HIV

Nikolas J.S. London and Emmett T. Cunningham Jr.

Contents

N.J.S. London, MD
Retina Consultants San Diego,
9850 Genesee Ave. Suite 700,
La Jolla, CA 92037, USA
e-mail: nik.london@gmail.com

E.T. Cunningham Jr., MD, PhD, MPH (✉)
The Uveitis Service, California Pacific Medical
Center, San Francisco, CA, USA

Department of Ophthalmology,
Stanford University School of Medicine,
Stanford, CA, USA

The Francis I. Proctor Foundation,
UCSF School of Medicine, San Francisco,
CA, USA

West Coast Retina Medical Group, Inc.,
San Francisco, CA, USA
e-mail: emmett_cunningham@yahoo.com

> **Core Messages**
> - Human immunodeficiency virus (HIV) is a retrovirus that may lead to development of acquired immunodeficiency syndrome (AIDS).
> - AIDS is a condition characterized by severely compromised cell-mediated immunity, predisposing patients with HIV/AIDS to opportunistic infections and neoplasms.
> - It is estimated that about 0.8 % of the world's population is infected with HIV [135]. Of these patients, more than 90 % are unaware that they are infected, and up to 70 % have ocular complications related to HIV/AIDS [21].
> - HIV retinopathy is the most common retinal manifestation of HIV/AIDS. It is characterized by the formation of cotton-wool spots, hemorrhages, and microaneurysms, and it is typically asymptomatic.
> - Important ocular infections seen in patients with HIV/AIDS include CMV retinitis, the most common, VZV herpetic retinitis, toxoplasmic retinochoroiditis, syphilis, *Pneumocystis jirovecii* choroiditis (PCP), *Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis*, and cryptococcal choroiditis.

- Noninfectious causes of uveitis observed in patients with HIV/AIDS include neoplastic disease, drug-induced uveitis, and immune recovery uveitis (IRU).

111.1 Definition

Acquired immunodeficiency syndrome (AIDS) was first recognized in Los Angeles and New York in 1981 when outbreaks of what was then called Pneumocystis carinii pneumonia (PCP; now called pneumocystis pneumonia) and Kaposi's sarcoma were observed in previously healthy young men. Before this date, both conditions were very rare and restricted almost exclusively to immunocompromised patients. Epidemiologic data collected at the time suggested that a single blood- and semen-borne virus had predisposed these patients to infection, but it was not until several years after this outbreak that Barré-Sinoussi and associates in Paris and Gallo and associates in the United States independently isolated what was later termed the human immunodeficiency virus (HIV) [4, 40], now known to be the cause of AIDS.

The World Health Organization (WHO) defines AIDS as a disease of compromised cell-mediated immunity (an "AIDS-defining illness") occurring in a person with no known cause for immunodeficiency other than the presence of HIV. The major diseases associated with HIV/AIDS are listed in Table 111.1. The Centers for Disease Control and Prevention (CDC) definition also includes HIV+ adults with a CD4+ count of less than 200 cells/µl.

It is estimated that 33.2 million people are infected with HIV worldwide, with approximately

Table 111.1 Recognized AIDS-defining illnesses (CDC category C)

Microbe class	Entity
Protozoal	Toxoplasmosis of the brain
	Intestinal cryptosporidiosis or isosporiasis with diarrhea >1 month
Fungal	*Pneumocystis* pneumonia (PCP)
	Candidiasis other than oral thrush
	Extrapulmonary *Cryptococcus*
	Coccidioidomycosis, disseminated or extrapulmonary
	Histoplasmosis, disseminated or extrapulmonary
Viral	*Cytomegalovirus* – retinitis, pneumonitis, colitis, or encephalitis
	Herpes simplex – mucocutaneous disease >1 month, or bronchitis, or pneumonitis, or esophagitis
	Progressive multifocal leukoencephalopathy (PML)
Bacterial	Disseminated or extrapulmonary *Mycobacterium avium-intracellulare* (MAI) or *M. kansasii*
	M. tuberculosis, any site
	Recurrent non-typhoid salmonella septicemia
Tumors	Kaposi's sarcoma
	Primary CNS lymphoma
	Non-Hodgkin's B-cell lymphoma, Burkitt's lymphoma
	Invasive cervical cancer[a]
Others	HIV encephalopathy
	HIV wasting syndrome
	Lymphoid interstitial pneumonitis in a child <13 years old

Modified from Centers for Disease Control [48]. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. MMWr 1992, 41 (RR-17). http://hiv.net/link.php?id=184

[a]Must meet at least one of the following criteria: (a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity or (b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection

2.5 million new infections and 2.1 million AIDS-related deaths in 2007 [134]. The prevalence of HIV infection appears to be stabilizing, with a decline in the incidence and improved survival of patients living with HIV/AIDS. However, the pandemic persists in several areas, including (A) the severe epidemic in sub-Saharan Africa, which accounts for 65 % of all new HIV infections, where an estimated 22.5 million persons are infected and where AIDS remains as the leading cause of death, and (B) global epidemics in high-risk populations including IV drug abusers, prostitutes, and men who have sex with men [134].

111.2 Clinical Manifestations

111.2.1 General Involvement

Acute HIV infection often manifests as a flu-like illness, followed by an asymptomatic period that may last from 2 to 10 years and during which CD4+ helper T cells typically decline in number. Patients frequently develop generalized lymphadenopathy and may experience malaise, diarrhea, weight loss, fever, and chills. Later on, as a consequence of declining cell immunity, these patients may manifest clinical signs related to opportunistic infections or neoplasms. These manifestations will depend on the involved organ.

111.2.2 Ocular Involvement

Up to 70 % of patients infected with HIV exhibit clinical signs of ocular disease, and postmortem findings suggest that the prevalence of ocular involvement may be as high as 95 % [62, 102]. HIV has been detected in most parts of the eye, including structural components, the aqueous humor [69], the vitreous [127], and the tear film [38]. The virus appears to have a particular affinity for the retina. The spectrum of ocular disease varies substantially between industrialized and developing countries due to poorer medical care and treatment availability [7, 21].

HIV Retinopathy

In the pre-HAART era, HIV retinopathy occurred in 40–60 % of patients with AIDS [35, 54], with the prevalence being inversely related to the degree of immune compromise [71]. Characteristic AIDS-related retinopathy includes the formation of cotton wool spots, hemorrhages, and microaneurysms [21, 35, 43]. Cotton wool spots are produced by focal areas of microvascular closure in the inner retina [102]. Hemorrhages and microaneurysms are also found in the superficial retina, typically along or within the vascular arcades. The presence of HIV antigen in retinal endothelial cells has been suggested to play a role in the development of microangiopathy, while other pathogenic hypotheses have included immunoglobulin deposition and rheological changes secondary to hyperviscosity and increased leukocyte rigidity [31, 35, 74, 77, 102, 105, 133].

While patients with HIV retinopathy are typically asymptomatic, the microvasculopathy may contribute to several processes, including electroretinographic abnormalities, color vision loss, visual field changes, progressive optic atrophy, and diminished contrast sensitivity [21]. While unproven, HIV retinopathy-induced vascular damage is believed to also play a role in the pathogenesis of CMV infection [14, 30, 49, 53].

Ischemic Maculopathy

Ischemic maculopathy is an uncommon disorder of unknown pathogenesis that can cause profound vision loss in patients with HIV/AIDS [22]. Vision loss is typically abrupt and accompanied by opacification of the superficial retina, often in association with hemorrhage formation in or near the fovea. Angiographic findings may include an enlarged foveal avascular zone and mild staining of the juxtafoveal vessels. Ischemic maculopathy should be considered in all patients with HIV/AIDS who experience unexplained loss of vision.

Cytomegalovirus (CMV) Retinitis

CMV retinitis is the most common ocular OI in patients with AIDS and previously affected

30–40 % of HIV-positive patients in developed countries prior to the widespread use of HAART [50, 54] (also see Chap. 107). While the incidence of CMV retinitis has decreased substantially in recent years, it remains the leading cause of vision loss in HIV [124].

CMV is a double-stranded DNA herpesvirus. Retinitis typically occurs at CD4+ cell counts under 50 cells/μl [59, 60, 71]. Symptoms of CMV retinitis include blurred vision, visual field defects, and new-onset floaters or photopsia [110]. Clinical examination often reveals minimal anterior or posterior chamber inflammation and full-thickness focal or sectoral retinal whitening, often with associated intraretinal hemorrhages. Optic nerve involvement occurs in 5–10 % of patients and is associated with a poorer visual prognosis [20, 21]. CMV retinitis is bilateral in 30–50 % of patients [18] and can occur in association with other OIs of the retina or choroid. Retinal detachment is a common complication, reported in up to one-third of patients, and typically requires vitrectomy with silicone oil placement [21].

Non-CMV Herpetic Retinitis

Non-CMV herpetic retinitis is the second most common cause of posterior segment infection in patients with HIV/AIDS and may be caused by varicella-zoster virus (VZV) or herpes simplex virus (HSV) type 1 or type 2 (see also Chaps. 107 and 117). VZV retinitis is the most common of these entities, occurring in roughly 5 % of patients with AIDS, while HSV retinitis in this group is rare [21]. VZV and HSV produce a similar clinical picture, and clues to distinguish the two include the association of HSV retinitis with recent or concurrent encephalitis and association of VZV retinitis with recent or concurrent zoster dermatitis.

Two clinical forms of non-CMV herpetic retinopathy have been recognized, acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN), classically occurring in relatively healthy and severely immunosuppressed patients, respectively. Intermediary forms may

also occur [136]. The majority of patients with either form have a history of extraocular VZV infection [5, 72], whereas 4–17 % of patients with HIV/AIDS develop necrotizing herpetic retinitis after herpes zoster ophthalmicus [82, 118]. PORN is a rare cause of necrotizing herpetic retinopathy seen in patients with severe immune suppression, including AIDS [62]. It is characterized as a rapidly progressive infection, primarily affecting the retina with early macular involvement and minimal vitritis. Ophthalmoscopic findings include multifocal and/or confluent deep yellow-white lesions and, with time, a "cracked mud" pattern of perivascular clearance [81]. Papillitis can also occur and bilateral involvement and retinal detachment are common. PORN is a difficult infection to diagnose and treat. It is commonly confused with CMV retinitis or ARN and tends to be poorly responsive to therapy with intravenous (IV) acyclovir, intravitreal ganciclovir, or foscarnet [32, 34, 81].

The following important features commonly seen in ARN help to distinguish it from PORN: the presence of moderate to severe vitritis, retinal vasculitis, less apparent involvement of the inner retina, and anterior segment involvement. ARN typically affects healthy adults but has been reported in patients with HIV/AIDS as well [58, 84, 118]. CD4+ cell counts tend to be higher than those observed in association with either CMV retinitis or PORN, a factor believed to contribute to the more severe vitreous inflammation observed in ARN [19]. Common symptoms of ARN include eye pain, floaters, and visual field defects. ARN commonly progresses to retinal detachment with proliferative vitreoretinopathy [37, 56]. Bilateral involvement occurs in 59–70 % of patients, often in a sequential manner [5, 21, 68, 91].

Toxoplasmosis

Toxoplasma gondii is a frequent pathogen in patients with HIV/AIDS but is a relatively uncommon cause of AIDS-related retinal infection, affecting less than 1 % of HIV-infected

patients in the United States [16, 44, 62] (also see Chap. 138). Infection is more common in areas with a higher seroprevalence such as Brazil where the prevalence approaches 8 % [7, 21, 44]. Symptoms of ocular toxoplasmosis are nonspecific but may include eye pain, redness, and blurred vision [10, 39, 52]. Such symptoms are less common in CMV retinitis, and their presence can be used to help distinguish toxoplasmic retinochoroiditis from CMV retinitis.

The most important features that distinguish toxoplasmic retinochoroiditis from other forms of retinitis include (1) the presence of moderate to severe vitritis; (2) although relatively rare, the presence of adjacent or nearby chorioretinal scars; and (3) a smooth edge to the lesion (i.e., the absence of satellite or popcorn lesions at the leading edge, which are more characteristic of CMV retinitis). Differentiating toxoplasmic retinochoroiditis from other causes of retinitis can at times be challenging in patients with HIV/AIDS, however, but PCR-based analysis of intraocular fluids can be quite helpful [1, 25, 114, 137]. Positive serologies are supportive, although it is important to remember that the IgG may be negative soon after an acute infection and Toxoplasma-specific IgM titers have relatively poor sensitivity and specificity [106, 109]. All patients with HIV/AIDS thought to have toxoplasmic retinochoroiditis should undergo MRI scanning of the brain to rule out central nervous system (CNS) toxoplasmosis.

Compared to infection in immunocompetent patients, HIV/AIDS-related ocular toxoplasmosis is more commonly bilateral and multifocal [52], lesions can be larger, and vitritis can be more prominent. In addition, the characteristic retinochoroidal scars seen with immunocompetent infection are observed less commonly, suggesting that infections are more frequently acquired than reactivated [39, 51].

Syphilis

In the developed countries, syphilis is the most common bacterial ocular infection in patients with HIV/AIDS, historically affecting up to 2 % of patients [6] (also see Chap. 97). Recent estimates suggest that the current prevalence is on the order of 6–9 %, paralleling an increase in syphilis infections in general [3]. Additionally, patients with a history of successfully treated syphilis prior to HIV seroconversion may manifest a reactivation of latent infection [96].

Syphilis may produce either uveitis or neuro-ophthalmic disease in HIV-positive patients, who usually present with blurred or decreased vision. Concurrent skin disease is common. Posterior segment involvement is more common in HIV-infected patients and may include retinitis, choroiditis, retinochoroiditis, or papillitis [6, 100, 121, 128, 129]. Patients with HIV/AIDS are also more prone to bilateral disease than HIV-negative patients [121]. Other potential findings include anterior uveitis, intermediate uveitis, panuveitis, optic neuritis, and retinal vasculitis [13, 129]. A relatively common presentation is vitritis associated with either a solitary or multifocal chorioretinitis characterized by large, yellow-white, placoid, subretinal, and/or choroidal lesions [9, 41]. The lesions often produce RPE alterations and can exhibit central fading. Solitary lesions may be difficult to distinguish from toxoplasmic retinochoroiditis and CMV retinitis [128].

The diagnosis of ocular syphilis is based on clinical examination and supportive serologic testing, and most patients coinfected with HIV and syphilis exhibit the above features [80]. Serologic testing in patients suspected of having ocular syphilis, including either an RPR or VDRL-test, together with either FTA-ABS or MHA-TP-test may have decreased sensitivity in the setting of immune suppression [100]. Lumbar puncture and CSF analysis should be performed in all patients with ocular syphilis as up to 85 % of patients have concurrent CNS infection [6, 76, 87, 100]. All patients with syphilis should also be tested for HIV.

Syphilis may have a more aggressive course in patients with HIV/AIDS and may also be difficult to eradicate. Compared to non-HIV/AIDS patients, IV penicillin may need to be given at higher doses and for a longer duration. Current CDC guidelines recommend 18–24 million units of daily IV aqueous crystalline penicillin G for

14 days. Alternatively patients may be given 2.4 million units of intramuscular procaine penicillin daily plus 500 mg of oral probenecid four times daily for 10–14 days [120]. Any treatment for neurosyphilis should involve consultation with an infectious disease specialist. To monitor the response to treatment and for recurrence, both serum and CSF reagin titers should be measured each month for 3 months following the completion of treatment and every 6 months thereafter until the CSF white cell count normalizes and the CSF-VDRL becomes nonreactive [100].

Cryptococcus

Cryptococcal choroiditis is uncommon in patients with HIV/AIDS, despite the relatively high prevalence of CNS disease (also see Chap. 123). When *Cryptococcus* does infect the eye, however, it usually produces choroiditis as a result of either hematogenous spread from the lungs or direct extension from infected meninges [36]. Ocular infection with *Cryptococcus* is often subclinical and identified only at autopsy [92, 102]. Neuro-ophthalmic complications, on the other hand, are relatively common, occurring in 25 % of patients with cryptococcal meningitis, and should increase suspicion of *C. neoformans* [54].

Cryptococcal lesions typically appear as single or multiple, well-demarcated, yellow-white spots in the choroid or deep retina, ranging in size from 500 to 3,000 μm [46, 47]. The differential diagnosis of infectious choroiditis includes *P. jirovecii* (*previously P. carinii*), *C. neoformans*, and *M. tuberculosis*, which account for the majority of infectious choroiditis in HIV/AIDS. Less common entities include *M. avium* complex, *H. capsulatum*, *Candida* spp., and *Aspergillus* spp. [21]. Cryptococcal choroiditis can also involve the optic nerve, producing progressive optic atrophy and permanent visual loss [12, 112, 115]; these findings may help the clinician identify the offending organism.

Early diagnosis of ocular *Cryptococcus* and prompt initiation of therapy with systemic therapy are important to preserve vision in affected patients. Treatment depends on the presence of meningitis. Isolated choroiditis should be treated with IV fluconazole (400 mg/day) plus flucytosine (100–150 mg/kg/day) for 10 weeks. When meningitis is present, treatment includes IV amphotericin B (0.7–1 mg/kg/day) plus flucytosine (100 mg/kg/day) for 2 weeks, followed by IV fluconazole for at least 10 weeks. In some patients, the infection may progress to endophthalmitis, requiring vitrectomy and intravitreal amphotericin B in addition to IV therapy.

Choroidal Pneumocystosis

PCP is common in HIV/AIDS patients, with a prevalence approaching 80 % in untreated patients, and is often the presenting infection [48, 83, 119] (also see Chap. 135). Aerosolized pentamidine, used for PCP prophylaxis, has been associated with an increased risk of extrapulmonary infections and so is no longer used [98].

Although originally termed *P. carinii*, *P. jirovecii* is now the recognized name for the *Pneumocystis* pathogen in humans. In the eye, *P. jirovecii* preferentially infects the choroid producing characteristically bilateral, elevated, multifocal, creamy yellow-white lesions with little or no vitritis [35, 70, 111, 115, 122]. Pneumocystis choroiditis is typically asymptomatic, but a minority of patients may experience floaters or visual field defects.

P. jirovecii choroiditis is rare in the absence of systemic infection [70, 115], and so all patients found to have *Pneumocystis* choroiditis should be treated for presumed systemic infection. The lesions should regress following 3–12 weeks of treatment, leaving little or no residual RPE changes.

Neoplastic Diseases of the Choroid and Retina: Non-Hodgkin's Lymphoma

Intraocular lymphoma is uncommon but has a higher incidence and carries a worse prognosis in patients with HIV/AIDS [28, 86] (also see Chap. 147). In one large retrospective study, the proportion of intraocular lymphoma as an AIDS-defining illness has risen from 4.4 to 6.3 % following the advent of HAART [28]. Symptoms include floaters and vision loss.

Dilated ophthalmoscopic examination characteristically reveals vitritis overlying numerous subretinal yellow-white infiltrates [21, 33, 113, 117]. Intraocular lymphoma should be on the differential diagnosis in any HIV/AIDS patient with vitreal inflammation, necrotizing retinitis, or choroidal infiltrates, particularly in the context of poor response or disease progression with empiric therapy. All patients suspected of having intraocular lymphoma should have a lumbar puncture and a brain MRI since concurrent CNS lymphoma is quite common [85]. Treatment options include radiation and chemotherapy (see Chap. 147). Initial response may be robust, but the overall prognosis tends to be poor.

Drug-Induced Uveitis

Several medications used to treat patients with HIV/AIDS can cause uveitis, particularly rifabutin and cidofovir [15, 90, 116] (also see Chap. 155). Drug-induced uveitis often responds to intensive topical corticosteroid therapy, but the offending medication may need to be discontinued in patients with inflammation that is severe or unresponsive to corticosteroid therapy.

Immune Recovery Uveitis (IRU)

IRU is a noninfectious intraocular inflammation first recognized soon after the advent of HAART. It is seen in patients with quiescent CMV retinitis who experience a substantial increase in the CD4+ cell count following initiation of HAART [140], most probably due to expansion of previously depleted anti-CMV T-cell populations. Clinical findings include moderate to severe vitritis, cystoid macular edema, papillitis, epiretinal membrane formation, retinal neovascularization, and proliferative vitreoretinopathy [8, 11, 66, 108, 140]. Risk factors for IRU include a history of CMV retinitis involving more than 25 % of the retina and prior use of IV cidofovir [67]. The complications of IRU can be severe and vision threatening. While variably effective, current treatment options include prolonged use of topical, periocular, and intraocular corticosteroids [95].

111.3 Etiology and Pathogenesis

AIDS is caused by infection with the human retroviruses HIV-1 and HIV-2. HIV-1 accounts for the vast majority of cases worldwide, with HIV-2 seen predominantly in western Africa. These viruses are passed through bodily fluids, and the principal modes of infection are through sexual contact, through contact with blood or blood products, via contaminated IV needles, intrapartum or perinatally, or via breast milk. As such, the incidence of HIV infection is higher in groups with certain high-risk behavior, including men having sex with men and unprotected sexual intercourse, particularly if involving multiple partners and/or anal intercourse, and IV drug abusers.

HIV leads to immunosuppression by targeting and slowly destroying CD4+ cells, mainly CD4+ helper T cells and CD4+ monocytes. Shortly after becoming infected, most patients undergo a viremic stage, often associated with a mononucleosis-like syndrome known as the "acute antiretroviral syndrome." During this phase, the virus is disseminated throughout the body but is relatively controlled by an antibody-mediated immune response. Despite this response, HIV is rarely cleared from the body. Instead the infection persists as a chronic, clinically latent infection, with a progressive depletion of CD4+ T cells. After some period of time, often 10 years or longer, CD4+ T-cell counts fall below a critical level (approximately 200 cells/μL), and patients become increasingly susceptible to opportunistic disease.

111.4 Diagnosis

Routine laboratory diagnosis of HIV infection is based on the demonstration of antibodies to HIV. Most patients seroconvert to HIV positivity within 4–10 weeks of exposure and over 95 % seroconvert within 6 months [17, 123, 125]. Enzyme-linked immunosorbent assay (ELISA) is an extremely sensitive and specific test for the

presence of HIV antibodies. However, ELISA was designed to screen donated blood, not to diagnose infection. The most common confirmatory test in patients with a positive ELISA is Western blot, which detects anti-HIV antibodies of specific molecular weights.

111.5 Differential Diagnosis

Table 111.2 shows a list of typical HIV-related infections for various levels of immune deficiency. The ocular manifestations of HIV/AIDS also depend on the degree of immune suppression (Table 111.3). These manifestations may be divided into five major categories: noninfectious retinal microvasculopathy, opportunistic infections (OIs), neuro-ophthalmologic disorders, neoplasms, and drug-related complications [7, 23]. Uveitis can play a substantial role in OI, neoplastic disease, and drug-related

complications. Table 111.4 shows the differential diagnosis of HIV-related uveitis within these categories (Table 111.5).

111.6 Treatment

The cornerstone of management for HIV/AIDS is combination antiretroviral (ARV) therapy, known as HAART (highly active antiretroviral therapy). These medications fall into six classes: (1) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), (2) nonnucleoside reverse transcriptase inhibitors (NNRTIs), (3) protease inhibitors (PIs), (4) fusion inhibitors (FIs), (5) CCR5 antagonists, and (6) integrase inhibitors. NRTIs include zidovudine (AZT, ZDV), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC). Coformulations

Table 111.2 Systemic disease in patients with HIV/AIDS by CD4+ cell count

CD4+ cell count	Disease	Other risk factors
Any	*Mycobacterium tuberculosis* Lymphoma Streptococcus pneumonia	Positive PPD exposure
<200 cells/µL	*Pneumocystis* pneumonia (PCP) Kaposi's sarcoma	Prior PCP CD4+ cells <14 % total Unexplained fever Oral candidiasis
<100 cells/µL	Toxoplasmosis Histoplasmosis Coccidioidomycosis Candida esophagitis	IgG seropositivity Exposure Exposure Prior colonization High viral load
<50 cells/µL	*Mycobacterium avium-intracellulare* *Cryptosporidium* Cytomegalovirus Cryptococcal meningitis CNS lymphoma	Prior colonization High viral load Prior OI Exposure IgG seropositivity CMV viremia Prior OI High viral load Exposure

Modified from 2002 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV. Washington DC: U.S. Department of Health and Human Services. Nov 28, 2001

PPD purified protein derivative, *OI* opportunistic infection, *CNS* central nervous system

Table 111.3 HIV-associated uveitis by CD4+ cell count

CD4+ cell count	Disease
<500 cells/μL	Lymphoma
<200 cells/μL	Cryptococcosis
	Pneumocystosis
	Syphilis
	Toxoplasmosis
<100 cells/μL	Retinal/conjunctival microvasculopathy
<50 cells/μL	CMV
	PORN
>60 cells/μL	ARN
Substantial increase (to >100 cells/μL)	Immune recovery uveitis

Modified from Cunningham and Belfort [21]

Table 111.4 Differential diagnosis of common causes of HIV/AIDS-related uveitis

Category	Entity or specific cause
Viral	*Cytomegalovirus*
	Herpes simplex virus
	Herpes zoster virus
Protozoal	*Toxoplasma gondii*
Fungal	*Cryptococcus neoformans*
	Pneumocystis jirovecii
	Candida species
Bacterial	*Treponema pallidum*
	Staphylococcus aureus
	Histoplasma capsulatum
	Bartonella henselae
Neoplastic disease	Non-Hodgkin's lymphoma
Drug-induced uveitis	Rifabutin
	Cidofovir
	Clarithromycin
	Fluconazole
Immune recovery uveitis	Immune reconstitution in a patient with a history of CMV infection

Table 111.5 Uncommon causes of ocular infection in HIV/AIDS patients

Entity	Key facts
Candida choroiditis or endophthalmitis [56]	Prevalence less than 1 %
	Usually associated with drug use
	Treat with vitrectomy and IV amphotericin
Aspergillus choroiditis [93]	Multifocal choroiditis
	Clinically silent; identified in autopsy studies
Histoplasma chorioretinitis [79, 126]	May involve retina, choroid, or optic nerve
	Usually from hematogenous spread
Cryptococcus choroiditis/retinitis [56, 93, 102]	Choroiditis more common
	Seen in patients with cryptococcal meningitis
	Commonly associated with neuro-ophthalmic findings
Sporothrix schenckii endophthalmitis [73]	Single case report
	Granulomatous anterior uveitis associated with cutaneous disease
Mycobacterium avium complex choroiditis [56, 93]	Clinically silent; identified in autopsy studies
	Associated with CD4+ counts <100 cells/μL
Unknown bacterial retinitis [24]	Described in two patients
	Responded to tetracycline
M. tuberculosis choroiditis [26]	Multifocal yellow choroidal nodules
	Incidence may be higher in patients with miliary Tb
Bipolaris hawaiiensis [101]	Complete resolution of lesions was achieved by surgery and amphotericin B and fluconazole therapy
Fusarium sp. [42]	Culture-proven case report
	Severe necrotizing acute granulomatous reaction
	Fungal elements in multiple ocular tissues
HIV retinitis [75]	Mid-peripheral multifocal, chronic retinitis
	Gray-white or yellow, irregularly shaped lesions <200 μM
	Minimal vitritis or vasculitis
	Respond to ARV therapy with good visual prognosis

include Combivir (3TC + ZDV), Trizivir (ABC + ZDV + 3TC), Epzicom (ABC + 3TC), Atripla (EFV + TDF), Truvada (FTC + TDF), and Atripla (EFV + FTC + TDF). NNRTIs include nevirapine (NVP), delavirdine (DLV), etravirine (ETR), and efavirenz (EFV). PIs include darunavir (DRV), fosamprenavir (FPV), indinavir, nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), tipranavir (TPV), lopinavir, and atazanavir (ATV). Kaletra is a coformulation of lopinavir and low-dose ritonavir. NNRTIs and PIs are extremely potent but commonly induce drug resistance when used as monotherapy and should only be used in combination with other ARVs.

A typical HAART regimen employs two or more NRTIs with either a PI or a NNRTI. Integrase

inhibitors (e.g., raltegravir, RAL), fusion inhibitors (e.g., enfuvirtide, T20), and CCR5 antagonists (e.g., maraviroc, MVC) are newer treatment options that are not yet in widespread use. The decision to initiate HAART as well as specific regimens is based on the individual clinical situation and is beyond the scope of this chapter. Please visit the following Web sites for current guidelines:

- www.aidsinfo.nih.gov/Guidelines
- www.niaid.nih.gov/factsheets/treat-hiv.htm

See earlier sections as well as other chapters for details of the specific entities discussed above.

111.7 Prognosis

HAART has impacted the AIDS epidemic on several levels. In areas where it is widely available, it has improved both the quality and duration of life. HAART has led to a significant reduction in AIDS-related illnesses, hospitalizations, and deaths [27, 88, 89, 99, 103, 132]. Successful HAART can change HIV disease from an illness that was almost always a death sentence into a chronic but manageable condition.

HAART has changed the face of AIDS-related uveitis, with substantial impact on incidence, progression, and management. The most noticeable impact has been on CMV retinitis [45]. Recent studies have shown that HAART has reduced the incidence of CMV retinitis by about 75 % [63] and has reduced the odds of retinitis progression by 50 %, even among those patients with low CD4+ cell counts [57, 60]. As such, the rate of secondary complications, including retinal detachment, has decreased nearly 90 % [54, 61]. Paralleling these changes has been a substantial decline in CMV-related visual impairment and blindness [130, 131]. However, CMV retinitis can still occur in patients with CD4+ cell counts well above 100 cells/μL, however, and so regular screening is important, even for patients successfully treated with HAART [60, 61, 64, 65, 104].

The impact of HAART on non-CMV ocular OIs has paralleled that of CMV retinitis. Patients with non-CMV herpetic retinitis experience shorter durations of reactivation [107], and spontaneous regression of PORN has been described

[139]. The prevalence of ocular toxoplasmosis [2] and *Cryptococcus* [29] in HAART-treated HIV/AIDS patients has also declined. PCP- and AIDS-related ocular lymphomas are similarly less common, and affected patients tend to survive longer [86, 94, 99]. In addition, HAART-induced immune reconstitution may enable the discontinuation of prophylactic treatment for many OIs, including CMV retinitis [55, 138], *T. gondii* [141], *P. jirovecii* [78], and *C. neoformans* [97].

> **Take-Home Pearls**
> - CMV retinitis remains the most common cause of infectious retinitis and ocular morbidity in patients with HIV/AIDS. Infectious retinitis not due to CMV is most commonly caused by other herpesviruses or toxoplasmosis.
> - Proper diagnosis of HIV/AIDS-related ocular complications is critical because specific therapy is available for many of the more common disorders, because failure to diagnose can lead to severe and permanent vision loss, and because ocular disease may be the initial manifestation of an underlying disseminated infection.
> - HAART has had a substantial impact on HIV in wealthy countries, including immune reconstitution for many patients with resultant improved survival and declines in opportunistic infections. However, HIV/AIDS remains a leading cause of death in developing countries, particularly sub-Saharan Africa.

References

1. Aouizerate F, Cazenave J, Poirier L et al (1993) Detection of Toxoplasma gondii in aqueous humour by the polymerase chain reaction. Br J Ophthalmol 77:107–109

2. Arruda RF, Muccioli C, Belfort R Jr (2004) Ophthalmological findings in HIV infected patients in the post-HAART (Highly Active Anti-retroviral Therapy) era, compared to the pre-HAART era. Rev Assoc Med Bras 50:148–152

3. Balba GP, Kumar PN, James AN et al (2006) Ocular syphilis in HIV-positive patients receiving highly active antiretroviral therapy. Am J Med 119(448): e21–e25

4. Barre-Sinoussi F, Chermann JC, Rey F et al (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220:868–871

5. Batisse D, Eliaszewicz M, Zazoun L et al (1996) Acute retinal necrosis in the course of AIDS: study of 26 cases. AIDS 10:55–60

6. Becerra LI, Ksiazek SM, Savino PJ et al (1989) Syphilitic uveitis in human immunodeficiency virus-infected and noninfected patients. Ophthalmology 96:1727–1730

7. Belfort R Jr (2000) The ophthalmologist and the global impact of the AIDS epidemic LV Edward Jackson Memorial Lecture. Am J Ophthalmol 129:1–8

8. Biswas J, Choudhry S, Kumarasamy et al (2000) Immune recovery vitritis presenting as panuveitis following therapy with protease inhibitors. Indian J Ophthalmol 48:313–315

9. Browning DJ (2000) Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy, and the influence of human immunodeficiency virus status on response. Ophthalmology 107:2015–2023

10. Cano-Parra JL, Diaz LML, Cordoba JL et al (2000) Acute iridocyclitis in a patient with AIDS diagnosed as toxoplasmosis by PCR. Ocul Immunol Inflamm 8:127–130

11. Canzano JC, Reed JB, Morse LS (1998) Vitreomacular traction syndrome following highly active antiretroviral therapy in AIDS patients with cytomegalovirus retinitis. Retina 18:443–447

12. Carney MD, Combs JL, Waschler W (1990) Cryptococcal choroiditis. Retina 10:27–32

13. Carter JB, Hamill RJ, Matoba AY (1987) Bilateral syphilitic optic neuritis in a patient with a positive test for HIV. Case report. Arch Ophthalmol 105:1485–1486

14. Cassoux N, Bodaghi B LeHoang P (1999) Ocular manifestations of AIDS. In: BenEzra D (ed) Ocular Inflammation. Martin Dunitz Ltd., London, pp 427–450

15. Chavez-de la Paz E, Arevalo JF, Kirsch LS et al (1997) Anterior nongranulomatous uveitis after intravitreal HPMPC (cidofovir) for the treatment of cytomegalovirus retinitis. Analysis and prevention. Ophthalmology 104:539–544

16. Cochereau-Massin I, LeHoang P, Lautier-Frau M et al (1992) Ocular toxoplasmosis in human immunodeficiency virus-infected patients. Am J Ophthalmol 114:130–135

17. Coutlee F, Olivier C, Cassol S et al (1994) Absence of prolonged immunosilent infection with human immunodeficiency virus in individuals with high-risk behaviors. Am J Med 96:42–48

18. Culbertson WW (1989) Infections of the retina in AIDS. Int Ophthalmol Clin 29:108–118

19. Culbertson WW, Atherton SS (1993) Acute retinal necrosis and similar retinitis syndromes. Int Ophthalmol Clin 33:129–143

20. Cunningham ET Jr (2000) Uveitis in HIV positive patients. Br J Ophthalmol 84:233–235

21. Cunningham ET Jr, Belfort R Jr (2002) HIV/AIDS and the eye: a global perspective. American Academy of Ophthalmology, San Francisco

22. Cunningham ET Jr, Levinson RD, Jampol LM et al (2001) Ischemic maculopathy in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 132:727–733

23. Cunningham ET Jr, Margolis TP (1998) Ocular manifestations of HIV infection. N Engl J Med 339:236–244

24. Davis JL, Nussenblatt RB, Bachman DM et al (1989) Endogenous bacterial retinitis in AIDS. Am J Ophthalmol 107:613–623

25. De Groot-Mijnes JD, Rothova A, Van Loon AM et al (2006) Polymerase chain reaction and Goldmann-Witmer coefficient analysis are complimentary for the diagnosis of infectious uveitis. Am J Ophthalmol 141:313–318

26. DiLoreto DA, Rao NA Jr (2001) Solitary nonreactive choroidal tuberculoma in a patient with acquired immune deficiency syndrome. Am J Ophthalmol 131:138–140

27. Domingo P, Guardiola JM, Ris J et al (1998) The impact of new antiretroviral regimes on HIV-associated hospital admissions and deaths. AIDS 12:529–530

28. Dore GJ, Li Y, McDonald A et al (2002) Impact of highly active antiretroviral therapy on individual AIDS-defining illness incidence and survival in Australia. J Acquir Immune Defic Syndr 29:388–395

29. Dromer F, Mathoulin-Pelissier S, Fontanet A et al (2004) Epidemiology of HIV-associated cryptococcosis in France (1985–2001): comparison of the pre- and post-HAART eras. AIDS 18:555–562

30. Dunn JP, Jabs DA (1995) Cytomegalovirus retinitis in AIDS: natural history, diagnosis, and treatment. AIDS Clin Rev 99–129

31. Engstrom RE Jr, Holland GN, Hardy WD et al (1990) Hemorheologic abnormalities in patients with human immunodeficiency virus infection and ophthalmic microvasculopathy. Am J Ophthalmol 109:153–161

32. Engstrom RE Jr, Holland GN, Margolis TP et al (1994) The progressive outer retinal necrosis syndrome. A variant of necrotizing herpetic retinopathy in patients with AIDS. Ophthalmology 101:1488–1502

33. Espana-Gregori E, Hernandez M, Menezo-Rozalen JL et al (1997) Metastatic anterior chamber non-Hodgkin lymphoma in a patient with acquired immunodeficiency syndrome. Am J Ophthalmol 124:243–245

34. Forster DJ, Dugel PU, Frangieh GT et al (1990) Rapidly progressive outer retinal necrosis in the

acquired immunodeficiency syndrome. Am J Ophthalmol 110:341–348

35. Freeman WR, Chen A, Henderly DE et al (1989) Prevalence and significance of acquired immunodeficiency syndrome-related retinal microvasculopathy. Am J Ophthalmol 107:229–235

36. Freeman W, Gross JG (1988) Management of ocular disease in AIDS patients. Ophthalmol Clin North Am 1:91

37. Freeman WR, Thomas EL, Rao NA et al (1986) Demonstration of herpes group virus in acute retinal necrosis syndrome. Am J Ophthalmol 102:701–709

38. Fujikawa LS, Salahuddin SZ, Palestine AG et al (1985) Isolation of human T-lymphotropic virus type III from the tears of a patient with the acquired immunodeficiency syndrome. Lancet 2:529–530

39. Gagliuso DJ, Teich SA, Friedman AH et al (1990) Ocular toxoplasmosis in AIDS patients. Trans Am Ophthalmol Soc 88:63–86; discussion 86–8

40. Gallo RC, Salahuddin SZ, Popovic M et al (1984) Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 224:500–503

41. Gass JD, Braunstein RA, Chenoweth RG (1990) Acute syphilitic posterior placoid chorioretinitis. Ophthalmology 97:1288–1297

42. Glasgow BJ, Engstrom RE Jr, Holland GN et al (1996) Bilateral endogenous Fusarium endophthalmitis associated with acquired immunodeficiency syndrome. Arch Ophthalmol 114:873–877

43. Glasgow BJ, Weisberger AK (1994) A quantitative and cartographic study of retinal microvasculopathy in acquired immunodeficiency syndrome. Am J Ophthalmol 118:46–56

44. Glasner PD, Silveira C, Kruszon-Moran D et al (1992) An unusually high prevalence of ocular toxoplasmosis in southern Brazil. Am J Ophthalmol 114:136–144

45. Goldberg DE, Smithen LM, Angelilli A et al (2006) HIV-associated retinopathy in the HAART era. Retina 25:17

46. Henderly DE, Liggett PE, Rao NA (1987) Cryptococcal chorioretinitis and endophthalmitis. Retina 7:75–79

47. Hiles DA, Font RL (1968) Bilateral intraocular cryptococcosis with unilateral spontaneous regression. Report of a case and review of the literature. Am J Ophthalmol 65:98–108

48. HIV/AIDS surveillance supplemental report. Centers for Disease Control and Prevention (2003) 9(3):1–20

49. Hodge WG, Boivin JF, Shapiro SH et al (2004) Clinical risk factors for cytomegalovirus retinitis in patients with AIDS. Ophthalmology 111:1326–1333

50. Holbrook JT, Jabs DA, Weinberg DV et al (2003) Visual loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome before widespread availability of highly active antiretroviral therapy. Arch Ophthalmol 121:99–107

51. Holland GN (1989) Ocular toxoplasmosis in the immunocompromised host. Int Ophthalmol 13:399–402

52. Holland GN, Engstrom RE Jr, Glasgow BJ et al (1988) Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 106:653–667

53. Holland GN, Tufail A, Jordan MC (1996) Cytomegalovirus disease. In: Pepose JS, Holland GN, Wilhelmus KR (eds) Ocular Infection and Immunity. Mosby, St. Louis, pp 1088–1120

54. Jabs DA (1995) Ocular manifestations of HIV infection. Trans Am Ophthalmol Soc 93:623–683

55. Jabs DA, Bolton SG, Dunn JP et al (1998) Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. Am J Ophthalmol 126:817–822

56. Jabs DA, Green WR, Fox R et al (1989) Ocular manifestations of acquired immune deficiency syndrome. Ophthalmology 96:1092–1099

57. Jabs DA, Martin BK, Forman MS et al (2003) Cytomegalovirus resistance to ganciclovir and clinical outcomes of patients with cytomegalovirus retinitis. Am J Ophthalmol 135:26–34

58. Jabs DA, Newman C, De Bustros S et al (1987) Treatment of cytomegalovirus retinitis with ganciclovir. Ophthalmology 94:824–830

59. Jabs DA, Van Natta ML, Kempen JH et al (2002) Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Am J Ophthalmol 133:48–61

60. Jabs DA, Van Natta ML, Thorne JE et al (2004) Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 1. Retinitis progression. Ophthalmology 111:2224–2231

61. Jabs DA, Van Natta ML, Thorne JE et al (2004) Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. Ophthalmology 111:2232–2239

62. Jabs DA, Wingard J, Green WR et al (1989) The eye in bone marrow transplantation. III. Conjunctival graft-vs-host disease. Arch Ophthalmol 107:1343–1348

63. Jacobson MA, Stanley H, Holtzer C et al (2000) Natural history and outcome of new AIDS-related cytomegalovirus retinitis diagnosed in the era of highly active antiretroviral therapy. Clin Infect Dis 30:231–233

64. Jacobson MA, Zegans M, Pavan PR et al (1997) Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. Lancet 349:1443–1445

65. Johnson SC, Benson CA, Johnson DW et al (2001) Recurrences of cytomegalovirus retinitis in a human immunodeficiency virus-infected patient, despite potent antiretroviral therapy and apparent immune reconstitution. Clin Infect Dis 32:815–819

66. Karavellas MP, Azen SP, MacDonald JC et al (2001) Immune recovery vitritis and uveitis in AIDS: clinical

predictors, sequelae, and treatment outcomes. Retina 21:1–9

67. Kempen JH, Min YI, Freeman WR et al (2006) Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology 113:684–694

68. Kestelyn PG, Cunningham ET Jr (2001) HIV/AIDS and blindness. Bull World Health Organ 79:208–213

69. Kestelyn P, Van de Perre P, Sprecher-Goldberger S (1986) Isolation of the human T-cell leukemia/lymphotropic virus type III from aqueous humor in two patients with perivasculitis of the retinal vessels. Int Ophthalmol 9:247–251

70. Koser MW, Jampol LM, MacDonell K (1990) Treatment of pneumocystis carinii choroidopathy. Arch Ophthalmol 108:1214–1215

71. Kuppermann BD, Petty JG, Richman DD et al (1993) Correlation between CD4+ counts and prevalence of cytomegalovirus retinitis and human immunodeficiency virus-related noninfectious retinal vasculopathy in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 115:575–582

72. Kuppermann BD, Quiceno JI, Wiley C et al (1994) Clinical and histopathologic study of varicella zoster virus retinitis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 118:589–600

73. Kurosawa A, Pollock SC, Collins MP et al (1988) Sporothrix schenckii endophthalmitis in a patient with human immunodeficiency virus infection. Arch Ophthalmol 106:376–380

74. Lane HC, Masur H, Edgar LC et al (1983) Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N Engl J Med 309:453–458

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

76. Levy JH, Liss RA, Maguire AM (1989) Neurosyphilis and ocular syphilis in patients with concurrent human immunodeficiency virus infection. Retina 9:175–180

77. Lim MC, Cumberland WG, Minassian SL et al (2001) Decreased macular leukocyte velocity in human immunodeficiency virus-infected individuals. Am J Ophthalmol 132:711–719

78. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM et al (2001) A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. N Engl J Med 344:159–167

79. Macher A, Rodrigues MM, Kaplan W et al (1985) Disseminated bilateral chorioretinitis due to Histoplasma capsulatum in a patient with the acquired immunodeficiency syndrome. Ophthalmology 92:1159–1164

80. Margo CE, Hamed LM (1992) Ocular syphilis. Surv Ophthalmol 37:203–220

81. Margolis TP, Lowder CY, Holland GN et al (1991) Varicella-zoster virus retinitis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 112:119–131

82. Margolis TP, Milner MS, Shama A et al (1998) Herpes zoster ophthalmicus in patients with human immunodeficiency virus infection. Am J Ophthalmol 125:285–291

83. Martinez P, Munoz J, Santamaria JM et al (1992) Acute symptomatic HIV infection. Report of 10 cases. Enferm Infecc Microbiol Clin 10:205–210

84. Matsuo T, Date S, Tsuji T et al (1986) Immune complex containing herpesvirus antigen in a patient with acute retinal necrosis. Am J Ophthalmol 101:368–371

85. Matzkin DC, Slamovits TL, Rosenbaum PS (1994) Simultaneous intraocular and orbital non-Hodgkin lymphoma in the acquired immune deficiency syndrome. Ophthalmology 101:850–855

86. McGowan JP, Shah S (1998) Long-term remission of AIDS-related primary central nervous system lymphoma associated with highly active antiretroviral therapy. AIDS 12:952–954

87. McLeish WM, Pulido JS, Holland S et al (1990) The ocular manifestations of syphilis in the human immunodeficiency virus type 1-infected host. Ophthalmology 97:196–203

88. Mocroft A, Ledergerber B, Katlama C et al (2003) Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 362:22–29

89. Mocroft A, Vella S, Benfield TL et al (1998) Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 352:1725–1730

90. Moorthy RS, Valluri S, Jampol LM (1998) Drug-induced uveitis. Surv Ophthalmol 42:557–570

91. Moorthy RS, Weinberg DV, Teich SA et al (1997) Management of varicella zoster virus retinitis in AIDS. Br J Ophthalmol 81:189–194

92. Morinelli EN, Dugel PU, Lee M et al (1992) Opportunistic intraocular infections in AIDS. Trans Am Ophthalmol Soc 90:97–108; discussion 108–9

93. Morinelli EN, Dugel PU, Riffenburgh R et al (1993) Infectious multifocal choroiditis in patients with acquired immune deficiency syndrome. Ophthalmology 100:1014–1021

94. Morris A, Wachter RM, Luce J et al (2003) Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe pneumocystis carinii pneumonia. AIDS 17:73–80

95. Morrison VL, Kozak I, LaBree LD et al (2007) Intravitreal triamcinolone acetonide for the treatment of immune recovery uveitis macular edema. Ophthalmology 114:334–339

96. Musher DM, Baughn RE (1994) Neurosyphilis in HIV-infected persons. N Engl J Med 331:1516–1517

97. Mussini C, Pezzotti P, Miro JM et al (2004) Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. Clin Infect Dis 38:565–571

98. Northfelt DW, Clement MJ, Safrin S (1990) Extrapulmonary pneumocystosis: clinical features in human immunodeficiency virus infection. Medicine (Baltimore) 69:392–398

99. Palella FJ Jr, Delaney KM, Moorman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338:853–860

100. Passo MS, Rosenbaum JT (1988) Ocular syphilis in patients with human immunodeficiency virus infection. Am J Ophthalmol 106:1–6

101. Pavan PR, Margo CE (1993) Endogenous endophthalmitis caused by Bipolaris hawaiiensis in a patient with acquired immunodeficiency syndrome. Am J Ophthalmol 116:644–645

102. Pepose JS, Holland GN, Nestor MS et al (1985) Acquired immune deficiency syndrome. Pathogenic mechanisms of ocular disease. Ophthalmology 92:472–484

103. Perez-Hoyos S, del Amo J, Muga R et al (2003) Effectiveness of highly active antiretroviral therapy in Spanish cohorts of HIV seroconverters: differences by transmission category. AIDS 17:353–359

104. Petit N, Zandotti C, Riss JM et al (1998) Relapse of CMV retinitis in an AIDS patient with high CD4 counts. J Antimicrob Chemother 41:666–667

105. Pomerantz RJ, Kuritzkes DR, de la Monte SM et al (1987) Infection of the retina by human immunodeficiency virus type I. N Engl J Med 317:1643–1647

106. Porter SB, Sande MA (1992) Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. N Engl J Med 327:1643–1648

107. Posavad CM, Wald A, Kuntz S et al (2004) Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. J Infect Dis 190:693–696

108. Price P, Mathiot N, Krueger R et al (2001) Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol 22:279–287

109. Quinn TC, Piot P, McCormick JB et al (1987) Serologic and immunologic studies in patients with AIDS in North America and Africa. The potential role of infectious agents as cofactors in human immunodeficiency virus infection. JAMA 257:2617–2621

110. Raina J, Bainbridge JW, Shah SM (2000) Decreased visual acuity in patients with cytomegalovirus retinitis and AIDS. Eye 14(Pt 1):8–12

111. Rao NA, Zimmerman PL, Boyer D et al (1989) A clinical, histopathologic, and electron microscopic study of pneumocystis carinii choroiditis. Am J Ophthalmol 107:218–228

112. Rex JH, Larsen RA, Dismukes WE et al (1993) Catastrophic visual loss due to cryptococcus neoformans meningitis. Medicine (Baltimore) 72:207–224

113. Rivero ME, Kuppermann BD, Wiley CA et al (1999) Acquired immunodeficiency syndrome-related intraocular B-cell lymphoma. Arch Ophthalmol 117:616–622

114. Robert-Gangneux F, Binisti P, Antonetti D et al (2004) Usefulness of immunoblotting and Goldmann-Witmer coefficient for biological diagnosis of toxoplasmic retinochoroiditis. Eur J Clin Microbiol Infect Dis 23:34–38

115. Rosenblatt MA, Cunningham C, Teich S et al (1990) Choroidal lesions in patients with AIDS. Br J Ophthalmol 74:610–614

116. Saran BR, Maguire AM, Nichols C et al (1994) Hypopyon uveitis in patients with acquired immunodeficiency syndrome treated for systemic Mycobacterium avium complex infection with rifabutin. Arch Ophthalmol 112:1159–1165

117. Schanzer MC, Font RL, O'Malley RE (1991) Primary ocular malignant lymphoma associated with the acquired immune deficiency syndrome. Ophthalmology 98:88–91

118. Sellitti TP, Huang AJ, Schiffman J et al (1993) Association of herpes zoster ophthalmicus with acquired immunodeficiency syndrome and acute retinal necrosis. Am J Ophthalmol 116:297–301

119. Sepkowitz KA (2002) Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis 34:1098–1107

120. Sexually transmitted diseases treatment guidelines 2002. Centers for Disease Control and Prevention (2002) MMWR Recomm Rep 51:1–78

121. Shalaby IA, Dunn JP, Semba RD et al (1997) Syphilitic uveitis in human immunodeficiency virus-infected patients. Arch Ophthalmol 115:469–473

122. Shami MJ, Freeman W, Friedberg D et al (1991) A multicenter study of pneumocystis choroidopathy. Am J Ophthalmol 112:15–22

123. Sheppard HW, Busch MP, Louie PH et al (1993) HIV-1 PCR and isolation in seroconverting and seronegative homosexual men: absence of long-term immunosilent infection. J Acquir Immune Defic Syndr 6:1339–1346

124. Shukla D, Rathinam SR, Cunningham ET Jr (2007) Contribution of HIV/AIDS to global blindness. Int Ophthalmol Clin 47:27–43

125. Simmonds P, Lainson FA, Cuthbert R et al (1988) HIV antigen and antibody detection: variable responses to infection in the Edinburgh haemophiliac cohort. Br Med J (Clin Res Ed) 296:593–598

126. Specht CS, Mitchell KT, Bauman AE et al (1991) Ocular histoplasmosis with retinitis in a patient with acquired immune deficiency syndrome. Ophthalmology 98:1356–1359

127. Srinivasan A, Kalyanaraman S, Dutt K et al (1989) Isolation of HIV-1 from vitreous humor. Am J Ophthalmol 108:197–198

128. Stoumbos VD, Klein ML (1987) Syphilitic retinitis in a patient with acquired immunodeficiency syndrome-related complex. Am J Ophthalmol 103:103–104
129. Tamesis RR, Foster CS (1990) Ocular syphilis. Ophthalmology 97:1281–1287
130. Thorne JE, Jabs DA, Kempen JH et al (2006) Causes of visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 113:1441–1445
131. Thorne JE, Jabs DA, Kempen JH et al (2006) Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 113:1432–1440
132. Torti C, Casari S, Palvarini L et al (2003) Modifications of health resource-use in Italy after the introduction of highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection. Pharmaco-economic implications in a population-based setting. Health Policy 65:261–267
133. Tufail A, Holland GN, Fisher TC et al (2000) Increased polymorphonuclear leucocyte rigidity in HIV infected individuals. Br J Ophthalmol 84:727–731
134. UNAIDS (2007) AIDS epidemic update, Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) 60
135. UNAIDS (2008) Report on the global epidemic, Geneva
136. Vrabec TR (2004) Posterior segment manifestations of HIV/AIDS. Surv Ophthalmol 49:131–157
137. Westeneng AC, Rothova A, de Boer JH et al (2007) Infectious uveitis in immunocompromised patients and the diagnostic value of polymerase chain reaction and Goldmann-Witmer coefficient in aqueous analysis. Am J Ophthalmol 144:781–785
138. Whitcup SM, Fortin E, Lindblad AS et al (1999) Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. JAMA 282:1633–1637
139. Woo SJ, Yu HG, Chung H (2004) A case of atypical progressive outer retinal necrosis after highly active antiretroviral therapy. Korean J Ophthalmol 18:65–69
140. Zegans ME, Walton RC, Holland GN et al (1998) Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. Am J Ophthalmol 125:292–300
141. Zeller V, Truffot C, Agher R et al (2002) Discontinuation of secondary prophylaxis against disseminated mycobacterium avium complex infection and toxoplasmic encephalitis. Clin Infect Dis 34:662–667