PERSPECTIVE
AIDS and Ophthalmology: The First Quarter Century

GARY N. HOLLAND

• PURPOSE: To describe changes in the acquired immunodeficiency syndrome (AIDS) epidemic that are important to ophthalmologists, to provide an overview of issues relevant to current evaluation and treatment of human immunodeficiency virus (HIV)-related eye disease, and to identify problems related to the eye and vision that require continued study.
• DESIGN: Literature review and commentary.
• METHODS: Selected articles from the medical literature and the author's clinical and research experiences over 25 years were reviewed critically.
• RESULTS: The AIDS epidemic has had a profound impact on ophthalmology since the ophthalmic manifestations of AIDS were first described in 1982. The introduction of highly active antiretroviral therapy (HAART) has markedly reduced the incidence of cytomegalovirus (CMV) retinitis, but has not eliminated new cases altogether. Treatment strategies for CMV retinitis have evolved over the past decade. Current issues of importance include choice of initial anti-CMV drugs; time at which anti-CMV drug treatment is discontinued in patients who achieve immune recovery; strategies for monitoring patients at risk for disease reactivation; and management of complications (retinal detachment, immune recovery uveitis). Attention also is being directed to the problem of visual disturbances (reduced contrast sensitivity, altered color vision, visual field abnormalities) that can occur in HIV-infected individuals without infectious retinopathies.
• CONCLUSIONS: Ocular disorders associated with HIV disease remain important problems in the United States, despite HAART, and increasingly are important worldwide. The approach to management of CMV retinitis has evolved from short-term treatment of a preterminal infection to the long-term management of what has become a chronic disease. Many challenges remain to be addressed. (Am J Ophthalmol 2008;145:397–408. © 2008 by Elsevier Inc. All rights reserved.)

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From the Ocular Inflammatory Disease Center, Jules Stein Eye Institute and the Department of Ophthalmology, David Geffen School of Medicine at UCLA, and the Greater Los Angeles Veteran Affairs Healthcare Service, Los Angeles, California.

Inquiries to Gary N. Holland, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095; e-mail: uveitis@jsei.ucla.edu

ON JUNE 5, 1981, THE CENTERS FOR DISEASE CONtrol and Prevention (CDC) announced a cluster of five homosexual men in Los Angeles who had been hospitalized with *Pneumocystis carinii* pneumonia, cytomegalovirus (CMV) infections, and candidiasis,[1] thus marking the start of the acquired immunodeficiency syndrome (AIDS) epidemic. With two additional patients who were seen shortly thereafter, these five patients also constituted the first series to describe the ophthalmic manifestations of AIDS, which was published by the *American Journal of Ophthalmology* less than one year later.[2] Since those earliest days of the AIDS epidemic, ophthalmologists have played an important role in the care of people with human immunodeficiency virus (HIV) infection; the importance of eye disease is reflected in the fact that literally thousands of research articles and reviews have been published on CMV retinitis and other HIV-related ophthalmic disorders during the past 25 years.

Profound changes have occurred since I prepared a similar Perspective in 1992, marking the end of the first decade of the AIDS epidemic.[3] Demographics have changed in the United States,[4] and AIDS is a growing problem in the developing world.[5] More than anything else, the introduction of highly active antiretroviral therapy (HAART) in the late 1990s changed the face of the AIDS epidemic; HAART resulted in a marked reduction in mortality and a decreased incidence of associated opportunistic infections and neoplasms, including those of the eye.

AIDS is no longer the focus of attention in the popular media and medical literature that it once was; in fact, there is a widespread belief among the American public that AIDS is no longer a serious problem,[6] which, unfortunately, is not true. HAART has indeed decreased the incidence of some ophthalmic problems, such as CMV retinitis, but it seems not to have affected others, and it has brought with it new challenges, such as immune recovery uveitis (IRU). A pair of recent articles in the journal illustrate the transition of CMV retinitis from the period before the availability of HAART to the HAART era.[7,8] As they show, CMV retinitis remains a problem, even among HAART-exposed individuals.

The twenty-fifth anniversary of the initial CDC report was cause for reflection on the progress made in the fight against HIV disease and on the impact of AIDS on the medical community.[4] Likewise, it provides an opportunity

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to reflect on the tremendous progress that has been made in the fight against AIDS-related blindness, to consider current approaches to treatment of CMV retinitis, and to identify issues that require continued attention. My 25 years of involvement in the study of AIDS and care for patients with HIV-related eye diseases has afforded me a valuable understanding of how current concepts have evolved. Although this article represents my own Perspective on AIDS, I believe that it provides a comprehensive overview of the important issues that currently face any clinician who deals with HIV-related eye disease. It is not intended to be a detailed review, of which there have been many, and an extensive reference list is not included.

EPIDEMIOLOGY

BY 2007, MORE THAN ONE MILLION PEOPLE WERE LIVING with HIV infection in the United States, and an estimated 33.2 million people were infected with HIV worldwide. In 2005 alone, there were more than 40,000 new cases of AIDS in the United States reported to the CDC. The demographics of the AIDS epidemic have changed in the United States over the past 25 years.[4] Women now account for one quarter of HIV infections, and HIV disease disproportionately affects racial and ethnic minorities. CDC statistics from 35 reporting areas show that during the period 2001 through 2004, 51% of new infections were among Blacks, although Blacks account for only 13% of the United States population. Men who have sex with men (MSM) remain an important risk group. Although CDC statistics indicate that MSM now account for only a little more than half of people with new diagnoses of HIV/AIDS, the yearly incidence of new HIV infections among MSM remains substantial (1.2 to 8/100/year), with young MSM being a subgroup at particularly high risk.[4] The prevalence of HIV infection among MSM from racial and ethnic minority populations is higher than among White MSM.[4]

Most HIV-infected individuals are in sub-Saharan Africa, but the number of new cases is increasing rapidly in other areas of the world, including India and Southeast Asia. In the vast majority of cases worldwide, HIV transmission occurs through heterosexual contact.

Without any reasonable prospect of a successful vaccine against HIV in the near future, public health efforts at disease prevention remain critical for control of the AIDS epidemic. There have been some notable public health achievements in the United States.[4] Infections attributed to perinatal transmission from mother to child and from transfusion of blood and blood products have dropped markedly. There has also been a steady decline in new HIV/AIDS diagnoses among injection-drug users. For updated epidemiologic data regarding AIDS worldwide, see http://www.unaids.org. Data from the United States is also available at http://www.cdc.gov/hiv.

TABLE. Human Immunodeficiency Virus–Related Ophthalmic Disorders

I. Opportunistic infections
A. Retina
1. CMV retinitis
a. Complications
(1) Immune recovery uveitis
2. Other retinal infections (caused by various agents, VZV, and *Toxoplasma gondii* being most common; most occur in less than 1% of patients with AIDS).
B. Choroid (uncommon; caused by various agents, fungi and mycobacteria being most common)
C. Ocular surface and adnexa (important agents include VZV, microsporidia, molluscum contagiosum virus).
II. Vascular abnormalities
A. Microvasculopathy
1. HIV retinopathy (cotton-wool spots, retinal hemorrhages)*
B. Retinal arteriolar and venular occlusions (uncommon)
III. Neoplasia†
A. Kaposi sarcoma (conjunctiva, eyelids)
B. Lymphoma (intraocular)
C. Squamous cell carcinoma (conjunctiva)
IV. Other disorders of uncertain pathogenesis
A. Intraocular inflammation
1. Chronic anterior uveitis (uncommon)
2. Chronic multifocal retinal infiltrates (uncommon)‡
3. Iatrogenic uveitis (drug related: cidofovir; rifabutin)
B. Blepharitis
C. Dry eye
V. Neuroophthalmic disorders associated with orbital or intracranial disease

AIDS = acquired immunodeficiency syndrome; CMV = cytomegalovirus; HIV = human immunodeficiency virus; VZV = varicella zoster virus.

*Clinical signs reflect focal ischemia, attributable to undetermined factors, on a background of the retinal microvasculopathy of HIV disease.

†Infection has been shown to be involved in the pathogenesis of tumors in severely immunodeficient individuals, as described in the text.

‡As described in Levinson RD, Vann R, Davis JL, et al. Chronic multifocal retinal infiltrates in patients infected with human immunodeficiency virus. Am J Ophthalmol 1998;125:312–324.

OPHTHALMIC MANIFESTATIONS OF AIDS

LOOKING BACK OVER THE PAST 25 YEARS, THE STUDY OF HIV-related eye disease can be divided into several eras separated by distinct periods of transition. The first era was a short period of rapid discovery, in which the spectrum of ophthalmic disorders associated with AIDS was identified; the Table lists the categories into which these disorders fall. Ophthalmic disorders that have come to be associated

with AIDS were nearly all known before the epidemic, although most were quite rare. Much more has been learned about these rare disorders as a result of the AIDS epidemic; it has been shown, for example, that human herpes virus 8 plays a role in the pathogenesis of Kaposi sarcoma, the most common AIDS-associated eyelid and conjunctival tumor. HIV infection has been associated with new presentations of known diseases; an example is the progressive outer retinal necrosis syndrome, a unique variant of varicella zoster virus (VZV) retinitis seen in patients with AIDS, which is distinct from acute retinal necrosis (ARN) syndrome, the form of VZV retinitis usually seen in immunocompetent patients. Few genuinely new ophthalmic disorders have been described as a result of the AIDS epidemic; they include chronic VZV infection of the corneal epithelium[9] and choroidal pneumocystosis.[10]

Infections are the most devastating of the HIV-related ophthalmic disorders. In the United States, only CMV retinitis has been seen commonly in patients with AIDS; other agents are believed to be responsible for less than 1% of HIV-related retinal infections. Before the AIDS epidemic, there had been only a few of CMV retinitis cases in the world's medical literature, all involving immunodeficient hosts, including organ transplant recipients and newborns with cytomegalic inclusion disease. In contrast, it was generally accepted in the pre-HAART era that in at least 30% of people with AIDS, CMV retinitis would eventually develop, and at one point in the epidemic, CMV retinitis was the most common retinal infection seen in urban areas, even by ophthalmologists in general practice.[11]

CMV retinitis occurs only in those HIV-infected individuals with the most severe levels of immunodeficiency, as manifested by CD4+ T-lymphocyte counts of fewer than 50 cells/μl. It is therefore a late manifestation of AIDS; in the pre-HAART era, patients rarely survived longer than one to two years after diagnosis of CMV retinitis. Retinitis is the most common clinical presentation of CMV end-organ disease in people with AIDS, but early autopsy studies showed that affected patients always had infection of other organs as well. Thus, AIDS-related CMV retinitis should be considered a systemic disease, which has implications for treatment, as discussed below.

The AIDS epidemic has provided an opportunity to understand the clinical characteristics and natural history of CMV retinitis.[7,12–14] There can be substantial variation in the clinical appearance of retinal lesions,[7] but a universal finding, and the most distinctive feature of CMV retinitis, is a dry granular border with multiple dot-like satellite lesions, caused by advancement of infection into normal retina. The absence of prominent inflammatory reactions in severely immunosuppressed individuals is in contrast to some other intraocular infections, such as toxoplasmic retinochoroiditis. CMV reaches the eye through the blood stream. Unlike many infectious retinopathies, which are multifocal, CMV retinitis starts as a single lesion in most cases. Infection then spreads centrifugally from that focus; new lesions are relatively uncommon, even with persistent viremia. Spread of infection has been shown to be relentless in the setting of continued immunodeficiency, with advancement of lesion borders toward the fovea at a median rate of 24 μm/day.[13]

Early in the AIDS epidemic, it was recognized that the presence of cotton-wool spots (sometimes in association with retinal hemorrhage) was the most common ophthalmic finding in people with AIDS.[2,12] It is widely accepted that these findings, termed *HIV retinopathy*, are related to a retinal microvasculopathy. Narrowing of retinal capillary lumina, loss of pericytes, and thickening of basal laminae have been universal findings at autopsy of patients who die with AIDS.[12] A distinction should be made between the microvasculopathy of HIV disease (a histologic finding) and the features of HIV retinopathy (clinical manifestations of focal ischemia). The microvascular changes, which resemble those of diabetic retinopathy, are themselves probably not sufficient to cause HIV retinopathy, as evidenced by the fact that cotton-wool spots are not always present, and they are related to the severity of immunodeficiency. HIV retinopathy then must reflect additional factors that intermittently cause ischemia. These factors, and the cause of the microvasculopathy, remain unknown, but my colleagues and I have explored the likelihood that alterations of retinal blood flow contribute to retinal ischemia.[15–18] Both leukocyte velocity through macular capillaries and erythrocyte flow are reduced, and determinants of blood flow (fibrinogen, erythrocyte aggregation, erythrocyte and leukocyte rigidity) are abnormal in HIV-infected individuals. Cotton-wool spots are a risk factor for subsequent development of CMV retinitis, suggesting that the microvasculopathy of HIV disease may play a role in the pathogenesis of the infection, perhaps by facilitating transit of CMV-infected leukocytes across vessel walls. Although patients with cotton-wool spots usually have no changes in central visual acuity, it is suspected that the microvasculopathy also results in retinal and optic nerve damage, manifested by thinning of the retina and loss of axons in the optic nerve.[19,20] These changes may be the cause for an increased prevalence of various vision abnormalities (abnormal color vision, reduced contrast sensitivity, and visual field abnormalities) in HIV-infected individuals when compared with the general population.[21–23]

Uveitis unrelated to known opportunistic infections has turned out not to be a common feature of HIV disease. There are, however, occasional patients who have chronic anterior uveitis[24] or panuveitis characterized by chronic multifocal retinal infiltrates.[25] The causes of these disorders, or even whether they represent single disease entities, has never been determined. Uveitis also may be drug induced; rifabutin and cidofovir were the most commonly reported causes in the pre-HAART era.[26,27]

Although retinal disorders have garnered more attention during the AIDS epidemic, eyelid and ocular surface infections and tumors have contributed to the morbidity of AIDS as well. The incidence of such problems (e.g., Kaposi sarcoma, herpes zoster ophthalmicus, corneal microsporidiosis, and molluscum contagiosum) also has dropped dramatically with HAART, although other, less severe problems, such as dry eye and blepharitis, continue to affect HIV-infected individuals. Anterior segment and external ocular diseases associated with HIV infection have been reviewed by Jeng and associates.[28]

The spectrum of AIDS-related eye diseases differs in various parts of the world.[5] Squamous cell carcinoma of the conjunctiva and ocular tuberculosis have been greater problems in Africa than CMV retinitis, attributed to the fact that patients die of other complications before reaching levels of immunodeficiency associated with CMV disease. During the early years of the epidemic in the United States, the prevalence of CMV retinitis increased as treatment of other life-threatening opportunistic infections improved, and patients survived longer. It is feared that the same phenomenon will be seen in the developing world; as treatments for HIV-associated opportunistic infections and neoplasms improve worldwide, CMV retinitis may emerge as a global problem.

TREATMENT OF CYTOMEGALOVIRUS RETINITIS

AT THE START OF THE AIDS EPIDEMIC, NO TREATMENTS FOR CMV retinitis were available. In 1984, the first anti-CMV drug, ganciclovir, was made available on compassionate use protocols, and treatment of CMV retinitis and its complications became a primary focus of attention in the next era, which lasted a dozen years. As a direct result of the AIDS epidemic, four anti-CMV drugs were developed and approved by the United States Food and Drug Administration (FDA) for marketing: ganciclovir (Cytovene; Roche Pharmaceuticals, Nutley, New Jersey, USA; approved in 1989), foscarnet (Foscavir; AstraZeneca LP, Wilmington, Delaware, USA; approved in 1991), cidofovir (Vistide; Gilead Sciences, Inc, Foster City, California, USA; approved in 1996), and fomivirsen (Vitravene; Novartis Ophthalmics AG, Bulach, Switzerland, and Isis Pharmaceuticals, Inc, Carlsbad, California, USA; approved in 1998). With the reduced demand for treatment of CMV retinitis, production of fomivirsen was stopped in 2004. Ganciclovir, foscarnet, and cidofovir are all administered intravenously. An oral form of ganciclovir was approved in 1994, but is less effective because of low bioavailability. More recently, a prodrug, valganciclovir (Valcyte; Roche Pharmaceuticals; approved in 2001), became available for oral use; induction with valganciclovir can achieve blood levels of the active compound that are comparable with those achieved with intravenous (IV) ganciclovir. All of these drugs inactivate CMV, but none eliminate virus from the eye; thus, treatment must be continued indefinitely for patients who remain severely immunodeficient.

With the development of anti-CMV drugs, there was a need for objective measures to assess drug response. The system adopted for drug studies[29] was based on an understanding of the course of untreated disease. Progression was defined as either enlargement of existing lesions or development of new lesions. The specific goal of anti-CMV therapy in the pre-HAART era was limiting progression of disease. The system, as originally proposed, included an assessment of lesion opacification (whiteness), thought to be a reflection of virus activity,[29] but this measure usually was not assessed in clinical trials. Often, smoldering disease activity persisted despite treatment, especially late in the course of disease; thus, the best that could be achieved for many patients was slowing of lesion enlargement, which was nevertheless usually sufficient for retention of functional vision during their limited lifespans.

A standardized treatment regimen was established empirically that balanced treatment effect vs drug toxicities, which are substantial (primarily bone marrow suppression for ganciclovir and valganciclovir; also renal toxicity for foscarnet and cidofovir). A set two- to three-week period of high-dose induction is administered to bring disease under control, followed by continuous, lower-dose maintenance therapy to sustain that control. Invariably, however, disease eventually progressed, and patients were treated with another, finite course of reinduction at the higher dose. This cycle was repeated until the patient's death, usually at decreasing intervals between reinductions. This approach was validated by industry-sponsored studies and clinical trials conducted by the multicenter Studies of the Ocular Complications of AIDS (SOCA) Research Group (http://www.jhucct.com/soca/default.htm), which has been funded by the National Eye Institute since 1988. As experience with these drugs grew, and ganciclovir-associated neutropenia could be managed with leukocyte growth factors such as filgrastim (granulocyte colony-stimulating factor; Neupogen; Amgen, Thousand Oaks, California, USA), some clinicians continued initial induction-level treatment as long as necessary to achieve disease inactivity; there was some evidence that doing so delayed eventual progression (Siegner SW, Holland GN, Stempien MJ, et al., unpublished data, presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology, May 1997, Abstract no. 4282).

Both ganciclovir and foscarnet can be injected directly into the eye to achieve high drug levels, but repeated intravitreous injections are impractical for routine, chronic therapy. To address the need for long-term, local drug delivery, the ganciclovir implant (Vitrasert; Bausch & Lomb, Inc, San Dimas, California, USA; approved 1996) was developed; it is placed through the pars plana and releases relatively high drug levels directly into the vitre-

ous humor for approximately eight months. Treatment with ganciclovir implants is associated with a significantly longer time to first progression when compared with IV ganciclovir treatment. Patients are probably at increased risk of retinal detachment in the period immediately after the implantation procedure because of disruption of the vitreous base, but that increased risk eventually is balanced by a reduced risk of retinal detachment because of better control of disease activity. Thus, during the course of most reported studies, the overall risk of retinal detachment was no higher in patients with ganciclovir implants than in patients treated with IV ganciclovir alone.

A disadvantage of local therapy is the fact that nonocular sites of CMV infection are not treated, and opposite, uninvolved eyes are not protected; by the end of the pre-HAART era, a popular therapy therefore was the combination of ganciclovir implant and oral ganciclovir (later oral valganciclovir).

Development of CMV resistance to antiviral medications was a growing problem in the pre-HAART era because the prevalence of resistance increases with duration of treatment, especially if suppression of disease activity is incomplete. Resistance is a relative phenomenon; in many cases, it can be overcome by increased drug doses. Mutations of two CMV genes that confer resistance have been studied extensively. Mutations of the *UL97* gene inactivate an enzyme necessary for conversion of ganciclovir to its active form, resulting in low-level resistance. Mutations of the *UL54* gene affect the viral deoxyribonucleic acid (DNA) polymerase, resulting in high-level resistance, not only to ganciclovir, but also to foscarnet and cidofovir. Knowledge of resistance status has practical implications for choice of drug therapy, but is not available for patients from whom virus or viral DNA cannot be isolated. A number of studies have shown a relationship between drug resistance of isolates from the blood or urine and progression of CMV retinitis, but it has also been shown that mutations arise locally in some patients (i.e., virus in the eye can have different resistance patterns than in the blood). Thus, isolates from the eye (e.g., obtained from vitreous humor at the time of retinal detachment surgery) are most useful for making treatment decisions. Resistance testing can be phenotypic (culture-based, requiring live virus) or genotypic (by polymerase chain reaction techniques, requiring only viral DNA), which is more rapid.

There are several potential reasons that CMV retinitis reactivates and becomes more difficult to control over time: further waning of immunity, inadequate intraocular drug levels, and drug resistance. Although initial therapy was fairly standardized in the pre-HAART era, there were multiple options for treatment of reactivation, including switching to another drug or using more aggressive therapy, such as combined IV ganciclovir and foscarnet or supplementation of systemic drug treatment with intravitreous injections of ganciclovir or foscarnet.

There were no "best" drugs or treatment regimens for CMV retinitis. Choice of agents was based on a variety of factors, including location and extent of lesions, medical status (leukocyte count, renal status, other drugs; in anticipation of possible toxicities), and lifestyle considerations. Ganciclovir implants usually were chosen for patients with fovea-threatening lesions, because they are more effective at preventing lesion enlargement, and thus, at preserving vision. In contrast, ganciclovir implants may be less appropriate for patients with large, peripheral lesions only, because of an increased risk of retinal detachment. It has been shown that visual outcome is not significantly better when a ganciclovir implant is used for initial therapy of patients with peripheral lesions only.[30] Vaudaux and I reviewed anti-CMV drugs and various treatment strategies in detail in 2004.[31]

THE ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

THE INTRODUCTION OF HAART, WHICH BECAME WIDELY available in 1996, was a watershed event in the AIDS epidemic. HAART refers to various combinations of multiple drugs (from different classes of antiretrovirals) that effectively suppress HIV replication. Successful treatment is manifested by clearing of HIV from the blood (often to undetectable levels) and an increase in circulating CD4+ T-lymphocytes (a primary target of HIV infection). Immune recovery may not be achieved for three months or longer, however, and during that interval, patients are still at risk for opportunistic infections, including CMV retinitis. There are now approximately 30 FDA-approved antiretroviral drugs and fixed-drug combinations, which are used in numerous drug regimens. Use of antiretroviral drugs has been summarized by an expert panel convened by the International AIDS Society-USA.[32]

HAART is not the panacea that some in the lay public assume it to be. Drugs are expensive, making them unavailable to many patients; treatment regimens are complicated, making compliance an issue; and HIV can become resistant to HAART, which again places patients at risk for the complications of AIDS. The incidence of adverse events is lower in HAART-failure patients than that seen in the pre-HAART era, however.

The SOCA Research Group is currently conducting the Longitudinal Study of Ocular Complications of AIDS (LSOCA) an epidemiologic study to evaluate changes in the incidence, spectrum, and complications of HIV-related eye disease in the HAART era. CMV retinitis remains a major problem. Many HIV-infected individuals had CMV retinitis before the introduction of HAART and must still deal with its complications, such as retinal detachments. It has been estimated that the incidence of new CMV retinitis in the HAART era is 5.6/100 person-years (PY),[33] which is substantially lower than in the pre-HAART era. Most occur

in HAART-failure patients who have low CD4+ T-lymphocyte counts, although there is more variation in counts at the time of diagnosis than in the pre-HAART era.[8]

The basic clinical features of CMV retinitis are similar to those seen in the pre-HAART era,[8,34,35] although there seems to be a mild reduction in disease severity among HAART-failure patients when compared with HAART-naïve patients.[8] An effect of HAART on the course of disease also has been documented; changes from the pre-HAART era include reduced incidences of progression[36] (including second eye involvement[37]) and retinal detachment.[37] These events can still occur with improved immune function, however; the incidence for each is approximately 0.02 events/PY for patients with CD4+ T-lymphocyte counts of more than 200 cells/μl. CMV retinitis has significant adverse effects on quality of life for patients receiving HAART, even when other health measures have improved,[38] emphasizing the importance of prevention. In a multivariant analysis, the SOCA Research Group demonstrated that CMV retinitis remains a risk factor for mortality in the HAART era after adjusting for other factors, including age, treatment, and immune status, although the effect is most apparent at lower CD4+ T-lymphocyte counts.[39]

It is feared that the incidence of CMV retinitis may rise again, as HIV resistance to antiretroviral drugs increases and as HIV infects racial and ethnic minorities, teenagers, and other individuals who remain poorly informed about the disease, have limited access to healthcare information, and are not yet receiving HAART.

CMV retinitis accounts for only 40% of vision loss to 20/200 or worse among LSOCA subjects.[40] Cataracts account for 25% of such vision loss; the pathogenesis of cataracts in HIV-infected individuals without intraocular infectious or inflammatory disease is not known. In more than 10% of LSOCA subjects, the cause of vision loss has not been determined.

Hemorheologic abnormalities persist despite use of HAART,[15–18] suggesting that HIV-infected individuals may be at risk for ongoing damage to the retina. Cotton-wool spots are not seen commonly after immune recovery; thus, factors other than blood flow that contribute to focal ischemia in severely immunodeficient individuals must improve with HAART. Unknown is whether the microvasculature remodels itself in long-term survivors.

Treatment of CMV retinitis has become more complicated in the HAART era because of the many treatment options available and the heterogeneity of patients in terms of demographics and immune status. A challenge has been to adapt previous short-term treatments to the long-term management of what has become, for many individuals, a chronic disease. There has been a paradigm shift in goals, from slowing of disease progression to long-term suppression of disease activity. As a result, I have returned to lesion opacity as a more important measure to observe than lesion border position. Treatment of CMV disease after the introduction of HAART was summarized in 1998 by an expert panel convened by the International AIDS Society-USA.[41] Outlined below are key management issues.

• **INITIAL DRUG TREATMENT:** The most important therapeutic maneuver for initial treatment of newly diagnosed CMV retinitis is to start HAART (for patients not taking antiretroviral drugs) or to reestablish immune recovery (for HAART-failure patients, by changing antiretroviral medications, if possible); however, it is a common practice among HIV specialists to delay the start of HAART for patients with systemic infectious diseases, such as tuberculosis, until treatments for the infections are started, to reduce the risk of systemic inflammatory reactions against the pathogens. The same may be true for reducing the risk of IRU, as discussed below. After the start of HAART, immune recovery is not achieved immediately; therefore, anti-CMV drugs should be given until certain immunologic (and possibly virologic) parameters are achieved, as discussed below. I also recommend that induction be continued until CMV retinitis is inactive, to limit the size of lesions. Doing so presumably reduces the risk of retinal detachment and vision loss in individuals who have the prospect of prolonged survival.

Valganciclovir is the drug used most commonly for initial therapy because of its convenience, lower cost, and lack of complications associated with IV administration. The ganciclovir implant generally is not used for initial therapy in HAART-naïve patients with newly diagnosed CMV retinitis because such patients may not need chronic anti-CMV therapy, and the potential long-term risks associated with having had a ganciclovir implant procedure therefore can be avoided. If a patient has a vision-threatening macular lesion, however, a ganciclovir implant still may be the best option because of its better suppression of virus activity. Risks associated with ganciclovir implants for such cases seem to be acceptable, even if immune recovery is achieved; a study found that the risk of implant-related complications was low, even among patients followed up for as long as seven years.[42] Cidofovir is not used for initial therapy if immune recovery can be expected because of its association with IRU, as discussed below.

• **DISCONTINUATION OF ANTI-CYTOMEGALOVIRUS TREATMENT:** Immune recovery allows eventual discontinuation of specific anti-CMV therapy without reactivation of infection. A decision to discontinue anti-CMV drugs usually is based on several factors: a sustained rise in CD4+ T-lymphocyte count; a drop in HIV blood level; duration of HAART that is sufficient to effect immune recovery; and inactivity of CMV retinitis lesions. The CDC has issued guidelines for discontinuation of anti-CMV drugs, based on the consensus opinion of an expert panel; patients receiving HAART should have CD4+

T-lymphocyte counts of more than 100 to 150 cells/μl for at least three to six months.[43] In a 2000 review of seven initial publications describing discontinuation of anti-CMV drug therapy,[44] I found that most patients for whom discontinuation of anti-CMV drugs was successful had values that far exceeded these guidelines, however. Also, some clinicians require additional evidence that HIV blood levels have dropped by $2\log_{10}$ units, to fewer than 200 copies/ml.[45] In my 2000 review,[44] I noted that the value of HIV blood level as a criterion for discontinuation of anti-CMV drugs was unclear; some patients with sustained inactivity after discontinuation of anti-CMV drugs had detectable HIV in the blood. Walmsley and associates[46] subsequently reported patients who have sustained inactivity without treatment despite HIV blood levels of more than 30,000 copies/ml. Nevertheless, there is evidence that HIV blood levels can be a useful marker for eventual reactivation, as discussed below. By addressing the issues of toxicity, expense, and complexity of treatment, discontinuation of anti-CMV drugs has contributed substantially to an improved quality of life for patients with CMV retinitis in the HAART era.

• **MONITORING PATIENTS:** CMV retinitis eventually can reactivate after anti-CMV drugs are stopped; studies have estimated that the risk of recurrence is approximately 0.02 events/PY.[45,46] Thus, continued monitoring of patients is critical. CD4+ T-lymphocyte count is the laboratory measure followed most commonly, but a rising or very high HIV blood level may be an additional important indicator of risk for new CMV retinitis lesions or reactivation of disease after discontinuation of anti-CMV drugs.[8,47]

Relationships between detectable CMV antigen or DNA in the blood and development of new CMV retinitis or reactivation of existing lesions have been shown in multiple studies, but the predictive value of such tests is not sufficiently high for them to be useful in monitoring patients.[48] Before the HAART era, my colleagues and I were investigating a test of CMV DNA blood level as a guide in making treatment decisions for patients who had reactivation of CMV retinitis lesions.[49] Rising levels indicated active systemic disease as well, suggesting the need for reinduction, whereas lack of CMV DNA in the blood suggested the possibility of local reactivation only (either because of drug delivery problems or local drug resistance) that could be managed with supplementation by intravitreous drug injection alone or with a ganciclovir implant. Whether such inferences can be made in the HAART era is uncertain. In a clinical trial, preemptive anti-CMV drug treatment of subjects with viremia did not reduce the risk of CMV end-organ disease (Wohl D, Kendall M, Anderson J, et al., unpublished data, presented at 13th Conference on Retroviruses and Opportunistic Infections, February 2006). The number of subjects was small, however, and the incidence of disease was substantially lower than that seen in the pre-HAART era. Detection of CMV in the urine has not been useful in clinical practice for monitoring patients at risk for CMV retinitis.

CD4+ T-lymphocyte counts are nonspecific measures of immune function. Impaired CMV immunity is usually, but not always, reflected in low CD4+ T-lymphocyte counts, providing a possible explanation for the occasional patient in whom CMV retinitis develops with CD4+ T-lymphocyte counts of more than 50 cells/μl. A number of studies have shown that selective impairment of immune reactions against CMV can be present in patients with AIDS and CMV retinitis. For example, in a 2006 article, Sinclair and associates showed that cytokine response of CD4+ T-lymphocytes and CD8+ T-lymphocytes to CMV antigen, as well as characteristics of CD8+ T-lymphocyte profiles, differ between patients receiving HAART who have prolonged inactivity of CMV retinitis and those with active infections.[50] Although tests of CMV immunity are providing a better understanding of pathogenesis of CMV retinitis, they are not commercially available, and their ability to predict development or reactivation of CMV retinitis has not yet been demonstrated.

Serial ophthalmic examinations and patient education about symptoms of CMV retinitis are additional components of effective monitoring programs. Periodic screening examinations of patients with CMV retinitis for reactivation (and of people at risk for new disease) is a well-accepted practice, although there is little evidence to support the common recommendation that examinations be performed at three-month intervals. Substantial damage may result from progression of unrecognized CMV retinitis during that interval; thus, I have always emphasized the importance of educating at-risk individuals about the symptoms of CMV retinitis. Although CMV retinitis can be asymptomatic, even small peripheral retinal lesions can result in visual disturbance.

The results of our study of CMV retinitis in the HAART era[8] have public health implications with respect to detection of disease. The proportion of patients in this series who had large lesions at diagnosis was no different than the proportion seen during earlier years of the AIDS epidemic,[7] suggesting that there has been no improvement in the identification of disease early in its course. The percentage of asymptomatic patients seems to be higher among those who are experienced with HAART, possibly because of reduced disease activity; this observation highlights the need for screening programs. Because the incidence of CMV retinitis is decreased, screening will need to be targeted to those at greatest risk, and because the infection can occur in patients with good parameters on current laboratory tests, better markers of impaired CMV immunity are needed. The subject of screening examinations is discussed in greater detail in the Supplement to reference 7 (available at AJO.com) and in reference 8.

• **TREATMENT OF RECURRENT DISEASE:** Reactivation of CMV retinitis in a patient receiving HAART again can be treated successfully with resumption of anti-CMV drug therapy. In fact, anecdotal reports[46] suggest that lesions may be inactivated with less aggressive treatment than would have been required in the pre-HAART era for comparable findings and treatment history (e.g., control with monotherapy rather than combination drug therapy), presumably because of some residual CMV immunity. Of concern is the possibility that patients who have been previously treated with anti-CMV drugs harbor drug-resistant virus strains that will reemerge; however, the two-year incidence of ganciclovir resistance among CMV isolates has fallen from 28% before 1996 to 9% since 1996, attributable to better control of CMV replication with HAART.[51] Most important for long-term control of recurrent CMV retinitis is a change in antiretroviral drug therapy to reestablish immune recovery. If patients have no additional options for HAART, ganciclovir implants may be a good choice for long-term anti-CMV therapy.

• **IMMUNE RECOVERY UVEITIS:** The introduction of HAART brought with it the new ophthalmic problem of IRU, which can be devastating for patients whose health has otherwise improved, because it can result in vision loss. It is well accepted that IRU is caused by a response to CMV antigens, which is made possible by immune recovery. Thus, among patients with unilateral CMV retinitis, IRU occurs only in the eye with infection. The same phenomenon can occur in patients with other intraocular infections, such as toxoplasmosis or tuberculosis.

IRU generally is recognized in its most severe form by an increase in intraocular inflammatory reactions within several weeks after starting HAART, or later by the presence of complications of inflammation, including macular edema, epiretinal membranes, neovascularization of the retina or optic disk, posterior synechiae, and cataract. There are still no widely accepted, objective criteria for identification of IRU, however. Difficulty in defining IRU stems from the fact that mild inflammatory signs were seen in eyes with CMV retinitis in the pre-HAART era, and the severity of inflammation in patients with IRU varies markedly. Thus, IRU represents a change in inflammation, rather than an absolute level of inflammatory reactions or a specific set of complications.

The reported incidence of IRU has varied from 0.1 to 0.8/PY of follow-up[52]; these figures are difficult to interpret, however, if the risk of IRU is in fact not constant over time, as discussed below. In a cross-sectional study of 259 LSOCA subjects with CMV retinitis, IRU occurred in 9.6% of those who had immune recovery.[34]

Risk factors for IRU include larger lesions and previous use of cidofovir, presumably because it also is associated with intraocular inflammation.[53] Considering its pathogenesis, it is surprising that in more patients with CMV retinitis, IRU does not develop. There may be immunologic factors unique to those in whom IRU develops that explain its occurrence in only a subset of patients; this issue is under study, but it is not yet possible to identify at-risk patients on the basis of laboratory tests of immune function.

There has been conflicting information in the medical literature on the course of IRU, attributable to the fact that most studies have involved small numbers of patients with short periods of follow-up. Kuppermann and I reviewed findings from several studies of IRU in a 2000 Editorial.[52] Outlined below is my perception of IRU and its course, based on that review and my own experience with patients. Within weeks of starting HAART, and concurrent with a rising CD4+ T-lymphocyte count, patients developing IRU will have increased anterior chamber cells and vitreous haze; they may also have mild to moderate declines in visual acuity at this stage. The inflammatory reactions may improve, with recovery of central vision. Because of its transient nature, this stage can be missed by the clinician. In some patients, the complications listed above will develop, with marked loss of vision; macular edema in particular can persist. In my experience, IRU, if it is to occur, begins in the early stages of immune recovery; reports of IRU that is diagnosed years after the start of HAART may reflect delayed recognition of inflammation or the identification of late complications.

CMV retinitis lesions usually are inactive in patients with IRU, because of the same improvements in immune function that lead to inflammation; however, IRU can occur in eyes with active CMV retinitis, particularly at the onset of the inflammation. Also, I have seen on occasion patients who continue to have smoldering CMV retinitis, despite HAART, and have chronic intraocular inflammatory reactions substantially greater than those seen in the pre-HAART era. Such patients probably have achieved only limited recovery of CMV immunity: enough to mount an inflammatory response against CMV, but insufficient to prevent its reproduction in the retina. Such cases are particularly difficult to manage.

More aggressive anti-CMV drug therapy, especially during the initial period of immune recovery, seems to be associated with a reduced risk of IRU, presumably because of a decreased antigen load.[52] Despite some conflicting reports, most investigators have found no benefit to continued anti-CMV treatment of patients with inactive CMV retinitis after immune recovery, however.[45,54] From a practical standpoint, HAART-naïve patients found to have CMV retinitis should be treated aggressively with anti-CMV drugs, and treatment should be continued through the period during which immune recovery is achieved, before considering discontinuation of treatment. Also, as discussed above, initiation of HAART should be delayed until after the induction phase of anti-CMV therapy; a small study has shown a reduced risk of IRU with delay of HAART.[55]

Treatment of IRU-associated macular edema has been difficult. Several reports describe improvement with systemic or periocular injections of corticosteroid, but I have found such improvement to be incomplete with regard to resolution of edema, and to be transient. Many patients do not achieve a functional benefit, despite objective evidence of improvement. Intravitreous injection of triamcinolone acetonide may be more effective, but repeated injections are necessary.[56] In my experience, patients with IRU-associated cataracts are particularly prone to postoperative problems such as posterior synechiae, pupillary membranes, and inflammatory deposits on the lens implant.

In general, corticosteroid treatment is not associated with reactivation of CMV retinitis lesions. A case of reactivation has been reported,[57] although it is unclear whether the corticosteroid injection itself was responsible; the patient had been receiving HAART for a relatively short period, and it is possible that reactivation might have occurred anyway. Some authors advocate the reinstitution of anti-CMV drug therapy when treating IRU with corticosteroids to reduce the risk of reactivation.[56]

Loss of vision resulting from IRU can prevent individuals from returning to work and enjoying the activities of daily living. It is an unfortunate irony that the factors leading to improved general health for people with AIDS can also deprive some of useful vision. Additional study of IRU is necessary if this quality of life issue is to be addressed more effectively.

- **RETINAL DETACHMENT:** In the pre-HAART era, retinal detachments occurred in more than one-third of patients with CMV retinitis who survived one year or longer. Vitrectomy with silicone oil tamponade became the standard method for repair of these detachments, but several factors related to the presence of silicone oil limited postoperative vision; they include cataract formation, refractive error change (hyperopia), and aniseikonia not associated with anisometropia (paradoxical minification). Many patients lost vision for unknown reasons, unrelated to the aforementioned factors. The risk of detachment is substantially less among patients receiving HAART,[37] which has been attributed to better control of infection, resulting in smaller, inactive lesions, and therefore better healed and more adherent scars. Some clinicians therefore are trying cautiously (in selected cases) other techniques for repair that allow better visual function (including gas tamponade or scleral bucking alone). For those patients receiving HARRT who do have silicone oil in their eyes, visual rehabilitation is increasingly important because of longer survival and the ability to lead more active lives with greater visual needs. Clinicians have found that even unexplained vision loss in some patients is reversible with removal of silicone oil, for unclear reasons. Unfortunately, silicone oil cannot be removed safely from many eyes; retinal holes, especially in the presence of retinal traction from scarring, places patients at an unacceptable risk of repeat detachments if silicone oil is removed. This issue and others related to the management of retinal detachments were discussed in a 2005 Editorial by Davis.[58]

IMPACT ON OPHTHALMOLOGY

THE IMPACT OF THE AIDS EPIDEMIC ON THE FIELD OF ophthalmology extends beyond the care of patients with HIV disease. It has resulted in a greater understanding of several associated disorders and treatments developed for AIDS-related infections have been applied to other populations. For example, ganciclovir or foscarnet are now used to treat other necrotizing herpetic retinopathies, such as ARN syndrome, and valganciclovir is used as prophylaxis against CMV end-organ disease in transplant patients.

Perhaps the greatest impact of the AIDS epidemic for all ophthalmologists has been a focus on the potential for disease transmission in the workplace. The need for universal precautions to prevent transmission of infectious agents (e.g., HIV, herpes simplex virus, and adenovirus), regardless of whether patients are known to be infected, has been emphasized. Fortunately, there is little or no risk of HIV transmission in routine ophthalmic examinations or surgical procedures, including corneal transplantation. The American Academy of Ophthalmology has prepared an Information Statement, "Minimizing Transmission of Bloodborne Pathogens and Surface Infectious Agents in Ophthalmic Offices and Operating Rooms" (available at http://aao.org/education/statements), which summarizes universal precautions, identifies resources for management of occupation exposure, and provides a list of relevant publications.

FUTURE DIRECTIONS

THE NEXT ERA WILL BE ONE THAT IMPROVES OUR UNDERstanding of disease processes, refines treatments, and returns to the study of ophthalmic problems other than CMV retinitis. Listed below are issues that require continued study:

- A still better understanding of CMV retinitis is needed, especially with regard to risk factors for its development and recurrence. Studies of human genes that regulate the immune response to specific infections hold promise in this area. Additional studies of CMV immunity may lead to tests that are useful for predicting those at highest risk.
- Better long-term strategies for the management of CMV retinitis and its complications are required. Issues include not only treatment, but also prevention and visual rehabilitation. Strategies appropriate for the developing world must be considered.

- Retinal and optic nerve damage that occurs in the absence of clinically apparent infections needs additional study. Of particular importance is whether damage progresses despite HAART and immune recovery.
- The basis for alterations in vision that have been documented in the absence of clinical lesions (abnormal color vision, reduced contrast sensitivity, and visual field changes) should be explored further. Confirming a link to the microvasculopathy of HIV disease may help to clarify responsible disease mechanisms. The cause of cataracts in this population also needs to be explored. Such studies ultimately may help to improve the quality of life for people with HIV disease.
- Study of the retinal vasculature also may provide insights into other, nonocular disorders associated with HIV disease. Renal disease and cardiovascular disease have become important in the HAART era and may share disease mechanisms with the microvasculopathy of HIV disease.

HIV-related eye disease will remain an important problem for many decades to come, but a variety of factors will make its study more difficult in the future; they include the shift in demographics of HIV infection in the United States and the fact that the bulk of new disease will occur in the developing world. (For the same reasons, cost and access to care issues will be increasing important.) Unfortunately, interest in AIDS research among many investigators and funding agencies has diminished in recent years. Although the sense of urgency about AIDS-related CMV retinitis that was present in the 1990s has been lost, continued attention to HIV-related eye disease by the medical community is critical, for those already affected, and for the millions still at risk.

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Biosketch

Dr Gary N. Holland is the Vernon O. Underwood Family Professor of Ophthalmology at the David Geffen School of Medicine at UCLA, and Director of the Ocular Inflammatory Disease Center, Jules Stein Eye Institute. Since 1993, he has been Associate Editor of the *American Journal of Ophthalmology*. In 1982, Dr Holland authored the first article on the ophthalmic manifestations of AIDS. He continues to be involved in AIDS research and care of patients with HIV-related eye disease.