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In 1981, a new disease, characterized by opportunistic infections (OIs) and unusual neoplasms, was reported to the Centers for Disease Control and Prevention.[1] This disease, AIDS, was soon thereafter discovered to be caused by the human immunodeficiency virus (HIV), which invades cells of the immune system, particularly $CD4^+$ T cells, resulting in their loss and the subsequent immune deficiency. From the beginning, it was evident that the eye was a frequent target organ in AIDS.[2] The most frequent ocular manifestation was HIV retinopathy, consisting of cotton-wool spots with or without intraretinal hemorrhages.[2,3] Histologic and fluorescein angiographic studies also demonstrated the presence of other vascular abnormalities, including microaneurysms and telangiectatic vessels.[3-5] The most devastating ocular complications were ocular OIs, particularly cytomegalovirus (CMV) retinitis. Cytomegalovirus retinitis affected an estimated 30% of patients with AIDS sometime during the course of AIDS,[6] and the rate among patients with $CD4^+$ T-cell counts lower than 50 cells/μL was 0.20 cases/person-year (PY).[7] By the early 1990s, CMV retinitis became the most common intraocular infection seen by ophthalmologists at major urban centers.[8] Drugs to treat CMV retinitis were introduced in the late 1980s, including ganciclovir sodium (Cytovene; Roche Pharmaceuticals, Nutley, New Jersey; approved in 1989) and foscarnet sodium (Foscavir; AstraZeneca LP, Wilmington, Delaware; approved in 1991), and later, cidofovir (Vistide; Gilead Sciences, Inc, Foster City, California; approved in 1996) and fomivirsen sodium (Vitravene; Novartis Ophthalmics AG, Bulach, Switzerland, and Isis Pharmaceuticals, Inc, Carlsbad, California; approved in 1998). Treatment was initially given intravenously at higher doses for 2 to 3 weeks (induction therapy), followed by lifetime therapy at lower doses to prevent relapse of the disease (maintenance therapy or secondary prophylaxis). An oral form of ganciclovir with poor bioavailability was introduced and then replaced by valganciclovir hydrochloride (Valcyte; Roche Pharmaceuticals; approved in 2001), which had a good bioavailability after oral administration and produced ganciclovir blood levels similar to those of intravenous ganciclovir.[9] Intravitreal injections of ganciclovir and foscarnet also were used to deliver higher drug concentrations to the retina and avoid systemic adverse effects. To improve local delivery of ganciclovir, a sustained-released implant (Vitrasert; Bausch & Lomb, Inc, San Dimas, California; approved 1996), which lasts approximately 6 months, was developed and Food and Drug Administration approved in 1996.[10] However, because CMV is a systemic infection, local delivery of anti-CMV agents was associated with high rates of contralateral ocular and visceral disease and with an increased mortality.[3,11-13] Because of the disadvantages of local therapy, the implant typically was combined first with oral ganciclovir[14] and now with valganciclovir.

Despite treatment, CMV retinitis typically relapsed, particularly with systemic therapy. Relapse, which was measured by centrifugal advancement of the active lesion border (termed *progression*), could be treated with reinduction therapy, but the pace of relapse appeared to accelerate over time.[15] Early relapses were largely due to the limited intraocular drug levels with systemic therapy,[16,17] whereas later relapses (beyond 3 months) were associated increasingly with resistance to the administered anti-CMV drugs.[18-20] The estimated rates of resistance for ganciclovir and foscarnet were 0.25 cases/PY,[18-20] and the occurrence of resistance was associated with adverse ocular outcomes, including increased retinitis progression, increased loss of retinal area, and increased rate of visual impairment.[21] Rates of visual impairment (to 20/50 or worse) approximated 1.00 case/PY and of blindness (to 20/200 or worse), 0.50 case/PY.[3,22] Mortality among patients with CMV retinitis was substantial, with median survival estimated at 1 year after diagnosis of CMV retinitis. Other ocular OIs had a similar impact on vision but were much less frequent than CMV retinitis.[3]

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

In the AIDS epidemic, 1996 represented a watershed year because of the widespread introduction of highly active antiretroviral therapy (HAART). Highly active antiretroviral therapy is combination antiretroviral therapy with at least 1 very potent antiretroviral drug, such as a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. With HAART came immune recovery in many patients, characterized by an increase in $CD4^+$ T-cell counts and the ability to control OIs without antibiotics or antivirals. The incidence of OIs decreased by 75% to 80%, and there was an attendant decrease in mortality.[23-25] Among patients with sufficient immune recovery, secondary prophylaxis could be discontinued safely.[26-28]

CMV RETINITIS IN THE HAART ERA

The most obvious consequence of HAART and immune recovery has been a 75% to 80% decline in the inci-

Table. Suggested Treatment Algorithm for Patients With CMV Retinitis[a]

HAART CMV Retinitis Location[b]	Experienced	Naive
Zone 1	Ganciclovir implant + valganciclovir	Ganciclovir implant + valganciclovir
Zones 2 and 3	Valganciclovir ± ganciclovir implant	Valganciclovir

Abbreviations: CMV, cytomegalovirus; HAART, highly active antiretroviral therapy.

[a] Valganciclovir was given as valganciclovir hydrochloride.

[b] Zone 1 refers to an area of the retina extending 3000 μm from the center of the fovea or 1500 μm from the edge of the optic nerve. Zone 2 extends from the edge of zone 1 anteriorly to a circle identified by the vortex vein ampullae, and zone 3 extends from the edge of zone 2 to the ora serrata.

dence of CMV retinitis.[23-25] Data from the Longitudinal Studies of the Ocular Complications of AIDS (LSOCA) have provided an upper-limit estimate of the incidence of CMV retinitis in the HAART era as 5.6 cases/100 PY.[29] However, although there was a decline in the incidence of CMV retinitis, new cases continue to occur.[25] Most new cases of CMV retinitis appear to occur among patients who are HAART experienced and intolerant of or not responsive to HAART, rather than among patients who are HAART naive.[30,31] Nevertheless, the clinical characteristics of CMV retinitis in the HAART era appear to be similar to those from the pre-HAART era.[32]

A second consequence of HAART has been improved control of the retinitis. Rates of retinitis progression have declined from approximately 3.0 cases/PY pre-HAART to 0.10 case/PY in the HAART era.[33] Although most of this decline in retinitis progression is owing to immune recovery, even among patients with $CD4^+$ T-cell counts lower than 50 cells/μL, the rate (0.58 case/PY) is decreased from the pre-HAART era. However, retinitis progression does occur among patients with immune recovery; for those with $CD4^+$ T-cell counts higher than 100 cells/μL, the rate is 0.03 case/PY, and no $CD4^+$ T-cell count is completely safe.[33] These data suggest a need for ongoing ophthalmologic monitoring among patients with immune recovery, even if anti-CMV therapy has been discontinued (see later). With the decline in retinitis progression, there also has been a decline in retinitis complications. The rate of retinal detachment in the pre-HAART era was approximately 0.50 case/PY, whereas in the HAART era, it is 0.06 case/PY.[3,34] This decline occurred largely among patients with immune recovery; however, among those with $CD4^+$ T-cell counts lower than 50 cells/μL, the rate of retinal detachment is substantially greater, approximately 0.30 case/PY.[34]

A third change in the management of CMV retinitis in the HAART era has been the ability to discontinue anti-CMV maintenance therapy. Numerous case series have documented the ability to safely discontinue therapy without relapse of the retinitis.[26-28] The collective evaluation of these case series has led to the recommendation from the Department of Health and Human Services that for patients with a $CD4^+$ T-cell count higher than 100 to 150 cells/μL for 3 to 6 months, anti-CMV maintenance therapy be discontinued.[35] However, as noted earlier, relapse of the retinitis can occur in these patients and continued monitoring is needed.[33]

A fourth consequence of HAART has been the occurrence of immune recovery uveitis (IRU).[36-38] Immune recovery uveitis is one of the several immune recovery inflammatory syndromes described among patients with AIDS. Immune recovery uveitis consists of an increase in intraocular inflammation as immune recovery occurs in an eye with CMV retinitis. The presumed pathogenesis is that the recovering immune system can mount an immune response to CMV antigens, resulting in inflammation. Immune recovery uveitis is associated with ocular structural complications, including cystoid macula edema and epiretinal membrane formation. These structural complications can impair visual acuity.[38,39] Risk factors for IRU include larger areas of CMV retinitis and antecedent use of intravitreous cidofovir.[38] The use of HAART prior to control of CMV with anti-CMV drugs also may increase the incidence of IRU.[40] The best treatment for IRU is unknown, and periocular, intravitreal, and oral corticosteroids all have been used in small case series with an overall success rate of about 50%.[37,38,41] The best results were reported with high doses (20 mg) of intravitreal triamcinolone,[41] but the data come from a limited number of treated patients.

Along with improved control of the retinitis and the decline in structural complications, there has been a decline in visual impairment among patients with CMV retinitis. Overall, patients with CMV retinitis now have visual impairment at a rate of 0.10 case/eye-year (EY) and blindness at 0.06 case/EY.[39,42] Much of the improvement in visual prognosis has occurred as a consequence of immune recovery; rates of visual impairment and blindness are lowest among patients with immune recovery but without IRU.[42] Nevertheless, patients with active retinitis who are not receiving HAART still have lower rates of visual impairment (0.36 case/EY) and blindness (0.16 case/EY) than in the pre-HAART era.[40] Immune recovery uveitis is associated with visual impairment but not blindness, and the incidence of visual impairment among patients with IRU is 0.17 case/EY.[39,42] Much of the visual acuity loss among patients with CMV retinitis is due to those factors present in the pre-HAART era, including involvement of the fovea or optic nerve (zone 1 disease) and retinal detachment.[39] Cataract also was a substantial problem among patients with CMV retinitis, accounting for 22% of visual impairment and 29% of blindness.[39]

MANAGEMENT OF CMV RETINITIS IN THE HAART ERA

Treatment of a patient with CMV retinitis is individualized and the choice of therapy is typically based on several factors, including the location of the lesion and the patient's experience with HAART (**Table**). Several principles guide the choice of therapy. Because CMV retinitis is associated with an increased mortality,[12] and systemic anti-CMV therapy decreases this mortality,[13] all patients who can tolerate systemic therapy should be given it. Because it is orally bioavailable, valganciclovir typi-

cally is the drug initially chosen. The ganciclovir implant is associated with better control of the retinitis and lower rates of retinitis progression than systemic therapy.[14] For patients with zone 1 disease, who are at risk for immediate and permanent visual loss, addition of the ganciclovir implant often is preferred. While awaiting surgery, many patients will be given an initial intravitreal injection of ganciclovir or foscarnet to provide high intraocular drug levels. Because the structural complications of CMV retinitis, including retinal detachment and IRU, are related to lesion size, control of retinitis with anti-CMV therapy even in a HAART-naive patient is appropriate.[3,34,38] Consideration should be given to delaying HAART until the retinitis is controlled, as there are some data to suggest this delay will decrease the incidence of IRU.[40] Because the recovery of specific immunity to CMV requires approximately 3 to 6 months after the initiation of HAART,[43] HAART-naive patients will need treatment for a minimum of 6 months prior to an attempt to discontinue therapy after immune recovery.[35] Therefore, the treatment algorithm outlined in the Table is a reasonable first approach to the management of CMV retinitis in the HAART era. Fortunately, the rates of resistance to anti-CMV agents appear to have decreased in the HAART era (about 0.05 case/PY) relative to the pre-HAART era.[44] Nevertheless, some patients may need treatment with foscarnet or cidofovir if they do not have immune recovery and are treated for sufficiently long that resistance may occur.

OTHER OCULAR COMPLICATIONS OF AIDS

Most ocular OIs, including varicella zoster retinitis, ocular toxoplasmosis, *Pneumocystis* choroidopathy, and other infectious choroidopathies, are seen among patients with low $CD4^+$ T-cell counts. As the number of patients with AIDS with low $CD4^+$ T-cell counts has been reduced by HAART, the incidence of these problems also has decreased.[29] Human immunodeficiency virus retinopathy also is more common among patients with low $CD4^+$ T-cell counts[45] and, therefore, now is seen less often.[29,32]

In the pre-HAART era, some patients with HIV infection without ocular OIs had evidence of a neuroretinal visual problem, including abnormalities of contrast sensitivity, visual fields, and electrophysiology.[46,47] Histologic studies showed a loss of optic nerve axons.[48] The etiology of this HIV neuroretinal disorder was uncertain, but proposed hypotheses included a cumulative effect of multiple retinal infarcts from HIV retinopathy, a direct toxic effect of HIV infection, or a secondary effect on neuroretinal cells of the response to HIV infection. Analysis of the LSOCA cohort has demonstrated that patients with AIDS but without ocular OIs continue to have these problems in the HAART era.[49] The distribution of visual acuities, visual field scores, and contrast sensitivity is worse than that expected in a similarly aged population.[49] Approximately 12% of eyes have contrast sensitivity scores sufficiently low to impair reading speed. Hence, despite the use of HAART, there appears to be an ongoing problem with this disorder. The long-term consequences of the HIV neuroretinal disorder are unknown. Finally, when causes of visual impairment among patients without ocular OIs were evaluated in the LSOCA cohort, cataract accounted for approximately 21% of new-onset visual impairment and 25% of blindness.[50]

Although much has been learned, several questions remain. For example, the data on progression, structural complications, and visual impairment come from analyses of the LSOCA cohort, with an average of 3 years of follow-up. Unknown is what happens after 5 and 10 years. Because this cohort is ongoing, it is anticipated that longer-term data will become available in the future. Similarly, outcomes of the HIV neuroretinal disorder are unknown, and long-term data are needed to evaluate whether the problem will be progressive and determine its impact on vision. Because patients with HIV infection now are estimated to live for at least 15 years,[51] long-term data are critical in terms of developing management strategies and affording patients prognostic information.

In conclusion, in the HAART era, the eye remains an important target organ for patients with AIDS, and the improved longevity has created the need for long-term data on these patients.

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