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Editorials

Uveitis in HIV positive patients

The dawn of the 21st century brings with it the sobering realisation that the human immunodeficiency virus (HIV) epidemic continues to exact an enormous human, social, and economic toll on the world.^{1,2} As of December 1999, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO) estimated that nearly 34 million people are infected by HIV worldwide, and stated further that the prevalence of HIV infection continues to rise at an alarming rate, perhaps doubling early in this century. While more than 95% of all HIV positive people live either in sub-Saharan Africa or south or South East Asia, most parts of the world have been affected to a greater or lesser extent. Latin America, eastern Europe, and central Asia, for example, each have rapidly growing HIV positive populations which together now approach 2 million, and North America and Western Europe both report in excess of 900 000 and 500 000 HIV positive people, respectively, despite well developed and long standing prevention programmes. To compound matters, it has been estimated that nearly 50% of HIV positive people in the industrialised world, and more than 90% of HIV infected people in developing nations, are unaware of their HIV status.

Ocular complications occur in up to 70%–80% of untreated HIV infected patients, and more than half of these are associated with intraocular inflammation or uveitis (Table 1).³ Conditions associated with uveitis in HIV positive patients include opportunistic infections, such as cytomegalovirus (CMV) retinitis⁴ and herpes zoster ophthalmicus (HZO),⁵ unusual neoplasms, such as intraocular lymphoma,⁶ and possibly inflammation due to HIV infection itself.⁷ These complications are usually observed during advanced stages of disease, most often as CD4+ T lymphocyte counts drop below 50 cells $\times 10^6/l$.⁸ In addition, HIV positive patients who receive treatment can develop intraocular inflammation related to drug toxicities, such as rifabutin (Mycobutin, Pharmacia and Upjohn)⁹ or cidofovir (Vistide, Pharmacia and Upjohn)^{10–12} associated uveitis, as well as immune recovery uveitis (IRU),^{13–15} a paradoxical worsening of intraocular inflammation observed in eyes with inactive CMV retinitis that occurs as CD4+ cell counts climb and functional immunity to CMV is recovered in response to highly active antiretroviral therapy (HAART).

The study by Ambati and colleagues¹² reported in the October 1999 issue of the *BJO* highlights the inherent difficulties in identifying the cause of uveitis in many patients

with HIV disease. These authors retrospectively investigated the clinical characteristics and risk factors for the development of anterior uveitis in a moderately sized cohort of HIV positive patients with CMV retinitis who were taking the antiviral agent cidofovir. Their findings confirmed previous reports describing uveitis in 25%–50% of patients taking this medication, and that cidofovir associated uveitis tends to be anterior and related to cumulative exposure to the medication.^{10,11} Kaplan–Meier analysis performed by the authors showed that cidofovir associated uveitis tended to occur following a median of 11 weekly doses of medication, on average 4 days after infusion. Ambati and associates' results further suggested that an elevated CD4+ T lymphocyte count observed in the setting of partial immune recovery may be an independent risk factor for cidofovir uveitis. Moreover, while the uveitis occurred most often in eyes with inactive CMV retinitis, inflammation was also observed in a significant number of eyes with no evidence of CMV infection. Although cidofovir associated inflammation was often controlled with a topical corticosteroid and cycloplegic/mydriatic agent, recurrences were frequent with subsequent infusions in this study. Ambati and colleagues were not able to identify the cause of the increased risk of cidofovir associated uveitis in patients with higher CD4+ T lymphocyte counts. Suggested mechanisms included increased toxicity related to elevated circulating levels of cidofovir in the setting of HAART, a mechanism previously suggested for rifabutin,¹⁶ and an increased number of uveitogenic CD4+ T lymphocytes following HAART, in some way perhaps activated by cidofovir. Hypotony occurs in 10%–20% of HIV positive patients with CMV retinitis who are treated with intravenous cidofovir but appears not to be influenced by total CD4+ cell count or the use of HAART.^{10–12}

As with all patients with uveitis, the approach to the HIV positive patient with intraocular inflammation should start with a complete history and review of systems.¹⁷ This should include the duration of HIV disease, recent measurements of CD4+ cell count and HIV load, current medications, and any history of other sexually transmitted infections or acquired immune deficiency syndrome (AIDS) defining illnesses or complications. Such questions often reveal a relevant history, suggestive symptoms or signs, or immune variables that increase a given patient's risk for diseases known to cause uveitis. For example, a history of syphilis,^{3,18,19} the

Table 1 Causes of uveitis in HIV positive patients*

Location†/cause	Distinguishing features
Anterior uveitis	
Herpetic anterior uveitis (VZV, HSV‡)³ ⁵	Any CD4+ cell count. Prior or concurrent dermatitis, blepharoconjunctivitis, keratitis, or encephalitis. Often associated with decreased corneal sensation, elevated intraocular pressure, or patchy or sectoral iris atrophy. Almost always unilateral.
Cidofovir associated uveitis¹⁰-¹²	CD4+ cell count usually less than 50 cells ×10⁹/l. Risk may increase with HAART and rising CD4+ cell counts. Often granulomatous and associated with posterior synechiae. May be accompanied by hypotony. More common in eyes with inactive CMV retinitis. Dose related. May be unilateral or bilateral.
Rifabutin associated uveitis⁹	CD4+ cell count usually less than 50 cells ×10⁹/l. Often associated with hypopyon. Dose related. Serum concentration and risk increase with concurrent use of antifungal azole agents and some protease inhibitors. May be unilateral or bilateral.
Intermediate and diffuse uveitis	
Necrotising herpetic retinitis (CMV, VZV, HSV)³ ⁵	CD4+ cell counts usually less than 50 cells ×10⁹/l. CMV retinitis is the most common opportunistic infection in HIV positive patients, and typically has one or two foci of active retinitis with mild vitreous inflammation. VZV and HSV retinitis, by contrast, occur in less than 5% of HIV positive patients. Intraocular pressure may be elevated, and the retinitis is typically rapidly progressive with large, confluent or multiple areas of retinitis.
Toxoplasmic retinochoroiditis²⁰	CD4+ cell count usually less than 250 cells ×10⁹/l. Rapid onset. Occurs in up to 10% of HIV positive patients in some parts of the world. Intraocular pressure may be elevated. Typically a single focus of retinitis with adjacent or nearby retinochoroidal scars. Vitreous inflammation is often moderate to severe. Usually unilateral, although bilateral cases have been described.
Intraocular lymphoma⁶	CD4+ cell counts usually less than 50 cells ×10⁹/l. Insidious onset. Vitritis, retinitis, or retinal vasculitis transiently or incompletely responsive to corticosteroids. May be unilateral or bilateral. Vitreous or retinal biopsy usually required to make the diagnosis.
Endogenous endophthalmitis‡§	Any CD4+ cell count. Usually rapid onset with moderate to severe vitritis, often with one or more foci of retinitis or a subretinal abscess. Most common in injecting drug users.
Immune recovery uveitis¹³-¹⁵	Improving CD4+ cell count in the setting of HAART. Observed in eyes with inactive CMV retinitis. Inflammation is usually most heavy in the vitreous cavity but may also involve the anterior chamber. Common complications include cystoid macular oedema, epiretinal membrane formation, vitreomacular traction syndrome, retinal neovascularisation, and cataract.
HIV associated uveitis⁷	CD4+ cell count usually less than 50 cells ×10⁹/l. Usually mild to moderate severity in eyes with no evidence of active retinitis. May be anterior, intermediate, or diffuse. Responds to antiretroviral therapy.
Posterior uveitis	
<i>Pneumocystis carinii</i> choroiditis³ ²²	CD4+ cell count usually less than 250 cells ×10⁹/l. Usually a bilateral, multifocal choroiditis with little vitreous inflammation. Foci of choroiditis seldom cause haemorrhage in the overlying retina.
Cryptococcal choroiditis³ ²²	CD4+ cell count usually less than 50 cells ×10⁹/l. Usually a bilateral, multifocal choroiditis with little vitreous inflammation. Foci of choroiditis may cause haemorrhage in the overlying retina. Meningeal involvement with secondary elevated intracranial pressure and optic disc oedema may occur.

*HIV positive patients may develop forms of uveitis also seen in immunocompetent patients, including idiopathic anterior uveitis, idiopathic intermediate uveitis (pars planitis), anterior uveitis associated with the seronegative spondyloarthropathies in the presence or absence of HLA-B27 positivity (ankylosing spondylitis, Reiter's syndrome, inflammatory bowel disease, psoriatic arthritis), sarcoid uveitis, syphilitic uveitis, tuberculous uveitis, and other less common causes of uveitis.^{3 17-19 23 24}

†As defined by the International Uveitis Study Group.²⁵

‡Varicella zoster virus (VZV) associated eye disease is more common in HIV infected patients, whereas herpes simplex virus (HSV) related infections appear not to occur more frequently. HSV infections may, however, be more severe and more difficult to control in immunocompromised patients.³

§Endogenous endophthalmitis appears to be related mostly to injecting drug use.

presence of active HZO,^{3 5} or prior systemic infection with *Toxoplasma gondii*^{3 20} are all germane to evaluating the HIV infected patient with intraocular inflammation. Moreover, most HIV related ocular complications occur with advanced HIV disease, when lymphocyte counts drop well below the AIDS defining level of 200 cells ×10⁶/l.^{3 8} Necrotising herpetic retinitis, for example, occurs most often at CD4+ cell counts of less than 50 cells ×10⁶/l.^{3 4}

Once the history and review of systems are obtained, a complete eye examination can provide important clues to the cause of uveitis.¹⁷ The goal here is to identify the laterality and severity of the inflammation, as well as any associated eye findings that might suggest the diagnosis. Examples include the characteristic dendritic keratitis, decreased corneal sensation, elevated intraocular pressure, and anterior chamber inflammation of herpetic keratouveitis,^{3 5} the hypopyon uveitis associated with rifabutin therapy,⁹ or the focal retinochoroiditis, and moderate to severe diffuse uveitis of ocular toxoplasmosis.^{3 20}

It is important to remember that uveitis in HIV positive patients is usually the result of posterior segment disease.³ The most common cause of uveitis in patients infected by HIV is CMV retinitis,^{3 4} which is slowly progressive and tends to produce a mild, diffuse uveitis. Early involvement of the optic disc or fovea by CMV may result in rapid loss of vision, however, and a minority of patients with active CMV retinitis will show significant intraocular inflammation. Varicella zoster virus (VZV)⁵ and herpes simplex virus (HSV)²¹ can also cause uveitis in the setting of retinitis,

which tends, unlike CMV retinitis, to be rapidly progressive and involves large, confluent or multiple areas of retina simultaneously. A history of HZO⁵ or viral encephalitis²¹ can support the diagnosis of VZV or HSV retinitis in some patients. Ocular toxoplasmic retinochoroiditis occurs in a significant percentage of HIV positive patients, and is often distinguished by a focal retinitis with one or more adjacent or nearby retinochoroidal scars, typically with a moderate to severe amount of vitreous inflammation.^{3 20} Uveitis may also be associated with a focal or multifocal choroiditis. In these cases, the inflammation is typically very mild and tends to be limited to the vitreous cavity. Choroiditis in HIV positive patients results most often from *Pneumocystis carinii* or cryptococcal infection, both of which typically produce multiple lesions involving both eyes.^{3 22} *Pneumocystis carinii* often affects the lungs, whereas *Cryptococcus* has an affinity for the meninges, and frequently produces increased intracranial pressure and secondary swelling of the optic discs. Intraocular lymphoma is uncommon but appears to occur with increased frequency in HIV positive patients.⁶ A strong clue to the diagnosis includes the presence of vitreous inflammation, retinitis, or retinal vasculitis that responds only transiently or incompletely to corticosteroids. A vitreous or retinal biopsy is often required to make the diagnosis.

Less frequently, HIV related uveitis can be the result of drug toxicity,⁹⁻¹² IRU,¹³⁻¹⁵ or HIV itself.⁷ The most common drugs associated with uveitis in HIV infected patients are rifabutin⁹ and cidofovir,¹⁰⁻¹² which both tend to produce an anterior uveitis that may be either unilateral or bilateral. Whereas cidofovir uveitis is often granulomatous and tends

to be associated with numerous synechiae,^{10–12} rifabutin uveitis tends to be non-granulomatous, is less likely to produce synechiae, and is more often accompanied by hypopyon formation.⁹ Immune recovery uveitis occurs exclusively in the setting of successful HAART therapy, and only in eyes with inactive CMV retinitis.^{13–15} The inflammation is invariably intermediate or diffuse, and inflammatory complications are common, including cystoid macular oedema, epiretinal membrane formation, vitreomacular traction syndrome, retinal neovascularisation, and cataract. HIV associated uveitis can be anterior, intermediate, or diffuse but, by contrast with IRU, occurs in patients with advanced HIV disease and low CD4+ T lymphocyte counts, is observed in eyes with no evidence of retinitis, and tends to improve with successful HAART therapy.⁷

Considerations should also be given to causes of uveitis seen in HIV negative patients, including sarcoidosis, syphilis, and tuberculosis.¹⁷ Sarcoidosis accounts for 10%–20% of uveitis in adults, and may be screened for with a chest x ray, serum angiotensin converting enzyme or lysozyme levels, and intradermal injection of mumps, tetanus toxoid, or *Candida* antigen to test for anergy.^{17–23} Syphilis is the most common bacterial eye infection in HIV positive patients,^{3 18 19} and should be tested for in all HIV infected patients with uveitis. Specific treponemal serum antibody tests, such as the FTA-ABS or MHA-TP, are both sensitive and specific but provide no indication of disease activity. Non-specific treponemal serum antibody tests, such as the rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL), provide information regarding disease activity but may be falsely negative in up to 30% of cases. Most patients, therefore, should have both a sensitive (FTA-ABS or MHA-TP) and titratable (RPR or VDRL) test for syphilis. Screening for tuberculosis in HIV positive patients²⁴ usually involves both a chest x ray and a Mantoux test. The Mantoux test consists of a 0.1 ml intradermal injection of 5 unit strength purified protein derivative (PPD), and is considered positive in HIV infected patients if greater than 5 mm of induration results at 48–72 hours.

Treatment of uveitis is more challenging in patients with HIV disease than in immunocompetent patients.³ Every attempt should be made to encourage the use of HAART to promote immune reconstitution and to minimise the risk of HIV related complications. Any identified infections or neoplasms should be treated with specific antimicrobial or antineoplastic therapy, and drugs associated with uveitis should be discontinued, if possible, and replaced with alternative medications. Finally, inflammatory complications such as heavy vitritis, cytooid macular oedema, or posterior synechiae should be treated with corticosteroids, often in conjunction with a cycloplegic/mydriatic agent. While this sort of systematic approach to the management of uveitis in HIV positive patients can be time consuming, and requires a close working relationship between the ophthalmologist, the patient, and the

patient's primary medical doctor, such coordinated efforts are often successful at restoring and maintaining good vision.

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