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Editorials

Combination HIV therapy and opportunistic infections of the eye in people with AIDS

The past 2 years have seen a dramatic improvement in the prognosis for people with HIV infection owing to the success of a strategy of using a combination of antiretroviral drugs to bring about a profound and durable suppression of viral replication. The drugs currently available all work through inhibiting key HIV specific enzymes—reverse transcriptase and HIV protease. The use of a three drug cocktail, usually consisting of two reverse transcriptase inhibitors (RTI) and one protease inhibitor (PI), has shown itself to be superior to single¹ and dual^{2,3} drug therapy in terms of the degree of viral suppression and also the ability to stall the development of resistance.⁴⁻⁷

HIV damages the immune system primarily by promoting the destruction of CD4 T lymphocytes, and this leaves the individual vulnerable to a greater number of infections as the cell numbers decline. Following the instigation of triple combination, highly active antiretroviral therapy, often called "HAART", most recipients experience a rise in blood CD4 T cell numbers, initially in the first month as a result of a release of cells from the reticuloendothelial system, and thereafter because of the production of new cells.^{8,9} This rise may occur even in people with quite advanced HIV related immunodeficiency and low CD4 counts. A reduction in the number of opportunistic infections,^{10,11} including cytomegalovirus (CMV) retinitis,^{12,13} a reduction in the number of hospital admissions,¹⁴ and an improvement in the length¹⁵ and quality of life have all been shown to occur in the majority of recipients of HAART. Walsh *et al* have recently shown a dramatic increase in survival of AIDS patients with CMV retinitis who were treated with HAART.¹⁶

Before the era of combination antiretroviral therapy, most serious infections with CMV in HIV infected individuals occurred only once the CD4 T lymphocyte count fell below $100 \times 10^6/l$. Clearly, with the use of combination therapy in those whose CD4 count never falls below 100, there should be no risk of CMV. Those who start combination therapy with CD4 counts below $100 \times 10^6/l$ may be vulnerable to CMV disease until their immune system recovers sufficiently. When the point of immunocompetence to CMV is regained is something we are unable to measure at present. This is of even more significance in those AIDS patients with existing CMV disease who start HAART and experience an improvement in immune function that may at some point make it unnecessary for them

to continue maintenance anti-CMV treatment (which is often toxic, inconvenient, and expensive).^{17,18}

Van den Horn *et al* report in this issue of *BjO* (p 988) on 15 patients with AIDS related CMV retinitis, who were receiving maintenance therapy with anti-CMV drugs, and who, as would be expected, had very low CD4 T lymphocyte counts. They document the recurrence rate of CMV retinitis in these patients after receiving combination therapy including a protease inhibitor. Recurrences occurred in seven patients all of whom had failed to achieve a rise in their CD4 lymphocyte count above $100 \times 10^6/l$. Those patients who successfully obtained CD4 counts above $100 \times 10^6/l$ did not suffer any recurrence of CMV retinitis, and one might speculate that it may be safe for those individuals to stop maintenance anti-CMV therapy.

Paradoxically, the improvement in immune function that follows the instigation of HAART may have its drawbacks. Some patients with CD4 T lymphocyte counts below $50-100 \times 10^6/l$ may have hitherto unrecognised and asymptomatic infection with CMV retinitis. As immune function returns, so there is an increased inflammatory response which, in the case of CMV retinitis, results in visual loss and an abnormal funduscopic appearance, often quite different from the classic "pizza pie" or "ketchup and scrambled egg" appearances of CMV retinitis.^{19,20}

The practice of the ophthalmologist looking after people with HIV has changed. The widespread use of HAART has reduced the incidence of CMV retinitis and indeed other opportunistic infections of the eye.²¹ The enhanced immune function that follows the commencement of HAART may produce unexpected appearances of retinitis with severe inflammation.²² Anti-CMV maintenance therapy may now be necessary only for a few months until immune restoration has occurred,²³ but specific tests to gauge an individual's cell mediated immune function against CMV would be useful to tell when this time has been reached. Additionally, some of the drugs used in the HAART combination may have ophthalmic side effects.

One fear is that the effects of HAART will be temporary, lasting perhaps only a few years, after which we may see CMV retinitis and other opportunistic infections becoming commonplace again.

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Seeing beyond acuity

What are the effects of unocular disorders on visual outcome? Are some treatment strategies more effective than others? Has the good eye been compromised? Does the age of onset matter? What is the influence of deprivation versus abnormal competition between an affected eye and a fellow good eye? These are all important questions. In answering these questions, we often turn primarily to the “gold standard”—Snellen acuity. But good vision involves more than being able to decipher small details at high contrast. It also involves sensitivity to objects of low contrast, stereopsis, being able to accurately align easily visible objects, the perception of motion, and a host of other aspects of vision. Studies of animals indicate that some aspects of vision are more susceptible to abnormal visual input than others and that the sensitive period differs for different aspects of vision.¹ Thus, a clear understanding of visual outcome requires the assessment of more than just visual acuity.

Patients with strabismic amblyopia, for example, have a variety of deficits in the amblyopic eye and often have similar but milder deficits in the dominant eye. Motor deficits include irregular tracking of moving objects,^{2–5} eccentric fixation and/or unsteady fixation,^{3,6–8} and asymmetrical optokinetic nystagmus (OKN) such that OKN, when tested monocularly, can be elicited easily when a repetitive pattern moves from the temporal visual field towards the nasal visual field but not when it moves in the opposite direction.^{9–11} Sensory deficits include not only reduced acuity, but also abnormal scotopic sensitivity,¹² reduced contrast sensitivity especially at high spatial frequencies,^{13–15} difficulty in aligning stimuli accurately even when they are well above threshold,^{16–18} and reports of distorted perception in the amblyopic eye.¹⁹

Strabismic amblyopes also show deficits in their perception of motion. They judge temporalward motion to be

slower than nasalward motion of the same speed, especially at slow velocities^{20–22}; they are poor at identifying form from motion defined cues²³; and they sometimes show deficits in perceiving the direction of motion.⁹

In this issue of the journal (p 991), Kelly and Buckingham identify another abnormality of motion perception in childhood amblyopia. Children aged 5–7½ years, most of whom had strabismic amblyopia, were asked to identify which of two vertical bars was oscillating. A staircase procedure was used to determine the minimum amount of horizontal oscillation that could be detected reliably (coined as the “oscillatory movement displacement threshold”). Overall, thresholds in the amblyopic eyes were almost 50% worse than in the dominant eyes, which were the same as those of children with normal vision. When patients were divided into those with no stereopsis versus those with at least gross stereopsis, only those with no stereopsis, and hence those with the greatest imbalance of interocular competition, showed significantly elevated thresholds for detecting oscillatory movement with their amblyopic eye.

The article by Kelly and Buckingham raises several issues for further consideration. Firstly, the results from normal children were correlated with age at the time of the test. In fact, a previous article by these same authors testing oscillatory thresholds in large groups of normal children and adults showed that thresholds improve by 64% between 5 and 7½ years of age and do not reach adult values until after 8 years of age.²⁴ Thus, it would be interesting to calculate the ratio of each patient's threshold in the amblyopic eye to that of age matched normals. The size of the threshold elevation relative to normal could then be correlated with the age of onset of strabismus in an attempt to identify the sensitive period. Only when strabismus begins before 2 years of age do patients show abnormalities

in visually evoked potentials to oscillating motion,²⁵⁻²⁶ in perceiving the direction of motion,⁹ and in the symmetry of OKN.⁹⁻¹⁰ The same may be true for oscillatory movement thresholds. Secondly, it is surprising that oscillatory thresholds were normal in the dominant eye, especially since subtle deficits have been reported for many aspects of vision, including other measures of the integrity of motion processing.⁹⁻¹¹ Perhaps an analysis of thresholds like the one suggested above for the amblyopic eye would reveal subtle deficits in the dominant eye after early onset strabismus. Thirdly, it would be useful to separate the results for strabismic versus anisometropic amblyopes since, at least on some tasks, the two groups perform differently¹⁷ and are thought to have different underlying neural deficits.²⁷⁻²⁹ None the less, the study by Kelly and Buckingham adds to our understanding of amblyopia, an understanding that goes far beyond that achievable from only traditional clinical measures of visual outcome.

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