



## Review Article

### HIV and EYE - A mini review

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#### A B S T R A C T

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Human immune deficiency virus (HIV)/ AIDS pandemic is on the rise. Ocular examination is critical in every symptomatic and asymptomatic patient. Ocular changes and manifestations may help in suspecting HIV like CMV retinitis and thus, this aspect of ocular manifestation in HIV patient has been dealt in detail but there are other aspects like intraocular viral loads, effect of HAART etc which requires further evaluation. These aspects are important to the treating clinician. This mini-review underscores the importance multi-disciplinary approach to HIV and eye involvement, rather than focussing only on ocular manifestations.

#### Introduction

Acquired Immunodeficiency Syndrome (AIDS) affects the body's ability to fight illness, caused by the Human Immunodeficiency Virus (HIV) by attacking lymphocytes especially CD4+ T-cells. It affects all the organs of the body including the eye directly by infecting the eye with various opportunistic infections affecting the anterior and posterior segments and indirectly causes neurological conditions affecting the brain leading to vision defects. Though much has been talked about HIV, its manifestations, treatment and prevention but its impact on eye has not been discussed to the same extent. Here this mini-review emphasizes on the impact of HIV/AIDS on the eye, its manifestations and management.

#### Ocular manifestations

Ocular manifestations were first described in 1982. The pattern and prevalence of ocular manifestations changed, after the introduction of highly active antiretroviral therapy (HAART) which restores the immune system. Ocular manifestations can be divided as orbital, adnexal, anterior segment, posterior segment and neurological manifestations.

Orbital manifestations of HIV infection are not seen very often. However, some cases of orbital cellulitis and orbital lymphoma have been reported. The most common adnexal manifestations in AIDS patients are Kaposi's sarcoma, herpes zoster ophthalmicus, moluscum contagiosum and conjunctival

microvasculopathy. Primary non-Hodgkin's lymphoma (NHL) of the orbit and ocular adnexa is a rare disease. Kaposi's sarcoma is a highly vascularized, painless mesenchymal tumor that affects the skin and mucous membranes. Around 20% of these patients have asymptomatic Kaposi's sarcoma of the eyelids, conjunctiva and rarely the orbit. However, there are a lower proportion of cases associated with low incidence of human herpes virus 8 in India and homosexual behaviour (Biswas, J., and Sudharshan, S., 2008.).

Conjunctival and lid involvement are commonly seen in Herpes zoster ophthalmicus and molluscum contagiosum. Herpes ophthalmicus is the reactivation of latent varicella zoster virus in the ophthalmic division of the trigeminal nerve and presents as vesicobullous rash. It may present as keratitis, scleritis, uveitis, retinitis or encephalitis especially in patients with depressed cellular immunity and receiving immunosuppressive therapy. Molluscum contagiosum is caused by a DNA poxvirus which affects the skin and mucous membranes. It presents as translucent papules with a central umbilication. In HIV patients it occurs commonly and lesions are large, often more numerous and rapidly growing. Involvement of the eyelids may also occur in HIV infected patients. Conjunctival Microvasculopathy presents as asymptomatic microvascular changes and no treatment is necessary.

These changes correlate with retinal microvasculopathy seen as microaneurysms, segmental vascular dilatations and narrowings. The cause is not clear yet, but it may be associated with the deposition of immune complexes related to HIV or the direct infection of HIV in the conjunctival vascular

endothelium (Kestelyn, P.G. and Cunningham, E.T., 2001).

The anterior segment involvement is commonly seen as Keratitis, keratoconjunctivitis sicca and iridocyclitis. Herpes simplex keratitis is a painful condition of peripheral cornea with longer course and higher recurrences in AIDS patients. Corneal scarring and iritis may be seen. Varicella-Zoster Virus Keratitis present with elevated intraocular pressure. It is commonly associated with zoster ophthalmicus. As in herpes simplex keratitis, the course of the disease tends to be longer in AIDS patients. Bacterial and fungal infections are generally more severe in HIV infected patients.

Spontaneous fungal keratitis secondary to *Candida albicans* has been reported in patients with advanced HIV disease particularly common in intravenous drugs users. Although uncommon, Microsporidia is associated with a bilateral diffuse punctate epithelial keratopathy and conjunctivitis (Biswas, J., and Sudharshan, S., 2008). keratoconjunctivitis sicca (dry eye syndrome) results from deficiency of any of the tear film layers. It is likely caused by both the destruction of primary and secondary lacrimal glands and inflammation mediated by the HIV virus (Ormerod, L.D. and Dailey, J.P. 1999.). Symptoms may include foreign body sensations, photophobia and decreased visual acuity.

An HIV infected patient complaining of photophobia and red eye may have iridocyclitis. It may be associated with retinal or choroidal infection with multiple opportunistic organisms, such as cytomegalovirus, herpes simplex virus, varicella zoster virus, *Candida* species, *Cryptococcus* species, *Mycobacterium* species, infection with syphilis or

toxoplasmosis should always be considered (Cano-Parra, J.L. *et al*, 2000.). The posterior segment of the eye (retina, choroid and optic nerve head) is affected in more than 50% of AIDS patients by either infectious causes or non infectious causes. Decreased visual acuity, visual field defects and photopsias are among the most common symptoms. Retinal Microvasculopathy are microvascular changes in the retina presenting with cotton-wool spots (CWS) in the retina, intraretinal hemorrhages, and retinal microaneurysms, especially when CD4+ T lymphocyte count is lower than 100/ $\mu$ l.

Retinal infections may result from different pathogens, which may affect the retina at the same time. Syphilis, candida, varicella-zoster, toxoplasmosis, herpes simplex and cytomegalovirus retinitis are most common (Robinson, M.R. *et al*, 2000.). Although these infectious may also occur in immunocompetent hosts, the course tends to be longer in AIDS patients, with high recurrences. Varicella zoster virus has been associated with acute retinal necrosis and it is characterized by peripheral retinal whitening, often accompanied by intraretinal hemorrhages associated with rapidly progressing necrosis over several days. Multifocal lesions are commonly seen. Retinal detachment with proliferative vitreoretinopathy as well as the involvement of the other eye may also occur.

CMV infection is usually subclinical in immunocompetent hosts whereas it is most common intra-ocular infection in immunocompromised hosts. It may affect around 25% of patients and may cause progressive loss of vision and blindness. Syphilis may affect the retina, characterized by a deep yellow lesion along with retinal vasculitis and

intraocular inflammation. The diagnosis can be confirmed by the serum fluorescent treponema antibody absorption test (FTA ABS) and microhemagglutination assay (MHA-TP).

Candidal endophthalmitis generally presents as a focal white infiltrate in the choroid, and may break through the retina into the vitreous. Usually, an overlying vitritis is present. Mycobacterium tuberculosis, Candida species, Cryptococcus species, Pneumocystis carinii and Treponema pallidum are among the most common entities related to infectious choroiditis, which is seen in less than 1% of HIV positive patients. Toxoplasmic retinochoroiditis presents as bilateral and multifocal sites of infection. Patients usually complain of seeing floaters, pain and decrease in visual acuity. Retinochoroidal scars and retinal hemorrhage may be absent. PCR of the ocular fluid may be helpful in distinguishing between toxoplasmic retinochoroiditis. Multiple, bilateral, round or ovoid, yellow-white lesions characterizes Pneumocystis carinii choroiditis. They are usually slowly progressive and are not associated with iritis, vitritis, or vasculitis (Robinson, M.R. *et al*, 2000.).

Optic neuropathies in HIV positive patients may be related to compression, infiltration, infection, vaso occlusion or inflammation. Cryptococcal meningitis and intracerebral toxoplasma cysts cause's intracranial manifestations. Other neuro ophthalmic complications are visual field defects, papilledema, secondary to elevated intracranial pressure and ocular motility disorders, occurring in up to 15% of HIV-infected patients. HIV may also cause diplopia due to palsies of cranial nerves III, IV, and VI. Neurosyphilis, progressive multifocal

leukoencephalopathy (PML), meningeal and parenchymal lymphoma, and intracerebral infection with herpes virus have also been related to neuro-ophthalmic manifestations. Premature atherosclerosis is also seen in HIV-infected patients due to an unknown mechanism. Few studies on site of involvement of ocular infections in HIV are shown in Table.1.

### **Intraocular Viral Loads**

In infected patient, all body fluids contain HIV virus. Fluids that ophthalmologist should be careful with are; blood, aqueous humour, vitreous, cerebrospinal fluid. The HIV virus is found in the tears of people infected with AIDS. However, no AIDS cases have ever been reported from tear contact, aqueous or vitreous fluids. As a precaution, ophthalmologists are particularly careful when cleaning lenses and instruments which come in contact with tears or instruments used during an ocular surgery. Various modalities are available for measuring plasma viral loads in patients, commonly used is reverse Transcriptase PCR which help to assess the treatment outcome and also gives an early indication of virological failure. But only few studies have been performed to assess the relation of plasma viral loads with intra aqueous and intra-vitreous viral loads.

In a study by, Plasma and intraocular human immunodeficiency virus-1 (HIV-1) viral loads in patients with cytomegalovirus (CMV) retinitis and was found that patients with plasma viral loads less than 250,000 copies/ml had undetectable (<200 copies/ml) HIV-1 in their aqueous and vitreous (Ciulla, T.A., *et al.* 1999). Hence, intraocular viral levels have several determinants in addition to plasma viral loads, with which they only partially correlate

Another study demonstrated high HIV loads in aqueous humor and vitreous fluids in patients with concomitant CNS and ocular involvement due to AIDS-related cryptococcosis. HIV levels in the vitreous fluid also correlated with levels in CSF (Peng, C.H., *et al*, 2005). It was also revealed that there is intrathecal and intraocular HIV replication in patients with cryptococcosis. So, care should be taken by ophthalmologist while operating HIV patient with nervous system manifestations and follow strict infection control practices.

### **Management**

The HIV virus increases the incidence of eye infections. Therefore, regular eye examinations by an ophthalmologist are important. Early diagnosis of these conditions can prevent serious vision loss. All HIV patients should undergo complete ocular examination as even in asymptomatic cases ophthalmological findings were present. Ophthalmological examination is mandatory before starting ART and during ART for drug induced side effects. It is recommend that patients with CD4 count <200 $\mu$ l should undergo 6 monthly/SOS and yearly examination for patients with CD4 count >200 $\mu$ l. HAART along with symptomatic management of the ocular condition is done along with regular CD4 count monitoring.

### **Effect of HAART**

#### **1. Ocular IRIS:**

Over the past two decades, symptomatic deterioration in patients on ART has been described, this phenomenon is known by multitude of names including, “immune reconstitution inflammatory syndrome (IRIS)”, “immune reconstitution” or

“restoration disease (IRD)”, and “immune reconstitution syndrome (IRS)”. The immunopathology of IRIS is determined by the inciting pathogen. IRIS is most often associated with CD4+ Th1-mediated immune response; however, both CD4+ and CD8+ effector T-cells are involved. The pro-inflammatory Th17 cell and the regulatory T cell (Treg) play an important role. Macrophages and natural killer cells are also suspected to play a role in herpes IRIS.

Among patients with CMV in the HAART era, immune recovery may be associated with complications including macular edema and epiretinal membrane formation. Eye disease is the most common presentation of cytomegalovirus (CMV) IRIS. Three distinct ocular lesions associated with CMV-IRIS have been described: retinitis, vitritis, and uveitis. The immune recovery uveitis secondary to HAART has become a major visually-threatening condition.

AIDS patients with CMV are less likely to experience necrotizing retinitis and retinal detachment. Immune recovery vitritis is seen following treatment with protease inhibitors, which may be associated with increased cytomegalovirus-specific lymphocyte proliferation and production of inflammatory cytokines (Robinson, M.R., et al, 2000). Clinically important complications of immune-recovery uveitis may include cataract, epiretinal membrane formation, and cystoid macular edema. Drug induced uveitis was strongly correlated with prior use of cidofovir and rifabutin (Biswas, J., and Sudharshan, S., 2008).

## **2. Stevens Johnson syndrome**

HIV-infected individuals are frequently exposed to medications, especially nevirapine, which are capable of causing hypersensitivity or toxic reactions. Altered cell-mediated immunity and associated dry eye may also lead to increased risk of SJS as a response to infectious agents as well. (Biswas, J., and Sudharshan, S., 2008.).

## **3. Effect of intra-ocular viral loads**

HIV loads of aqueous humor declined to undetectable levels (< 400 copies/ml) after 4-8 months of HAART. (Hsu, W.M., et al, 2004) HIV virus levels in the plasma of AIDS patients were significantly decreased, and the CD4 counts of these patients were significantly increased after initiation of HAART.

**4. Vortex keratopathy:** It can be caused by antivirals such as ganciclovir, acyclovir or atovaquone. Patients may be asymptomatic or may complain of a mild irritation, foreign body sensation or photophobia. Characteristic whorl-like pattern of gray white opacities is seen at the level of the corneal epithelium( Kestelyn, P.G. and Cunningham, E.T., 2001).

Clinicians should be aware of changes in the clinical presentation of ocular manifestations of HIV since the introduction of HAART. As studies on HIV disease after the introduction of HAART continue to become available, more thorough descriptions of treated patients with ocular opportunistic infections will include side-effects and toxicities on therapy.

**Table.1** Studies on site of ocular involvement in HIV

Sl. No	Studies	Anterior segment	Posterior segment	Neuro-ophthalmic
1	Acharya, P.K. <i>et al</i> , 2012	7%	9.94%	5.79%
2	Mehta, S. <i>et al</i> , 2013.	4%	23%	-
3	Tan, S.Y., 2009.	15.35%	17%	-
4	Kusagur, S., <i>et al</i> , 2013	3-6%	12%	4%
5	Purushotam, J., <i>et al</i> , 2012	9.7%	32.03%	1.2%
6	Sahu, D.K., <i>et al</i> ,1999	0 %	35-39%	0%

As increasing number of HIV-infected individuals present with treatment failure in resource-limited settings such as India, the risk of ophthalmic complications may increase. Further research is needed to study the effects of the restored immune system following HAART on the eye and to identify the best therapeutic approach for HIV-infected patients.

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