# The Changing Global Epidemic of HIV and Ocular Disease

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**ABSTRACT**

**Purpose**: Overview of the evolving epidemiology of human immunodeficiency virus (HIV)-related ocular disease over time.

**Method**: Narrative review.

**Results**: HIV enhances susceptibility to opportunistic eye infections, has direct pathogenic effects, and places patients at risk of immune recovery inflammatory syndromes in previously infected eyes after starting highly-active antiretroviral therapy (HAART). Widespread availability of HAART has resulted in a decrease of infectious ocular conditions such as cytomegalovirus retinitis, toxoplasmic retinitis, squamous cell carcinoma of the conjunctiva, and microvascular retinopathy. However, large coexisting burdens of tuberculosis, herpesvirus infection and syphilis (among others) continue to contribute to the burden of ocular disease, especially in low-resource settings. Growing risks of cataract, retinopathy and retinal nerve fiber thinning can affect patients with chronic HIV on HAART; thought due to chronic inflammation and immune activation.

**Conclusion**: The changing epidemic of ocular disease in HIV-infected patients warrants close monitoring and identification of interventions that can help reduce the imminent burden of disease

**Key words**

HIV, ocular disease, opportunistic infection, highly active antiretroviral therapy (HAART), eye, retinopathy, nerve fiber layer.

**The global HIV Epidemic**

The Human Immunodeficiency Virus (HIV) pandemic is a global health priority. As of 2018, it is estimated that close to 38 million people are HIV-infected across the world; the majority (21 million) residing in Eastern and Southern Africa.[1] The HIV epidemic in these resource-constrained settings is generalised—well-established throughout the population and driven by transmission through heterosexual contact and from mother-to-child. In contrast, most resource-rich countries have an epidemic that is concentrated in specific population groups such as men who have sex with men, migrants and intravenous drug users.[2] HIV programmes have been scaled globally over the past two decades providing widespread availability of highly-active antiretroviral therapy (HAART). However, despite major strides in the global HIV response, considerable disparities in programme implementation and access to HAART remain.[1,2] For example, an estimated 56% of people living with HIV are taking ART in Mozambique, 62% in South Africa, 72% in Uganda, 78% in Zambia, 88% in Zimbabwe and 92% in Namibia.[1] In South Africa, one-third of patients initiate HAART only at an advanced stage of immunodeficiency, i.e. with CD4 cell count of less than 200 cells/mm$^3$, which is associated with AIDS-defining illness and excess morbidity and mortality.[3,4] High rates of programme loss, i.e. patients (temporarily) discontinuing HAART, have been reported; some of these only return to care at an advanced stage of immunodeficiency, or never.[5]

The clinical face of the HIV epidemic has changed dramatically over the past three decades. In the early 1980s people were dying of a clinical syndrome labelled the Acquired Immune Deficiency Syndrome (AIDS) for which there was no treatment; *Pneumocystis carinii* (now *Pneumocystis jirovecii*) pneumonia, cytomegalovirus (CMV) retinitis and Kaposi sarcoma were the most common presenting opportunistic infections at that time. In 1985, HIV was discovered; the first antiretroviral drug, zidovudine, was registered in 1987, the first nucleoside reverse transcriptase inhibitor (NRTI). The effect of monotherapy with zidovudine on

morbidity and mortality was favorable but limited due rapid emergency of resistance.[6] The same was observed for monotherapy with other drugs from the same class of NRTIs such as didanosine and stavudine.[7] Introduction of triple therapy consisting of a dual NRTI backbone combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor changed the prognosis of HIV dramatically, as the probability of resistance-inducing mutations was dramatically reduced with triple (or more) drug therapy. This approach (HAART), introduced in 1995-1996, has become the mainstay of HIV treatment; a wide array of therapeutic options are now available.[7] Widespread use of HAART, now including new classes of drugs with fewer side-effects and a higher genetic barrier to resistance, have resulted in a near-normal life expectancy of HIV-infected individuals on suppressive HAART.[8]

**The epidemiological intersection of ocular disease and HIV**

Low-resource countries are not only affected by a high burden of HIV, but also have a high prevalence of visual impairment and blindness. An estimated 285 million people worldwide are visually impaired and almost 90% of those reside in low-resource countries.[9,10] Visual impairment has major social and economic implications for affected individuals, caregivers and families which can be dependent on a single breadwinner.[11,12] For example, a study from West Africa showed that mobility was constrained among 83% of people with blindness compared to 49% for visually impaired and only 13% for sighted individuals; an active occupational status was reduced from 98% among sighted individuals to 62% and 21% respectively for those with visual impairment or blindness.[11]

There is substantial heterogeneity in the literature of ocular diseases and HIV with regards to study population, healthcare settings and type of ocular conditions included in the studies. There are many case reports, case series and cross-sectional studies, with inherent degree of selection bias based on what was observed in particular clinical practices; only a limited

number of cohort studies have been conducted. Heterogeneity and selection bias in the literature made it difficult to compare the results of individual studies and to define the prevalence or measure time trends effects of specific conditions in this article.

Globally, the conditions most commonly associated with visual impairment in low-resource countries are uncorrected refractive errors, cataract and glaucoma.[13] Although not as common at a population level as uncorrected refractive errors, cataract, glaucoma and specific HIV-related ocular conditions are highly prevalent in HIV-infected patients. Reports from the pre-HAART period estimated that 50% up to 75% in untreated HIV-infected individuals had ocular involvement.[14,15] A more recent study from Mumbai, India, reported an 18% prevalence of ocular disease among adult individuals prior to initiating HAART; 24% if CD4 count is less than 200 cells/mm$^3$.[16] There are limited data with regards to HIV-infected children, however, their risk may not be better than among adults given 54% ocular involvement was reported among children from Rwanda.[17]

The prevalence and spectrum of the various ocular conditions in HIV-infection is related to the geographic region, stage of HIV-disease upon presentation (as measured by CD4 count and/or WHO clinical stage), and access to HAART.[9,16] There is heterogeneity with regards to the type of subjects studied, level of healthcare setting, and the type of ocular conditions that were assessed amongst studies that have been conducted to assess the frequency of ocular disease among HIV infected patients. These variations make it difficult to determine the exact prevalence of ocular morbidity in HIV-infected patients, however, the reported burden is high in almost all studies: ocular disease was reported in 6%-48% of HIV-patients in Ghana, 8%-48% in India, 24%-46% in China, 25% in Ethiopia, 29% in Korea, 34% in Thailand, 38% in Turkey, 43% in Nepal, 45% in the USA, 54% Indonesia.[18-30] The most commonly reported ocular conditions were HIV retinopathy/HIV retinal microvasculopathy, dry eye syndrome, optic neuropathy and atrophy, CMV retinitis, other forms of infectious uveitis, and herpes

zoster ophthalmicus. Among children, perivasculitis of the peripheral retinal vessels is the most common presentation reported, followed by lacrimal gland dysfunction, retinal cytomegalovirus infection and herpes zoster ophthalmicus.[17]

**Changes in the spectrum of ocular disease in HIV-infected patients over time**

HIV-infected patients are at increased risk of eye disease through multiple pathophysiological mechanisms. First, there are direct effects of HIV on the (micro)vascular structures in the conjunctiva and retina as well as afferent nerve and retinal nerve fiber layer damage through increased levels of inflammatory cytokines, macrophage-associated immune response and chronic immune activation.[31] These result in HIV retinal microvasculopathy and some neuro-ophthalmic conditions. Second, advancing immunodeficiency associated with HIV progression along the spectrum to advanced AIDS predisposes to opportunistic infections that cause specific eye diseases such as herpesvirus retinitides (most commonly CMV retinitis), ocular tuberculosis, squamous cell carcinoma of the conjunctiva (SCCC) and Kaposi sarcoma. Third, provision of HAART may lead to immune reconstitution inflammatory syndromes (IRIS) with paradoxical deterioration or unmasking of existing clinical infection as the result of immune restoration.[32] Immune recovery uveitis following CMV-retinitis is the best-known example of ocular IRIS.[33,34] Lastly, there are the potential direct toxic effects of HAART on the eye such as didanosine-induced chorioretinal atrophy.[35]

Not surprisingly, the spectrum of ocular disease in HIV-infected patients has changed over the past three decades with the global scale-up of HIV testing and treatment programmes. There is increasing access to HAART, with increasingly better antiretroviral drugs, and individuals are initiating HAART at an increasingly early stage (i.e. higher CD4 cell count). This HIV programme growth has resulted in a reduction in ocular disease due to opportunistic infections associated with advanced immunodeficiency. Scale-up of HAART in the United States of

America (USA) was associated with a clear shift from infectious to non-infectious ocular pathology in HIV-infected patients.[36] The observed change was largely attributed to a 75%-95% reduction in cases of CMV retinitis; this pattern was also reported by other studies from the USA and Austria.[36-38] A study from Germany also reported a 90% decrease in CMV disease following the introduction of HAART, whereas studies from Italy and China reported reduced rates of CMV retinitis too [as well as toxoplasma retinochoroiditis, herpes simplex virus (HSV) and varicella-zoster virus (VZV) retinitis, optic neuropathy, and HIV-related microangiopathy].[39-42]

However, this success story based on data from Europe and the USA has not been fully replicated in resource-constrained settings. For instance, in India it has been reported that prevalence of ocular manifestations remained high and did not change significantly between the pre-HAART (42%) and the HAART eras (38%), with CMV retinitis and HIV retinopathy as the unchanged dominant causes of ocular morbidity.[43] Ultimately, the extent of access to/ effective use of HAART and the proportion of HIV-infected patients presenting at low CD4 count for (re)initiation of HAART will determine the prevalence and spectrum of ocular disease that is seen in HIV-infected patients in each local setting.

In contrast to the decrease in infectious ocular conditions associated with HAART, there are increases reported in non-infectious complications associated with chronic HIV infection and long-term HAART,[44] and accelerated aging probably occurs in this clinical setting.[45] Although the depth of data are still limited, higher age-adjusted incidences of cataract, glaucoma, chalazion, and diabetic and hypertensive retinopathy have been reported in HIV-infected individuals on HAART form Italy and South Africa compared to HIV-uninfected individuals.[40,44]

**HIV and increased susceptibility to ocular infections**

Immunodeficiency is associated with increased risk of ocular infections in HIV-infected patients through two major mechanisms: a) susceptibility to microorganisms that do normally not cause disease in immunocompetent individuals, b) increased frequency of reactivation of latent infections. An advanced stage of HIV infection with associated immunodeficiency places the individual at risk of infection with common microorganisms than are normally commensals and ubiquitous in the environment. For example, fungal infection with *Cryptococcus neoformans* (typically meningitis) almost exclusively occurs in HIV-infected patients with CD4 cell count less than 100 cells/mm$^3$. In a case series of 80 patients with *Cryptococcus neoformans* infection, papilledema was observed in 26 (33%), 7 (9%) had visual loss and another 7 (9%) had abducens nerve palsy; two had optic nerve palsy.[46] Chorioretinitis as manifestation of cryptococcal infection occurs but is uncommon.[46-48] Various non-tuberculous mycobacteria such as *Mycobacterium avium* complex, *Mycobacterium haemophilum* and *Mycobacterium Kansassi* may cause ocular infection presenting as endophthalmitis or various forms of uveitis.[49,50]

HIV-infection is a risk factor for herpes virus keratitis, with and without bacterial superinfection, due to higher frequency of reactivation of HSV and VZV.[51,52] However, there is no effect of HIV on the occurrence and etiology of bacterial keratitis.[52] The course of keratitis is more severe, and progression of herpesvirus keratitis to anterior uveitis or other intraocular complications occurs more frequently, in HIV-infected individuals—especially those with low CD4 count and with keratitis caused by VZV.[52,53,50] Reactivation of VZV manifesting as dermal herpes zoster is much more common in HIV-infected than immunocompetent individuals. A study from South Africa reported that the majority of cases of herpes zoster ophthalmicus were HIV-infected and that visual impairment due to corneal and choroidal complications was commonly due to delays in presentation, diagnosis and management.[53] Similar to keratitis,

HIV-infected individuals have a higher risk of infectious uveitis, in particular herpesvirus retinitides, and experience more severe disease compared to HIV-uninfected individuals.[54,55] There appear to be some geographic differences with regards to distribution of herpesvirus etiology in uveitis patients. Reactivation of CMV is the dominant cause of uveitis in HIV-infected patients in Asia, Europe and the USA, but the prevalence of this infection appears to be less common in sub-Saharan Africa where relatively low rates are reported from Malawi, Tanzania and South Africa and where HSV and VZV may be diagnosed more frequently as the aetiological agent.[26,27,43,56-58] The relatively low prevalence in sub-Saharan Africa may be attributed to survival bias; before entering the stage of advanced immunodeficiency (CD4 count <50 cells/mm$^3$) that puts them at risk for CMV retinitis, patients may die from a number of other opportunistic infections such as (extrapulmonary) tuberculosis, cryptococcal meningitis and salmonella sepsis.[59]

Other than a particularly perverse interaction with the family of herpesviruses, HIV is also associated with increased prevalence and severity of ocular disease by other infections, especially *Mycobacterium tuberculosis* (tuberculosis), *Treponema pallidum* (syphilis) and *Toxoplasma gondii* (toxoplasmosis).[60-64] Although newly acquired tuberculosis may play a role, especially in high tuberculosis endemicity areas, ocular disease occurs generally due to reactivation and disseminated spread of (latent) infection.[60-64] HIV-infected individuals are at increased risk of extrapulmonary and disseminated tuberculosis.[65] Tuberculous granulomas can be observed in 5-20% of patients with pulmonary and disseminated tuberculosis, however, these may also occur as isolated retinal lesions without obvious involvement of any other organ.[56,58,60] Ocular syphilis associated with HIV infection is on the rise globally, possibly due to sexual risk behaviors predisposing to both infections.[63,64] The ophthalmic presentation of syphilis is diverse and may involve all ocular segments.[66] Ocular involvement may happen

during any stage of syphilis, i.e. when presenting with concurrent genital ulcer (primary ulcer), with skin rash (secondary) as well as during longstanding (tertiary) infection.[62,66]

There is a strong association of HIV and SCCC, especially in resource-constrained settings in the Southern hemisphere, where other SCCC risk factors such as human papillomavirus (HPV) infection, exposure to sunlight and outdoor occupation are also common.[67] HIV-infected individuals have a 5-10 times higher risk of developing SCCC; women are more often affected than men possibly due to higher HPV coinfection rate.[67,68] HPV is detected in up to 75% of the SCCC lesions. Types 5, 8, 11, 16 and 38 are most commonly detected; however, multiple HPV types often are detected from a single lesion.[69-71] A risk increase for SCCC associated with HIV has been reported from the USA, although the overall incidence rate was lower.[70] The other two important ocular malignancies associated with HIV infection are ocular lymphoma (usually EBV-related), which risk is inversely related to CD4 cell count, and ocular Kaposi sarcoma that is caused by human herpes virus type-8 infection.[71] A trend of decreasing incidence of Kaposi sarcoma has been reported from the USA, but epidemiological data on incidence trends in ocular Kaposi sarcoma elsewhere in the world are not available.[72]

**Ocular manifestations directly attributed to HIV**

HIV-infected individuals may present with various ocular conditions that can be attributed directly to HIV itself and its effects on the human immune response. HIV-associated retinal microangiopathy and neuro-ophthalmic complications such as optic neuropathy and ocular movement disorders are the most commonly reported entities.

HIV infection may change the thickness, blood flow and structural morphology of the choroid through chronic inflammation and immune activation, resulting in swelling of the choroid, endothelial damage and microangiopathy. Choroidal thickness as measured by optical coherence tomography imaging is higher among HIV-infected patients compared to age- and

gender-matched HIV-uninfected individuals; the highest choroid thickness is observed in patients with clinically detectable retinopathy.[73,74] Choroidal thickness was not associated with distance to the fovea suggesting that this pathophysiological process is not topographically restricted.[74] HIV-associated microvascular retinopathy may manifest as cotton wool spots, retinal hemorrhage and/or microaneurysms; it presents as monocular in approximately half of the patients and visual impairment is generally relatively mild.[75] Although the prevalence of HIV-associated microvascular retinopathy has reduced with the scale-up of access to HAART, it may still be present in up to 15% of HIV-infected individuals without HAART, more commonly those with lower CD4 counts.[21,75] Moreover, HIV retinopathy still can develop in patients taking HAART especially in the context of therapeutic failure related to drug resistance and/or suboptimal treatment adherence.[76]

Neuro-ophthalmic conditions affect the afferent neurons and/or extraocular pathways resulting in visual loss, visual field defects and extraocular motility disorders. A study from the Democratic Republic of Congo, in the pre-HAART era, reported a very high prevalence of 60% prevalence of neuro-ophthalmic abnormalities in persons with AIDS, with eye movement disorders (51%), visual field defects (51%), optic neuropathy (31%) and ocular motor nerve palsies (26%) as most prominent manifestations.[77] Studies from the USA and India found a lower frequency of neuro-ophthalmic abnormalities among persons with AIDS (10/127 and 12/100 respectively); ocular motor nerve palsies, papilledema and optic neuritis were the most common conditions and could be attributed in most cases to opportunistic infections such as toxoplasmosis, cryptococcal meningitis, systemic CMV and HSV encephalitis.[78,79] Anecdotally, this burden has reduced dramatically now with the introduction of HAART, as might be expected with lower HIV load in blood as a result of effective therapy, but exact estimates are unavailable.

HIV-associated neuropathy occurs throughout the body, is associated with low nadir and current CD4 count, and may affect the optic nerve as well (optic neuropathy). Degenerative changes to the optic nerve are caused by the macrophage response to HIV infection with subsequent microvascular ischemia of the optic nerve head resulting in optic atrophy.[80] Patients may present with subacute painless optic neuropathy progressing to vision loss and blindness.[81] The damage is irreversible and does not improve with HAART; it may even progress in case of therapeutic failure.

Loss of the retinal nerve fibre layer is another important feature of HIV infection.[82,83] Although associated with low CD4+ T cell count, the pathophysiological process is not well-understood; (micro)vasculopathy, chronic inflammation, direct damage by HIV and chronic immune activation have been hypothesized to play a role.[83] Retinal nerve fibre layer loss may reduce contrast sensitivity, impair color vision, induce visual field loss and ultimately adversely impact quality of life.[82] The prevalence of this condition, reported in up to 10% among HIV-infected individuals, is strongly associated with low CD4 count. The estimated cumulative incidence within 20 years after the initial HIV diagnosis of 51%.[84] This condition may continue to develop under HAART, especially in the context of therapeutic failure defined by detectable viral load in blood, and may associate with accelerated cognitive ageing.[85]

Ocular movement disorders, if present, generally affect the 3$^{rd}$ and/or 6$^{th}$ cranial nerves. In most cases, these palsies are not the result of neurodegenerative changes, but rather secondary to infection with *Cryptococcus neoformans*, *Toxoplasma gondii*, and the herpes viruses.[81]

**Ocular disease related to HAART**

Despite its many benefits, HAART may predispose to specific ocular diseases, primarily through IRIS, direct ocular toxicity of specific antiretroviral drugs and long-term changes in metabolic and cardiovascular parameters.

Ocular IRIS occurs predominantly in HIV-infected individuals initiating HAART at low CD4 counts after the known or unknown establishment of opportunistic infection(s). Restoration of immune function results in paradoxical worsening of existing infection that is being treated and/or from unmasking of a subclinical or unrecognized infection. IRIS has been described for ocular opportunistic infections including CMV-retinitis, TB chorioretinitis and *Cryptococcus neoformans*.[86-88] Targeted treatment of IRIS etiology with continuation of HAART (given the overwhelming benefits of effective antiretroviral therapy) is required in case of IRIS. Visual outcome of ocular TB IRIS has been reported to be good while there is variable prognosis of IRIS associated with the body's inflammatory response to other opportunistic infections following immune restoration.[86] If possible, deferring HAART for a short time while specific anti-opportunistic infection treatment is initiated might reduce the incidence or extent of IRIS syndromes.[32] However, for CMV retinitis—associated with a high short-term mortality risk—deferring HAART is not advisable.[89]

An increasingly large spectrum of antiretroviral drugs for treatment of HIV-infection has become available globally. Rarely, these drugs might have direct toxic effects on the eye. For instance, retinal toxicity has been reported with didanosine; however, this drug has now been discontinued from HAART regimens in most countries[90,91] Recently, a case of toxic optic neuropathy has been reported with the relatively novel drug combination elvitegravir/cobicistat.[92] Two other drugs, ethambutol and linezolid, that are frequently used in the treatment of (drug-resistant) tuberculosis have also been associated with ocular toxicity, in particular optic neuropathy.[93,94] Cidofovir, used in the treatment of CMV retinitis, may cause anterior uveitis and chronic ocular hypotony.[95,96]

Patients with chronic HIV on HAART, especially those with low nadir CD4 counts, have an elevated risk of developing increased lens density and preclinical as well clinically detectable cataract.[45,97-100] Cataract manifests earlier in life in these patients, which is attributed to a high

degree of intraocular inflammation as shown by raised intraocular levels of granulocyte macrophage stimulating factor and the proinflammatory interleukins 8 and 10.[12] The postoperative course and outcomes of cataract surgery are similar for HIV-infected and HIV-uninfected individuals.[101]

**Conclusion**

The HIV epidemic has changed dramatically over the past decades, with increasing access to HAART and growing treatment programmes. There has been a clear reduction in the incidence of CMV retinitis over the past two decades, however it still causes significant visual impairment among HIV-infected individuals initiating HAART at advanced stage of immunodeficiency.[39-41,59,102,103] The burden of HIV-associated visual impairment has mirrored the changes in the HIV epidemic: a shift from infectious complications caused by immunodeficiency toward ocular conditions caused by immune recovery, drug treatment or accelerated aging has occurred. For example, the prevalence of conditions such as CMV retinitis, SCCC and microvascular retinopathy have reduced considerably over time, especially in resource-rich countries. In contrast, the coexistent burdens of infectious diseases such as tuberculosis, herpesviruses and syphilis which occur with lesser degrees of immunodeficiency contribute to the persistent burden of ocular infections in HIV-infected patients in resource-constrained settings. Despite substantially improved access to HAART, there is still a considerable proportion of HIV-infected patients who have not yet initiated HAART or may have (temporarily) discontinued HAART.[1,3,5] These people may (re)initiate HAART at a low CD4+ T-cell count, putting them at risk of infectious complications. Thus, clinicians must remain aware of the infectious complications associated with advanced immunodeficiency.[3,4] Ocular disease in HIV-infected children is an under-researched field that deserves more attention; most studies date from more than a decade ago.[17,104-107] Prevention of mother to child

transmission (PMTCT) programmes have substantially reduced the number of new infant HIV infections, but the burden of pediatric HIV remains large. For example, an estimated 680 000 children are estimated to live with HIV in Eastern and Southern Africa.[1] The availability and initiation of HAART at an earlier time in the course of infection is likely to have reduced the occurrence of ocular opportunistic infections in this group, similar to the trends in HIV-infected adults, but the long-term effects of chronic HIV and HAART on the developing eyes of growing infants is unknown. Such ocular effects, if present, could over time pose a significant burden on the quality of life of individuals with vertically acquired HIV infection.

HAART has dramatically improved the life expectancy of HIV-infected individuals and has dramatically reduced the incidence of CMV retinitis. However, HIV-infected individuals on HAART now are faced with an increased risk of non-infectious ocular diseases compared to the age-matched general population. Persistent chronic inflammation and immune activation in patients with chronic HIV, with and without virological suppression, predisposes these patients to a variety of ocular conditions related to long-term effects of chronic HIV and HAART. The burden of ocular disease associated with long-term HAART is not yet fully documented, but increased risk of cataract, retinopathy and retinal nerve fibre thinning related to accelerated ageing appear to be present.[73,74,85,97-99] There is a strong need to better characterize the ocular morbidity among HIV-infected persons on chronic HAART, to model the impact of chronic HIV on the global burden of visual impairment, and to identify interventions that may slow down ocular disease progression. An important step may be to introduce regular ophthalmic assessment, in a similar way that ophthalmic monitoring is done in diabetes care, to early identify ocular complications so as to reduce the global burden of visual impairment associated with HIV-infection.

## Conflict of interest statement

The authors have no conflict of interest to report.

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