silicone oil tamponade, with or without scleral buckling, is successful in achieving anatomic reattachment.47, 53, 69, 119, 134 Although early case series reported disappointing visual results, patient selection, earlier intervention, and absence of preoperative optic atrophy and macular CMV more recently have led to greater success in achieving visual acuity of 20/200 or better.90, 97 A good indicator of postoperative visual outcome seems to be the level of preoperative visual acuity.105, 134 Patients with preoperative vision of hand motion or worse tend to do poorly. Laser photocoagulation applied locally to delimit the area of detachment has been used for small, peripheral detachments.97, 106 Although laser photocoagulation has had limited success in preventing further detachments, McCluskey and co-workers67 suggest that a subgroup of patients with newly diagnosed CMV retinitis complicated by a detachment that is small and peripherally located would benefit from laser photocoagulation. Despite surgical intervention, postoperative vision may still decline because of progressive CMV retinitis, optic nerve atrophy, or the development of silicone oil–induced cataract formation. The last-mentioned complication is generally correctable with a cataract extraction and an intraocular lens implant.

Given the incidence of CMV disease in patients with AIDS, prevention of the disease is a highly desired goal. One unpublished study (Syntex 1654), reported only in abstract form as of December 1995, suggested that oral ganciclovir at a dosage of 1 g three times daily reduced the rate of CMV disease by 50% in patients with CD4+ T cells less than 100 cells/μL, and oral ganciclovir was approved by the FDA for primary prophylaxis in November 1995. A second study (the CPCRA trial), also unpublished and reported only in abstract form as of December 1995, reported no benefit from primary prophylaxis. Although both studies were randomized, placebo-controlled clinical trials, the Syntex study had routine, scheduled ophthalmologic examinations and the CPCRA study did not. Despite the methodologic differences, the different results between the two studies remain unexplained. How common the use of oral ganciclovir for primary prophylaxis will be remains to be seen. One potential concern about widespread use of oral ganciclovir as primary prophylaxis is how it would affect the emergence of ganciclovir-resistant CMV.

As of December 1995, there were two investigational drugs undergoing clinical trials. Cidofovir (hydroxy-phosphonyl-methoxy-propyl cytosine or HPMPC) is a nucleotide analogue, with a long half-life and a prolonged duration of clinical effect.86, 112 Its major side effect is nephrotoxicity, which in rare cases was irreversible. The use of probenecid, concomitant hydration, and intermittent dosing appears to have reduced the problem of nephrotoxicity. Intravenous cidofovir is given weekly for induction and every other week for maintenance therapy. The ability to administer the drug intermittently eliminates the need for
a central venous line, thereby improving the patient's quality of life. Cidofovir is also being investigated as an intravitreal agent. Intravitreally the duration of effect appears to be 4 to 6 weeks. As such, intermittent intravitreal injection therapy may be feasible. The dose administered most often is 20 μg because 100 μg has been found to be toxic as a single dose. Current studies are evaluating the long-term cumulative efficacy and toxicity of intravitreal cidofovir. Intravitreal liposome-encapsulated cidofovir used in animals with herpes simplex retinitis was shown to be less toxic to the retina and had longer-term efficacy. This form of drug delivery may prove more useful in the management of human CMV retinitis.

The second investigational agent is a neutralizing monoclonal anti-CMV antibody, MSL-109. One study suggested that higher levels of anti-CMV neutralizing antibody were associated with a more favorable clinical course and that antibodies may modulate the progression of CMV retinitis. This monoclonal antibody is being studied in clinical trials as an adjunct to primary therapy (anti-CMV drugs) to prolong the time to relapse.

Varicella Zoster Retinitis

Varicella zoster retinitis in HIV-infected patients occurs much less frequently than does CMV retinitis. Clinically a spectrum of disease exists, depending on the level of immunodeficiency at the time of onset. When the immune function is relatively preserved, the acute retinal necrosis syndrome is seen. There are usually prominent anterior chamber inflammation, vitritis, retinal vasculitis, and a circumferential peripheral necrotizing retinitis. Pain, floaters, and visual field defects are common complaints. Intravenous acyclovir usually causes a regression of the retinitis, but subsequent long-term suppressive therapy with oral acyclovir is necessary. Acute retinal necrosis occurring after unilateral herpes zoster ophthalmicus was the presenting sign of AIDS in one report. Selitti and colleagues reported that 5 of 29 (17%) immunocompromised patients developed acute retinal necrosis syndrome 0 to 9 months after the diagnosis of herpes zoster ophthalmicus. When the level of immunodeficiency is profound, usually with CD4+ counts less than 50 cells/μL, the progressive outer retinal necrosis syndrome may be seen. This syndrome was recognized in 1991 and is characterized by a rapidly progressive retinitis, initially involving primarily the outer retina. Multiple deep retinal yellowish lesions are seen, and early involvement of the macula is common (Fig. 3). These lesions rapidly coalesce and result in retinal destruction. Optic nerve inflammation may also be present. There is minimal anterior chamber inflammation, vitritis, and retinal vasculitis, and the response to intravenous acyclovir is poor. The prognosis for the progressive outer retinal necrosis syndrome has been dismal, with blindness in most cases despite treatment resulting from retinal detachment or total retinal destruction and optic atrophy. In one series, two thirds of patients progressed to no perception of light within 1 month of diagnosis. Limited success in controlling the retinitis has been obtained with different combinations of intravenous ganciclovir, intravenous acyclovir, and intravenous foscarnet. Maintenance therapy (secondary prophylaxis) with a combination oral acyclovir, oral or intravenous ganciclovir, or intravenous foscarnet is required. Unfortunately, secondary prophylaxis does not always prevent involvement of the second eye, and recurrent disease is frequent. Retinal detachment occurs in 70% of patients, and prophylactic laser photocoagulation has not been found effective.
Toxoplasmo\textit{\textsc{sis}}

\textit{Toxoplasma gondii} is the most common nonviral intracranial pathogen in patients with AIDS; however, intraocular infection is uncommon. Toxoplasmosis accounts for 1\% to 2\% of AIDS-related ocular infections in the United States\cite{70, 128}; 3\% in France\cite{18}, where the seroprevalence of antibodies to \textit{Toxoplasma} is higher; and as much as 8\% in Brazil\cite{64}. Features of ocular toxoplasmosis infection in patients with AIDS are different epidemiologically, clinically, and histopathologically, when compared to toxoplasmosis in immunocompetent patients\cite{4, 64, 107, 150}. With coexisting immunosuppression, ocular toxoplasmosis is more likely to be acquired and more frequently multifocal and bilateral, and histopathologically there is full-thickness retinal necrosis with minimal inflammatory cells. Early lesions are primarily perivascular, and preexisting retinochoroidal scars are usually absent, suggesting hematogenous spread to the eye. Ocular toxoplasmosis may be the first indication of intracranial or disseminated disease. Because 29\% to 50\% of patients with ocular toxoplasmosis have central nervous system involvement, neuroimaging studies are indicated when ocular toxoplasmosis is diagnosed\cite{18, 64}. Serologic tests are not helpful in making the diagnosis because many individuals are IgG positive with no active ocular disease.

Ocular toxoplasmosis generally occurs when CD4+ counts are less than 100 cells/\mu L. Ocular symptoms include decreased vision associated with a red, painful eye owing to moderate iridocyclitis and vitritis; these features help to distinguish toxoplasmosis from CMV retinitis. If only the outer retina is involved, however, ocular inflammatory signs may be minimal\cite{10, 64} and distinction from other necrotizing retinitis made more difficult. In such cases, an endoretinal biopsy may be necessary\cite{34}.

Ocular toxoplasmosis generally responds to treatment with the standard drugs, pyrimethamine, sulfadiazine, or clindamycin. Side effects of pyrimethamine and sulfonamide therapy occur frequently and include allergic reactions, leukopenia, and thrombocytopenia. Clindamycin may cause pseudomembr-
nous colitis. For patients intolerant to the standard drugs, atovaquone (formerly known as 566C80) may be effective. Long-term maintenance therapy is generally required to prevent relapse of disease. Oral corticosteroids, often given to immunocompetent patients with ocular toxoplasmosis, are not indicated in patients with AIDS and ocular toxoplasmosis.

**Fungal Chorioretinitis**

A variety of ocular fungal pathogens have been described in patients with AIDS, both from clinical and autopsy series. The overall frequency is low (<1%), and fungal disease occurs less frequently than varicella zoster retinitis or toxoplasmic chorioretinitis. The causative agents reported to date include *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Sporothrix schenckii* and *Candida* species. Intraocular infection with *C. neoformans* is usually subclinical, identified only at autopsy. Ophthalmic disease is almost always associated with cryptococcal meningitis, with spread of the organism either along the subarachnoid space or by hematogenous dissemination to the eye. Spread from the eye to the central nervous system may rarely occur. Rapid visual loss may develop as a result of direct invasion of the optic nerve causing optic nerve edema, or a gradual painless visual loss may develop over weeks to months as a result of chronic papilledema. Treatment with intravenous amphotericin B may produce improvement in patients with cryptococcal choroiditis; however, progressive optic atrophy may limit final vision.

Although mucocutaneous candidiasis is common in patients with HIV infection, disseminated or visceral infection with *Candida* is uncommon. *Candida* endophthalmitis may occur as a result of intravenous drug use or nosocomial infection. Treatment consists of vitrectomy and intravitreous amphotericin B.

**Ocular Syphilis**

There is an increased incidence of syphilis in HIV-infected individuals, and evidence exists that concurrent HIV infection alters both the course of syphilis and its response to treatment. Ocular syphilis may cause intraocular inflammation (uveitis) or neuro-ophthalmic lesions. Diagnosis may be complicated by altered serologic responses in HIV-infected patients. Examination of the cerebrospinal fluid to rule out neurosyphilis is recommended because more than 80% of HIV-positive individuals with ocular syphilis have clinical or laboratory evidence of neurosyphilis. The treatment of ocular syphilis in HIV-infected patients requires the use of high-dose intravenous aqueous penicillin G at 20 million U daily for 10 to 14 days, followed by weekly benzathine penicillin for 3 weeks. Response to therapy is guided by clinical control of the disease and at least a 2 dilution decrease in reagin titer by 6 months.

**Mycobacterial Choroiditis**

Ocular mycobacterial infections in patients with AIDS are fortunately still uncommon and are primarily caused by *Mycobacterium tuberculosis* or *Mycobacterium avium* complex (MAC). To date, ocular MAC infection has been
described primarily in autopsy series. In developed countries, the incidence of tuberculous choroiditis is low (<1%), but it may be greater in countries with higher rates of tuberculosis. Tuberculous choroiditis in patients with AIDS is associated with active systemic tuberculosis.

**Pneumocystis carinii Choroiditis**

First reported in 1989, this ocular manifestation was most often seen in patients treated with aerosolized pentamidine as *Pneumocystis carinii* pneumonia prophylaxis. The ocular lesions do not usually cause visual symptoms and generally resolve with systemic anti-*Pneumocystis* treatment, such as intravenous trimethoprim/sulfamethoxazole or intravenous pentamidine. With the present widespread and effective use of oral trimethoprim/sulfamethoxazole or dapsone as primary prophylaxis for *Pneumocystis*, the frequency of this ocular infection appears to be declining.

**Herpes Zoster Ophthalmicus**

Herpes zoster ophthalmicus (HZO) occurs in about 4% of patients with AIDS. Ocular complications are common and can be severe and protracted. In HIV-infected patients, HZO can cause a widespread necrotizing and destructive damage to the eyelids and surrounding areas. HZO may also be complicated by scleritis, iridocyclitis, cranial nerve palsies, and retinitis. Although HZO responds to systemic acyclovir therapy, long-term suppressive therapy may be required.

**Ocular Surface Infections**

Bacterial and fungal corneal ulcers have been reported in patients with AIDS but are uncommon and generally occur as a consequence of a primary ocular problem resulting in structural damage to the lids and corneal exposure (e.g., HZO, radiation therapy for Kaposi's sarcoma). Herpes simplex keratitis in HIV-infected patients appears to occur with the same frequency as in immunocompetent individuals but can be atypical in presentation with delayed healing and more frequent recurrences. Several cases of microsporidial keratoconjunctivitis have been reported. Ocular symptoms include photophobia, foreign-body sensation, and blurred vision. Diagnosis is based on light and electron microscopic findings on corneal epithelial scrapings. Treatment has been disappointing, although resolution of infection has been reported with corneal debridement and oral itraconazole, topical propamidine isethionate (Brolene), or topical fumagillin.

**OCULAR NEOPLASMS**

Kaposi's sarcoma involving the eye has been reported to occur in 2% of patients with AIDS. Of patients with AIDS and Kaposi's sarcoma, 15% to 22% develop lesions involving either the eyelids or conjunctiva (Fig. 4). Ocular adnexal Kaposi's sarcoma lesions usually spread slowly and are often asymptomatic. Treatment is indicated only when lesions compromise vision or when there is cosmetic disfigurement. Local excision, cryotherapy, radiotherapy, and
systemic chemotherapy have all been associated with a good response in some patients.30, 54, 133

Non-Hodgkin's lymphoma occurs more frequently in patients with AIDS than in the general population. Although second only to toxoplasmosis as a cause of mass lesions in the brain of AIDS patients, both orbital and intraocular lymphomas are rare.49, 70

**NEURO-OPTHALMIC LESIONS**

Neuro-ophthalmic complications are either due to opportunistic central nervous system infections or to HIV infection of the central nervous system itself23, 58, 96, 104, 133, 152 and were reported to occur in less than 10% of patients with AIDS.70 Cryptococcal meningitis caused 50% of neuro-ophthalmic lesions in one series.70 Of patients with AIDS and cryptococcal meningitis, one third have a neuro-ophthalmic complication on careful examination.70 Complications include cranial nerve palsies (particularly sixth nerve), papilledema (Fig. 5), optic neuropathy, and visual field defects.80 Other less common causes of neuro-ophthalmic lesions include herpes zoster ophthalmicus, central nervous system lymphoma, central nervous system toxoplasmosis, and viral encephalitis.

Subtle, less often appreciated neuro-ophthalmic abnormalities have been reported. These findings include subtle ocular motility defects (slowed saccades, fixational instability, and abnormal pursuit movements) and impairments in color vision and contrast sensitivity, which correlate with optic nerve fiber loss.23, 104, 114

**DRUG-INDUCED OCULAR LESIONS**

Some medications used to treat HIV-infected patients have potential ocular toxicity. One case of diffuse retinal degeneration was reported with clofazimine
Peripheral retinal pigment epithelial atrophy was reported in 7% of children treated with high-dose didanosine, although this complication has not been reported in adults. Hypopyon uveitis mimicking infectious endophthalmitis has been reported in patients treated with high-dose rifabutin or with a combination of rifabutin, clarithromycin, and an imidazole. This ocular complication responds to intensive topical corticosteroid therapy and either cessation of rifabutin use or reduction in rifabutin dose.

SUMMARY

HIV retinopathy, a noninfectious microangiopathy, is the most common ocular manifestation of HIV infection. Opportunistic infections, neoplasms, neuro-ophthalmic lesions, and drug-induced lesions may also cause ocular problems. Opportunistic ocular infections, particularly CMV retinitis, are a major cause of morbidity in patients with AIDS. Because of the underlying chronic and progressive immune dysfunction, the ocular symptoms, signs, clinical course, and treatment are often atypical and severe, requiring protracted medical therapy.

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