Eye Complications of Acquired Immune Deficiency Syndrome (AIDS)

Part 1. Ocular surface and anterior segment manifestations

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Introduction

Acquired Immune Deficiency Syndrome (AIDS) is the leading cause of sickness and death among young adults in developing countries. The introduction of highly active anti-retroretroviral therapy (HAART) has changed the epidemiology of AIDS from being a universally fatal illness to a chronic debilitating infection attended by multi-organ complications. Improved survival as a result of HAART has lead to increase in systemic and ocular complications as well as the appearance of syndromes related to immune reconstitution. HIV associated eye disease now occurs in 50-90% of patients at one point in the course of their illness[1]. Loss of sight is a feared complication because of its impact on the management of the systemic disease and the additional distress experienced by the patient who now has to rely on others for assistance with activities of daily living. This paper reviews anterior segment and external ocular disorders associated with AIDS in an effort to improve understanding of this disorder and facilitate early detection, referral and care of those presenting to any level of the health delivery system in South Sudan.

Southern Sudan is a country that has endured two decades of conflict during which infrastructure was destroyed and the population displaced to internally displaced camps and neighbouring countries. Although no population studies have been conducted to determine the prevalence of HIV in South Sudan, hospital based surveys suggest that prevalence may be low compared to that of countries in the region. This is likely to change and prevalence could increase rapidly due to increased movement within and between South Sudan and its neighbours. The prevalence of eye complications of HIV is likewise expected to increase, as patients survive longer due to availability of more effective anti-retroviral therapy and improved treatment for and prophylaxis against opportunistic infections. Eye complications of HIV can involve any ocular tissue and may indicate worsening of the underlying immune disorder. In some cases an eye lesion is the first sign of disease in a previously healthy patient. Diagnosis and treatment of anterior segment disorders and adnexial disease is an important component of comprehensive eye care strategy for HIV patients and must be undertaken aggressively in order to prevent disfigurement, preserve dignity and improve quality of life.

Table 1 describes the main eye complications of HIV and their relationship to CD4 count. This article focuses on those complications occurring on the anterior segment and adnexia that are easily recognised by inspection. Posterior segment and neuro-ophthalmological complications are difficult to diagnose at primary care level. Their diagnosis requires specialist knowledge and use of sophisticated equipment. A high index of suspicion should be maintained and prompt referral to an ophthalmologist made for any HIV patient who presents with cranial nerve palsies or complains of visual loss in a normally appearing eye. Detailed discussion of these complications will be the subject of a separate article.

Table 1. Eye Complications of HIV

CD4	Complications			
	Vascular	**Opportunistic infections**	**Tumours**	**Neuro-ophthalmological**
>500 cells/µl	Large vessel vaso-occulusive disease	1. Acute retinal necrosis 2. Molluscum contagiosium	Squamous cell carcinoma of the conjunctiva	HIV retinopathy
<500 cells/µl		HZO	1. Kaposi Sarcoma 2. Lymphomas	Cranial nerve neuropathy
<200 cells/µl		1. Pneumocystis Chroidopathy 2. Ocular TB		
<100 cells/µl	HIV retinopathy, conjunctival vasculopathy	3. CMV retinitis 4. Toxoplasmosis 5. Cryptococcal chroidopathy		Optic neuropathy Cranial nerve involvement

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Opportunistic Infections of Ocular Adnexia

Herpes Zoster Ophthalmicus (HZO)

Herpes Zoster is caused by varicella zoster virus, which is a member of the herpes virus group. Primary infection occurs in early childhood when it presents as chicken pox, a self-limiting generalised exanthema that rarely involves the eye and heals without sequela. Following primary infection the virus migrates to the trigeminal ganglion where it remains quiescent for many years. If cell mediated immunity is reduced for any reason including infection with Human Immunodeficiency Virus (HIV), cancer or immunosuppressive therapy, the virus becomes activated and travels down the branches of the trigeminal nerve causing a typical vesicular rash (figure 1). The ophthalmic division of the trigeminal nerve is involved more frequently than other branches, hence the name Herpes Zoster Ophthalmicus (HZO). It occurs early in the course of HIV infection when the CD4 count is more than 200 cells/µl. It is therefore not considered an AIDS defining illness although its occurrence in a young person should raise the possibility of immune suppression. HZO occurs more commonly in Africa than Europe and the United States[2] where Cytomegalovirus infection is more common. Other complications of HZO include inflammation and loss of sensation of the cornea *(Neurotrophic keratitis*), inflammation of the sclera, iris and retina *(sleritis, iritis and retinitis). Herpetic neuralgia (PHN)* refers to debilitating pain and itching in the involved branch of the nerve persisting many months after healing of the acute lesion. It is due to irritation of nerve endings by the resulting scar tissue. Presence of a blister on the tip of the nose predicts eye involvement and should prompt early treatment with systemic steroids, in order to lessen severity of eye disease.

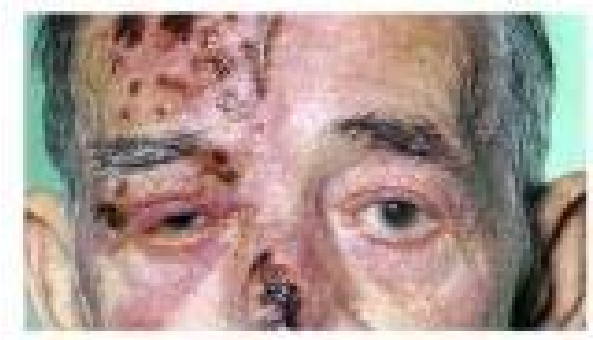

Figure 1. Herpes Zoster Ophthalmicus

Diagnosis of HZO can usually be made clinically without the need for laboratory work up. Treatment should begin with intravenous Acyclovir 10mg/kg for 5 days followed by oral Acyclovir 800mg five times daily for 9 days. This limits the duration of skin rash and reduces the prevalence of inflammatory eye complications. Patients who develop iridocyclitis and/or stromal keratitis may be treated with topical steroids. Options for treatment of PHN if it develops include:

- Topical lidocaine cream plus tricyclic antidepressants;
- Amitriptyline 50 mg nocte or
- Carbamazepine 200 mg every night.

Systemic steroids and antivirals may prevent loss of sight from uveitis and keratitis.

Molluscum Contagiosium

This is an infection caused by the poxvirus and is acquired sexually or through direct contact. It presents as small painless elevated round pearly white nodules about 2-4 mm in size around the eyes. Central umbilication is pathognomonic and differentiates it from other nodules of similar appearance[3]. Inflammation of the conjunctiva and cornea may occur as a complication. Disseminated lesions may occur in severe immune-suppression. Single or isolated lesions can be treated by curettage, excision or cryotherapy. Disseminated lesions can be treated by oral acyclovir. Reconstitution of immune function with HAART can result in resolution of molluscum contagiosium lesions without concurrent use of specific therapy.

Ocular Adnexal Tumours

Kaposi Sarcoma

Kaposi Sarcoma is a malignant vascular tumour caused by Human Herpes Virus 8 (HHV-8)[4] that was originally reported in elderly males of Mediterranean origin and Jewish ancestry. It affects skin, mucus membrane, internal organs and lymph nodes. Ocular Kaposi Sarcoma (figure 2) presents on the lid or conjunctiva as a painless diffuse violet nodule. Prior to the advent of the AIDS epidemic, ocular Kaposi Sarcoma was a rare entity reported in less than 30 cases worldwide. It is now one of the commonest malignant tumours in AIDS patients and not uncommonly the first manifestation of infection with the HIV virus.

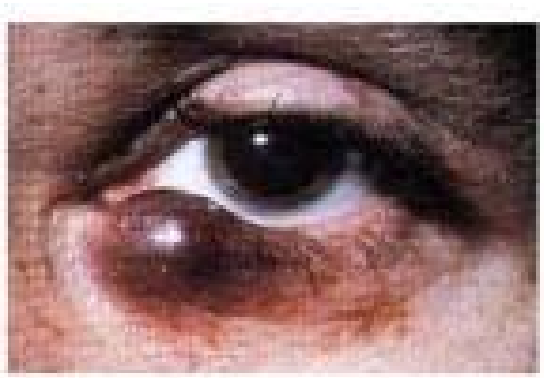

Figure 2. Kaposi Sarcoma of the lid presenting as a purple nodule

The main postulated mode of transmission is sexual[5] although vertical transmission from mother to child is thought to be common in sub-Saharan Africa[6,7] where the disease is endemic. Multiple factors may interact with HIV to cause Kaposi Sarcoma. This includes deregulated expression of oncogenes, decreased immune surveillance and release of *Cytokines* and *Growth factors* by the action of HIV upon infected cells. Although science is still far from understanding the mechanism by which HHV-8 causes oncogensis, some viral oncogenes believed to contribute to neoplasia have been isolated. Latency Associated Nuclear Antigen (LANA) encoded by HHV-8 genome is a protein consistently shown to be expressed in HHV infected cells. LANA interacts with tumour suppressor genes in a manner that promotes oncogensis. Treatment may include surgical resection. Regression may be achieved with radiotherapy or chemotherapy with Bleomycin

Squamous cell carcinoma of the conjunctiva (SCC)

SCC is the most common malignancy of the conjunctiva. The incidence of the indolent form of this disease has been shown to decline as one travels away from the equator. Thus in Uganda, an incidence of 1.2/100,000 persons/year has been reported compared to 0.02/100,000 persons/year in the UK which is further north of the equator[8]. The most common presentation is that of a friable white or pigmented nodule at the junction of the sclera with cornea (figure 3). This form of the tumour presents mainly in elderly African males who spend many hours in the sun working on farms or other occupations. Fair skin pigmentation, UV radiation and atopic eczema are the main risk factors for this form of SCC. It rarely invades the eyeball or adjacent structures and death is uncommon. Margin free surgery followed by cryotherapy or radiation has 100% cure rate. Recurrent lesions are treated with topical Mitomycin C, 5FU or interferon Alpha[9]

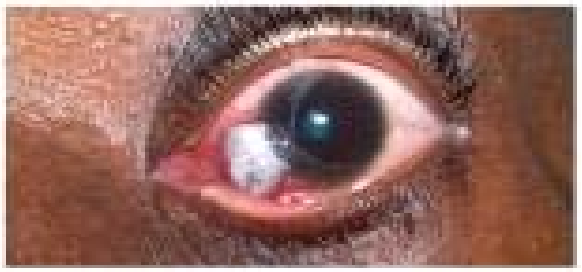

Figure 3. Squamous cell carcinoma of the conjunctiva presenting as a white mass with rough friable surface

An aggressive form of SCC has recently been described in young adults less than 50 years of age in whom the disease progresses relentlessly, invading the eyeball, orbit and adjacent adnexial tissue[10] and metastasising to regional lymph nodes[11]. Studies in Rwanda, Malawi and Uganda[12] have found high association of HIV with this form of SCC. In Zimbabwe, a nine-fold increase in cases from six cases/million to 35 cases/million in less than 5 years has been recorded since the onset of the HIV epidemic[13]. High titres of Human Papilloma Virus (HPV) type 16, 18 have been found in association with this tumour, raising the possibility that it may be caused by an infectious agent. It is not known precisely how HIV interacts with HPV and other oncogenic viruses to cause the aggressive form of this disease.

Theories abound that HIV directly induces neoplastic change in tissue by secreting viral oncogenes that inactivates tumour suppressor gene products secreted by host tissues, thereby promoting oncogensis. Integration of viral genome into host tissue is also postulated to lead to neoplastic transformation.

HIV induced immune suppression may reduce immune surveillance thereby priming the tissue for malignant transformation as has been the case in liver transplant patients who receive Azothriopine therapy[14]. HPV is known to increase the activity of *Transforming growth factor Beta* (TGFβ) which promotes differentiation and neoplastic transformation of cells. Pan activation of humeral immune system and increase in Cytokine release leads to a chronic inflammatory state that facilitates malignant transformation[15].

If the tumour is diagnosed early before it infiltrates the eyeball or conjunctiva of the lid, wide excision has 100% cure rate. A tumour that is fixed to the eyeball should be treated by enucleation of the eye to prevent lid invasion and subsequent systemic spread through vascular and lymphatic route. In Sakubva Eye Unit, Mutare, SCC is the commonest cause of enucleation of the eye in adults and a frequent cause of death from eye related disease among HIV patients. Early diagnoses followed by wide excision or enucleation can relieve pain and improve the quality of life of affected patients

Other conditions associated with HIV

Anterior Uveitis

Inflammation of the uveal tract (iris, ciliary body and choroid) is a common anterior segment manifestation of HIV. It is seen in up to 88% of HIV patients in Zimbabwe. Viral infections, tuberculosis and syphilis are the common etiological agents of infectious uveitis in HIV patients. In some cases, it is the initial presentation in undiagnosed patients. Idiopathic uveitis may occur in the background of immune reconstitution syndrome. This occurs when a patient whose cell mediated

immunity is being reconstituted as a result of treatment with HAART begins to develop uveitis as a part of autoimmune disease. Patients with uveitis will present with pain, photophobia, reduced vision and redness of the involved eye. Etiologic diagnosis can be made by examination of aqueous by use of polymerase chain reaction (PCR).

Secondary Cataract

We have seen and operated on young HIV positive patients in their early twenties who present with lens opacities that morphologically resemble juvenile cataract. These patients have no other associated conditions such as anterior iritis that would have accounted for their cataract. HIV induced lens changes may be responsible for this type of cataract. HIV virus has been isolated in lens tissue of patients with cataract. Visual prognosis following cataract surgery is good in this group of patients. Early surgery is important to prevent development of complications and to assure visual recovery, which will in turn help these patients to care for themselves and participate in the treatment of their illness.

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Thanks to Michele Marcoux for converting the images.

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March 8 2009 was **International Women's Day** with theme of 'Women and men united to end violence against women and girls." We hope to have some articles on this topic this soon.

Did you know?

A woman in South Sudan has a one in six chance of dying during the course of her lifetime from complications during pregnancy or delivery, according to the UN Children's Fund (UNICEF). Sudan's overall maternal mortality ratio is 1,107 deaths per 100,000 live births, but rates are far higher in the South, rising to 2,243 deaths per 100,000 live births, according to UNICEF.