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HIV/AIDS (C YOON, SECTION EDITOR)

Ophthalmologic Disease in HIV Infection: Recent Changes in Pathophysiology and Treatment

Michael W. Stewart[1]

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Abstract
Purpose of Review Ophthalmologic conditions were among the earliest described findings in patients with the acquired immunodeficiency syndrome (AIDS). The purpose of this review is to highlight recent changes in the pathophysiology and management of ophthalmologic conditions in patients infected with the human immunodeficiency virus (HIV).
Recent Findings The introduction of highly active antiretroviral therapy (HAART) in 1996 changed ophthalmologic findings from predominantly acute infectious diseases to chronic, slowly progressive, debilitating conditions. HIV-associated neuroretinal disorder infrequently leads to blindness, but it causes visual disability in a large percentage of patients. Cytomegalovirus retinitis is now seen less commonly in the USA, but it remains an important cause of blindness in HIV-infected patients from developing countries. Immune recovery uveitis has emerged as a major cause of visual disability in the USA.
Summary As HIV has become a chronic disease, visual disability due to chronic noninfectious diseases have become increasingly important.

Keywords Acquired immunodeficiency syndrome · Cytomegalovirus retinitis · HIV-associated neuroretinal disorder · Human immunodeficiency virus · Immune recovery uveitis · Valganciclovir

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✉ Michael W. Stewart
stewart.michael@mayo.edu

[1] Department of Ophthalmology, Mayo Clinic School of Medicine, 4500 San Pablo Rd, Jacksonville, FL 32224, USA

Introduction

The eye and ocular adnexae have been frequently affected by human immunodeficiency virus (HIV)-related diseases since the beginning of the acquired immunodeficiency syndrome (AIDS) epidemic. In the pre-antiretroviral era, HIV-infected individuals had a 70% chance of developing ocular diseases [1, 2]. Most of these patients were afflicted with opportunistic infections, with cytomegalovirus (CMV) being the major cause of vision loss. The introduction of CMV-specific anti-viral medications and the subsequent development of highly active antiretroviral therapy (HAART) significantly decreased the incidence of CMV-related vision loss and blindness, but new conditions, such as immune reconstitution inflammatory syndrome (IRIS), have emerged. Noninfectious comorbidities such as coronary artery disease, osteoporosis, chronic kidney disease, hyperlipidemia, liver disease, and non-AIDS-defining malignancies have been more commonly seen since the introduction of HAART, and some of them contribute to vision loss. As a result especially in the aging population, the emphasis on ocular care for HIV-infected patients has shifted from management of acute disease to care for chronic conditions.

Most HIV-infected patients receive life-long antiretroviral therapy (ART), so considerable interest has emerged regarding the effects of therapy on pathologic systemic processes. Many chronic diseases cause ocular problems, but the long-term effects of both HIV infection and ART are poorly understood.

This manuscript will discuss recent developments in HIV-related eye disease, with a focus on advances made during the past 5 years.

Historical Perspective and Current Epidemiology

Prior to the introduction of HAART, opportunistic infections were responsible for most HIV-related diseases. CMV retinitis affected from 20 to 40% of AIDS patients, usually in the setting of advanced HIV infection when CD4+ counts fell below 50 cells/μL. The absence of sufficient CMV immunosurveillance, the difficulty in administering anti-CMV drugs that produced significant side effects, and the emergence of drug resistance by CMV caused a large number of patients to become blind.

After the introduction of HAART in 1996, many academic centers reported 80% decreases in the incidence of CMV retinitis [3]. Despite this significant drop in the incidence of infectious retinitis, recent studies show that approximately 40% of patients with AIDS still have significant impairment of vision [4]. Not surprisingly, the spectrum of ocular conditions affecting these patients has shifted since 1996. For example, reconstitution of the immune system decreased the incidence of retinitis, but it led to the development of immune recovery uveitis (IRU).

Many of these newly described ocular conditions may be the result of persistent systemic inflammation or the increased incidence of non-AIDS-related co-morbidities such as diabetes and systemic arterial hypertension. Despite the improved immunologic function experienced by HAART-treated patients, decreased incidence of opportunistic infections, and prolonged life spans from improved anti-HIV therapy, immune-restored HIV-infected individuals still have shorter life expectancy than their non-infected peers. In addition, the geriatric syndrome with the accumulation of multiple co-morbidities, polypharmacy, and frailty in antiretroviral treated HIV-infected patients may occur 15–20 years earlier than in non-infected patients and has been described also as accelerated aging [5, 6]. The reasons for increased morbidity and mortality among patients receiving HAART are multifactorial and include the increased incidence of aging diseases such as cardiovascular conditions, malignancies, metabolic disorders, and cognitive decline.

The incidence of CMV retinitis decreased significantly with the introduction of HAART, but the overall incidences of infectious ophthalmologic diseases in patients receiving long-term ART are not well known. A retrospective study from the Wills Eye Institute detailed the ophthalmologic reasons for hospital admission of AIDS patients between 1995 and 2010. The cohort was sub-divided into "Early ART" (1995 through June 2003) and "Late ART" (July 2003 through 2010) groups [7]. The authors chose mid-2003 as the temporal divide, because newer, better tolerated anti-HIV medications such as atazanavir, fosamprenavir, and fixed-dose combination pills such as tenofovir/emtricitabine and tenofovir/emtricitabine/efavirenz become available at this time. Compared to patients in the Early ART group, those in the Late ART group had higher median CD4+ counts (108 vs. 40 cells/μL), fewer previous opportunistic infection (36.4 vs. 72.2%), a lower likelihood of an infectious ocular diagnosis (37.7 vs. 54.6%), and a lower likelihood of having CMV retinitis (7.4 vs. 28.6%). But they had more noninfectious complications including higher incidences of malignancies (15.9 vs. 1.8%) and diabetes (16.7 vs. 7%). Interestingly, the Late ART group had a higher rate of severe visual impairment (58 vs. 37.5%).

A study from South Africa determined the prevalence and severity of ocular diseases among patients with chronic HIV infection [8]. More HIV-infected individuals presented with external diseases, particularly blepharitis (18 vs. 7% non-infected) and anterior segment conditions (particularly keratoconjunctivitis sicca and pterygium; 50 vs. 27%). Compared to patients receiving short-term ART, those receiving long-term ART had higher prevalences of cataracts (57 vs. 38%) and posterior segment disease (particularly HIV retinopathy; 30 vs. 11%). Long-term ART was strongly associated with the development of HIV retinopathy.

Infectious-Related Disorders

HIV-Associated Neuroretinal Disorder (HIV-NRD)

Subtle structural and functional abnormalities of the optic nerve or retina in HIV-infected patients receiving combination ART represent neuroretinal degeneration. Patients with low nadir CD4+ counts below 100 cells/μL are at a greatest risk of developing HIV-NRD, but it remains to be determined if patients with higher CD4+ nadirs > 350 cells/μL on ART are also at risk. HIV-NRD can occur despite complete suppression of serum HIV RNA levels and evidence of immune reconstitution. Clinically observable retinal abnormalities such as narrowing of the retinal vascular caliber [9] and decrease in retinal blood flow [10] are associated with HIV-NRD, but these are associated with persistent viremia rather than the low CD4+ nadir (Fig. 1).

Thinning of the retinal nerve fiber layer has been measured by optical coherence tomography (OCT) [11]. Affected patients experience decreases in color vision, contrast sensitivity [4, 12], and visual field sensitivity [13] and have subnormal electrophysiologic amplitudes [14]. Though these visual changes are subtle, they decrease the quality of life [15•] by interfering with daily activities such as driving. Affected patients also experience increased incidences of falls [16], decreased reading speed [17], impaired color vision [18], and impaired facial recognition [19]. Affected patients have increased risks for visual impairment (best corrected visual acuity (BCVA) < 20/40) and blindness (BCVA ≤ 20/200) [20]. Fortunately, the risk of bilateral blindness due to HIV-NRD remains low at both 10 years (1.1%) and 15 years (2.1%).

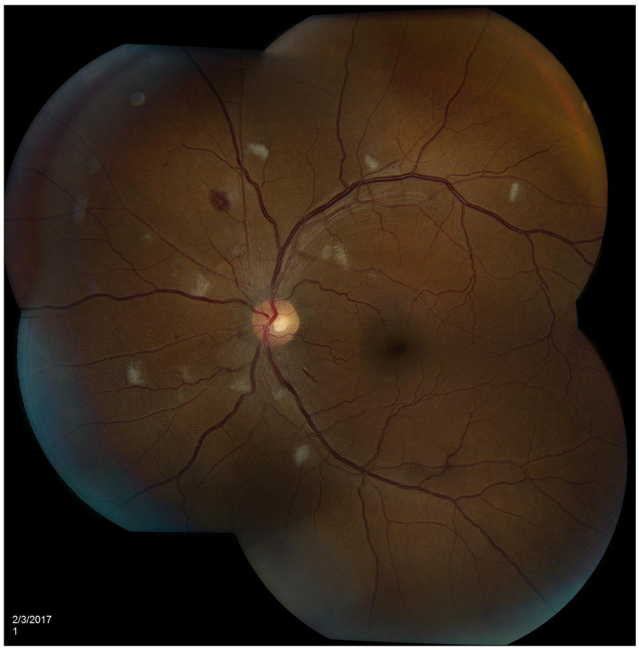

Fig. 1 This fundus photograph shows HIV-retinopathy in a patient with a CD4+ count of 76 cells/μL. Of note are scattered cotton-wool spots, a white-centered hemorrhage, and narrowing of the retinal arterioles

Since HIV has become a chronic disease with patients having longer life-spans, long-term retention of functional vision is an increasingly important ability.

The Longitudinal Study of the Ocular Complications of AIDS (LSOCA) group found that the incidence of HIV-NRD was 1.9/100 person-years and that risk factors included a detectable HIV viral load and not taking ART. The cumulative incidence for HIV-NRD by 20 years after the diagnosis of AIDS was 51%, and patients with HIV-NRD had increased risks of bilateral blindness and mortality (increased by 70%) [20]. Effective ART decreased but did not eliminate the risk of HIV neuroretinal disorder.

The pathophysiology of HIV-NRD was nicely summarized in a diagram by Demirkaya et al. in which HIV, ART, genetic factors, and associated risk factors lead to mitochondrial toxicity/dysfunction, immunological response/inflammation, microvasculopathy, and hemorheological abnormalities, all of which accelerated aging and immunosenescence. All of these features characterize HIV-NRD [21].

CMV Retinitis

The incidence of CMV retinitis dropped precipitously after the introduction of HAART, thereby making CMV retinitis a less frequently encountered problem in the USA [22]. HAART also changed the approach to patients diagnosed with CMV retinitis, as the optimal treatment now includes initiation of two separate lines of therapy.

Firstly, the diagnosis of CMV retinitis mandates that appropriate anti-CMV therapy be initiated. Previously, this meant the administration of intravenous ganciclovir or foscavir, and though these medications suppress CMV replication, extend the time to disease recurrence, and decrease the incidence of contralateral and extraocular disease, they require the placement of an in-dwelling venous catheter with frequent intravenous infusions, increase the risk of bacteremia, and suppress serum leukocyte counts. Since 2000, most physicians forgo intravenous therapy in favor of orally administered valganciclovir [23]. Systemic anti-CMV therapy is appropriate and sufficient for peripheral retinal disease, but for eyes with vision-threatening zone 1 retinitis (near the macula and optic nerve), many physicians add a 3-week course of twice weekly intravitreal ganciclovir before switching to oral valganciclovir monotherapy [24]. The previously used 9-month, sustained-release ganciclovir implant significantly prolonged the time to reactivation and was effective for zone 1 disease [25], but because of the declining incidence of CMV retinitis, it was discontinued in 2013.

Secondly, effective HAART needs to be administered to reconstitute the immune system. This may be by either initiating antiretroviral therapy or by changing drugs to improve an ineffective regimen. If a patient is already receiving HAART when CMV retinitis is diagnosed, poor compliance with the treatment regimen must be suspected and corrected.

Once regression of the CMV retinitis has been achieved and serum HIV titers have been rendered undetectable, serum CD4+ counts need to be followed. When CD4+ counts exceed 100 cells/μL for 6 consecutive months, anti-CMV therapy may be withheld [26], and patients can be followed with dilated eye exams, serum HIV titers, and CD4+ counts.

Though CMV retinitis is now diagnosed much less frequently in industrialized countries, it remains an important cause of blindness in developing countries that have limited medical resources. A tertiary ophthalmology center in Thailand reported that CMV retinitis affects 33% of AIDS patients, thereby constituting the second most common cause of blindness in their clinic [27]. A comparison of cohorts from the pre-HAART and post-HAART eras found similar incidences of CMV retinitis [28]. Findings from these clinics underscore the need to diagnose CMV retinitis early and to make HAART available to AIDS patients, since HAART prevents CMV retinitis and potentiates anti-CMV treatment [29].

CMV retinitis has traditionally been viewed as a "systemic disease" because of its association with extra-ocular infections. Intravitreal therapy plays an important role for rapidly controlling retinitis and limiting vision loss, but patients receiving systemic therapy have a 50% reduction in mortality, a 90% reduction in extraocular disease, and an 80% reduction in the incidence of contralateral retinitis. In many developing countries, limited financial resources prevent the regular use of intravenous and oral anti-CMV therapy, so intravitreal ganciclovir injections continue to be used as monotherapy [24].

Drug-resistant retinitis poses a significant challenge, because it leads to poorer outcomes, larger areas of retinitis, decreased visual acuity, and a high incidence of contralateral involvement. It occurs in patients receiving a long-term anti-CMV therapy particularly in the pre-HAART era. High level ganciclovir resistance typically occurs with mutations in both the UL97 (phosphotransferase) and UL 54 (DNA polymerase) gene, and is often associated with cross resistance to cidofovir and occasionally to foscavir [26]. Leflunomide, an immunosuppressive agent that inhibits virion assembly, has been administered to patients with drug-resistant CMV. Oral leflunomide has achieved long-term suppression of CMV retinitis in patients who are drug-resistant [30].

Retinal detachments (RD) tend to occur relatively soon (mean of 1.5 months) after the diagnosis of CMV retinitis [31]. The risk of retinal detachment has decreased significantly to 1.0–8.7/100 eye-years with HAART, but RD remains a major cause of vision loss [32••]. Because patients with RDs frequently have large areas of necrosis with multiple retinal holes, surgeons still treat these detachments with vitrectomy and silicone oil instillation. Reattachment rates are high and approximately one-third of these eyes achieve visual acuities of 20/50 or better, and two-thirds achieve 20/100 or better [33, 34]. Surgical outcomes in the HAART era are similar to those in the pre-HAART era [33].

Immune Recovery Inflammatory Syndrome

IRIS refers to a group of disorders experienced by some HIV-infected patients soon after beginning HAART [35]. Patients with a history of previous conditions such as Kaposi's sarcoma, tuberculosis, cryptococcus, and CMV develop inflammation after an exaggerated reactivation of the immune system. IRU occurs when patients develop uveitis (most commonly seen as a low-grade vitritis) after having previously been infected with CMV retinitis. This usually occurs after the serum CD4+ count increases by at least 50 cells/μL to at least 100 cells/μL. IRU has become an important cause of vision loss in HIV-infected patients receiving HAART [36], as it occurs at a rate of 2.2/100 person-years [20]. IRU leads to cataracts (52%), cystoid macular edema (91%), glaucoma, and the formation of epiretinal membranes (30%) [37].

A retrospective study reported that the risk of IRU-induced complications was proportional to the absolute difference in CD4+ counts between the start of HAART and the development of IRU ($P = 0.04$) [38]. Unlike some of the previous reports [39], the majority of the eyes in this study had only small areas of CMV retinitis (< 25%), and no cases of cystoid macular edema were noted (attributed by the authors to earlier treatment of inflammation). The authors state that consensus regarding the ideal time to begin anti-inflammatory (corticosteroid) therapy is lacking, but they acknowledge that most patients with IRU experience mild and asymptomatic uveitis, and that treatment should be reserved for patients with more severe, symptomatic uveitis [40, 41].

Syphilitic Uveitis

Unlike the remarkable decline in the incidence of CMV retinitis after the introduction of HAART, the incidence of syphilis doubled between 2000 and 2011 [42], possibly due to the increasing practice of unprotected sex in an era of effective HIV treatment [43]. HIV patients have been partly responsible for this trend, and the detection of positive syphilis serology should always trigger HIV testing [44]. A 30-year retrospective study from the Netherlands found that 35.9% of the patients with newly diagnosed syphilitic uveitis were HIV-positive [45].

Compared to visual outcomes in immunocompetent patients, those from HIV-infected patients vary among published reports. It has been recommended that ocular syphilis in HIV-infected patients be treated the same as in immunocompetent patients (usually with intravenous benzyl penicillin for 10–21 days), except in those with CD4+ counts below 350/μL [45].

Immunosuppression due to active HIV infection has been reported to increase the likelihood of patients developing syphilitic uveitis [46, 47]. An analysis of the United States National Inpatient Sample, however, found that the number of inpatient admissions for syphilitic uveitis remained stable at 17/year from 1998 to 2009 and that patients hospitalized due to syphilitic uveitis were far more likely to have AIDS (14.79 vs. 0.22% in controls) [48].

Another retrospective study showed that 53% of patients with ocular syphilis also had neurosyphilis. The visual prognosis in HIV-infected patients with ocular syphilis improved with early diagnosis and proper treatment (75% received benzyl penicillin) [49]. Syphilis-related optic neuritis occurs more commonly in HIV-infected patients (53%) than in those without HIV.

Syphilis is responsible for only 1 to 2% of all cases of uveitis [50], but its prevalence among HIV-infected patients is much higher. Underscoring the recent resurgence of syphilitic uveitis are the results from a 10-year study from Taiwan. Among patients found to have uveitis at the time they were diagnosed with AIDS, syphilis emerged as the most common etiology [51].

Noninfectious Disorders

Age-Related Macular Degeneration

The chronic use of antiretroviral medications by HIV-infected persons increases the incidence of several age-related disorders. Age-related macular degeneration, a common cause of

vision loss among patients over the age of 65 years, is characterized in its early and intermediate stages by the development of drusen and retinal pigment epithelium (RPE) changes. The LSOCA trials found that patients with AIDS have a 1.75 times increased risk of developing intermediate-stage age-related macular degeneration (AMD) compared to patients not infected with HIV. The risk of developing AMD among HIV-infected patients is higher with age, HIV transmission category (higher among injection drug users), and smoking. Development of AMD was associated with co-morbidities such as hypertension, diabetes, and cardiovascular disease, but not with the class of antiretroviral drugs [52•]. The increased incidence of AMD may be the result of chronic immune activation due to ongoing, low-grade, systemic inflammation [53]. The results from this study need to be interpreted carefully, however, since other data shows that nucleoside reverse transcriptase inhibitors decrease the risk of choroidal neovascularization, which is one of the defining characteristics of advanced AMD [54].

Cataracts

The accelerated aging and frailty experienced by patients receiving HAART affects ocular structures such as the lens, thereby leading to the premature formation of cataracts [55]. A nationwide, population-based study from Denmark characterized the introduction of ART as a risk factor for cataract development [56]. A study from Cape Town, South Africa, reported an increased incidence of cataracts in HIV-infected individuals who had low nadir CD4+ counts below 200 cells/μL [55].

Progressive lens opacification occurs among patients receiving ART, thereby increasing the need for cataract surgery. For many developing countries with an inadequate number of cataract surgeons, this advancing epidemic of cataracts in HIV-infected patients may further strain their ophthalmology delivery systems [57].

Medicamentosa

Several medications are toxic to the retina and the retinal pigment epithelium. Three drugs used in the treatment of AIDS-related disorders have been linked with RPE toxicity: ritonavir (a protease inhibitor) [58]; clofazimine (used for mycobacterium infections); and didonosine (a reverse transcriptase inhibitor) [59].

Lymphoma

Primary vitreoretinal lymphoma is usually seen in patients over the age of 50 years (mean age: 63 year) but tends to occur at a younger age in individuals infected with HIV.

Conclusions

Recent ophthalmologic findings in patients with AIDS are consistent with the shifting epidemiology of HIV morbidity and mortality, and they emphasize the continued need for routine eye care in the management of HIV-infected patients. Many physicians recommend routine ophthalmologic screening for patients at risk of CMV retinitis (CD4+ counts < 100 cells/μL), but in many countries with inadequate health care resources, only patients with poor vision or ocular symptoms receive examinations. The problem with inadequate routine screening was highlighted by the findings of a recent prospective, cross-sectional study. Visual symptoms (scotomata, itchy or watery eyes, and eye pain) were strongly correlated with the presence of CMV retinitis, but the absence of poor vision and symptoms did not rule out the presence of retinitis (negative likelihood ratios: 0.56 and 0.76) [60].

The persistently high rates of vision loss and chronic disease in HIV-infected patients affect quality of life in both the short and long term [61]. More research is needed to better define long-term ocular morbidity in this population, and treatments for neuroretinal degeneration are needed.

Compliance with Ethical Standards

Conflict of Interest Dr. Stewart declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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