Symposium

Impact of highly active antiretroviral therapy on ophthalmic manifestations in human immunodeficiency virus / acquired immune deficiency syndrome

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Highly active antiretroviral therapy (HAART) has changed the face of human immunodeficiency virus (HIV) acquired immune deficiency syndrome (AIDS) by leading to dramatic decreases in HIV-related morbidity and mortality in the developed as well as developing world. Since the introduction of HAART, the incidence of ocular opportunistic infections causing retinitis has dramatically decreased, and clinicians should be aware of changes in the clinical presentation of ocular manifestations of HIV. As studies of 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 of therapy. This review focuses on the impact of HAART on the ocular manifestations of HIV.

Key words: Acquired immune deficiency syndrome, eye, highly active antiretroviral treatment, human immunodeficiency virus, India, ophthalmology, therapy

Indian J Ophthalmol 2008;56:391-3

Highly active antiretroviral therapy (HAART) has changed the face of human immunodeficiency virus (HIV) acquired immunodeficiency syndrome (AIDS) by leading to dramatic decreases in HIV-related morbidity and mortality in the developed as well as developing world.[1,2] In India, generic HAART has been shown to be safe, well-tolerated, and effective in increasing CD4 counts, and suppressing plasma viral load in patients with advanced HIV.[3,4] The production of antiretroviral drugs by generic Indian drug manufacturers throughout the developing world has drastically reduced the price of HAART to less than one USD per day, and consequently increased access to treatment in resource-limited settings.[5] This review focuses on the impact of HAART on the ocular manifestations of HIV.

Since the introduction of HAART, the incidence of ocular opportunistic infections causing retinitis, such as cytomegalovirus (CMV), varicella zoster virus (VZV), tuberculosis, and toxoplasmosis, has dramatically decreased.[6] However, immune recovery uveitis secondary to HAART has become a major visually-threatening condition.[7-9] High rates of ocular syphilis have been documented as well among patients receiving HAART.[10] While HAART may have also decreased the incidence of other retinopathies associated with HIV, the reported incidence of these conditions was so low before the era of HAART that quantifying any changes in incidence is not feasible.

The standard HAART regimen since the late 1990s has consisted of combination therapy of three antiretroviral drugs from the three major drug categories, namely nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The goal of HAART has been to achieve sustained viral suppression, minimize drug resistance, and simplify dosage pattern. The immune recovery resulting from HAART is due to an absolute increase in CD4 cell count first through an increase in memory T cells followed by the renewed production of naïve CD4 T cells.[11] As in the developed world, the introduction of generic HAART in India has led to a dramatic reduction in the incidence of opportunistic infections.[2]

Changes in ocular manifestations of HIV in the pre- and post-HAART eras

There have been dramatic changes in the incidence of ocular manifestations of HIV between the pre- and post-HAART era. In the era prior to HAART, our center described the first two cases, one patient with CMV retinitis and the other with endogenous endophthalmitis, of ocular involvement of HIV in India in 1995.[12] Before the introduction of HAART, CMV retinitis affected 30-40% of HIV-infected individuals,[13] with visual loss primarily due to CMV involvement of the posterior retina and retinal detachment;[14] it was also suggested that upon careful examination, 30% of patients with CD4 cell counts below 50 cells/μl would be harboring CMV retinitis.[15] At that time a study from our center documented CMV retinitis and cotton-wool spots caused by HIV-related microvasculopathy as the most frequently encountered ocular lesions. A lower prevalence (45.7%) of ocular involvement was observed in HIV infection among Indian patients than other regional settings.[16,17] Additionally, a study conducted at our center in Indian children infected with HIV found a high prevalence of ocular and systemic lesions, most commonly anterior uveitis followed by CMV retinitis.[18]

In the HAART era, it has been suggested that there has been an estimated 80% decrease in the incidence of CMV retinitis;[1,19] however, there is evidence that suggests that this decrease has now been leveled off as patients continue to present with CMV retinitis after initiating HAART.[19,20] It has also been reported

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Manuscript received: 08.08.07; Revision accepted: 14.01.08

that the clinical picture and level of intraocular pressure are similar in the pre-HAART and post-HAART era.[21] Highly active antiretroviral therapy induces at least partial immune restoration and improves the long-term outcome of CMV retinitis.[6] However, after the initiation of HAART, a relapse of CMV retinitis as vitritis has been reported.[8] Recurrences of CMV can be due to progressive immune dysfunction, inadequate intraocular drug levels, and drug resistance. By studying CMV retinitis, physicians can investigate whether the rejuvenated immune system resulting from HAART can effectively control opportunistic infections caused by AIDS.

Treatment options for CMV and associated complications in the era of HAART

Treatment of CMV has changed since the introduction of HAART. Prior to HAART, patients had to remain on maintenance anti-CMV regimens to decrease rates of recurrence. However, HAART has led to low levels of CMV recurrence, even when anti-CMV regimens are stopped.[6,22] It has been suggested that patients who can sustain an elevated CD4 cell count due to HAART on two consecutive measurements three months apart and whose CMV retinitis remains regressed on anti-CMV therapy for more than four months may discontinue anti-CMV therapy with close clinical monitoring for reactivation.[23] The conventionally used definition of immune recovery is a CD4 cell count >100 cells/μl, which has been used as a guideline for discontinuation of anti-CMV therapy.[24] Despite the marked increase in CD4+ cell counts, it may be advisable to not discontinue anti-CMV medications during the first few months of initiating HAART.[25] Due to the small number of cases reported and the variable periods of follow-up, the relapse rate of CMV retinitis among patients who discontinue anti-CMV treatment remains unclear.

Since the advent of HAART, immune recovery uveitis (IRU) has become an ocular manifestation described in patients with inactive CMV retinitis.[8,26] The reported incidence of IRU has been shown to vary widely and limited data is available of possible risk factors.[27-29] Some HIV-infected individuals experience clinical deterioration after initiating antiretroviral therapy that is believed to be a result of the restored immune system to mount an exuberant inflammatory response. Immune reconstitution syndrome can cause posterior segment inflammation in CMV retinitis and can lead to visual morbidity in patients with AIDS.[29] We have reported a case of immune reconstitution in an HIV-infected Indian male receiving HAART with CMV retinitis who developed panuveitis with hypopyon, which was related to immune recovery mediated by combination protease inhibitors-based antiretroviral therapy.[30]

Conclusion: future clinical trajectories of treating ocular manifestations of HIV

Clinicians should be aware of changes in the clinical presentation of ocular manifestations of HIV since the introduction of HAART. Among patients with CMV in the HAART era, immune recovery may be associated with a greater number of inflammatory complications, including macular edema and epiretinal membrane formation.[21] Given the range of ocular manifestations of HIV, routine ocular examinations and screening for visual loss is recommended in patients with CD4 counts <50 cells/μl.[31] 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. 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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Source of Support: Nil, **Conflict of Interest:** None declared.