

## Short Communication

## Differing spectrum of HIV-associated ophthalmic disease among patients starting antiretroviral therapy in India and South Africa

Sophia Pathai<sup>1</sup>, Clare Gilbert<sup>1</sup>, Helen A. Weiss<sup>2</sup>, Matthew McNally<sup>3</sup> and Stephen D. Lawn<sup>1,4</sup>

<sup>1</sup> Department of Clinical Research, London School of Hygiene and Tropical Medicine, UK

<sup>2</sup> Medical Research Council Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, UK

<sup>3</sup> Hannan Crusaid Treatment Centre, Gugulethu, Cape Town, South Africa

<sup>4</sup> Desmond Tutu HIV Centre, University of Cape Town, South Africa

### Summary

Differences in the prevalence and spectrum of HIV-associated ophthalmic disease in Africa and Asia are not well documented. We studied two comparable cohorts of patients initiating antiretroviral therapy in Mumbai, India, and Cape Town, South Africa. The prevalence of HIV-associated ophthalmic disease was higher in the Indian population (17.5%) than in the South African population (12.1%). This was largely because of vitreo-retinal opportunistic infections (11.4% *vs.* 2.6%, respectively), notably cytomegalovirus retinitis. This difference persisted after adjusting for confounding factors (adjusted odds ratio = 11.32, 95% confidence interval: 2.67–48.13), confirming a marked geographical difference in the prevalence of HIV-associated retinal disease.

**Keywords** opportunistic infections, cytomegalovirus, cytomegalovirus retinitis, ophthalmology, Africa, Asia

HIV-associated eye disease is estimated to affect 50–75% of HIV-infected people worldwide at some point during their disease course (Kestelyn & Cunningham 2001). In resource-limited settings, patients typically start antiretroviral therapy (ART) at low CD4 counts and may be at high risk of ocular opportunistic infections (OIs). Retinal OIs such as cytomegalovirus retinitis (CMVR) can lead to chronic visual impairment or blindness if untreated. Additionally, immune reconstitution phenomena such as immune recovery uveitis after ART initiation may increase ocular morbidity (Karavellas *et al.* 1998; Price *et al.* 2001). Identification and treatment of ocular disease in HIV-infected individuals is therefore important.

Reports suggest that the prevalence and spectrum of HIV-related eye disease differs geographically. In Asia, the predominant manifestation is CMVR, followed by other retinal OIs. Estimates are highest in south-east Asia, where CMVR affects 27–33% of HIV-infected individuals

(Biswas *et al.* 2000; Ausayakhun *et al.* 2003; Gharai *et al.* 2008; Shah *et al.* 2008; Pathai *et al.* 2009). In contrast, the reported prevalence of CMVR in sub-Saharan Africa is low (0–16.5%), whereas complications affecting the anterior segment of the eye such as herpes zoster and molluscum contagiosum are more frequently reported (Lewallen *et al.* 1994; Jaffar *et al.* 1999; Kestelyn 1999). However, it is difficult to draw firm conclusions about these differences as study populations have differed with regard to levels of immunodeficiency, ART exposure and methods of case ascertainment.

We previously reported on the prevalence of ophthalmic disease among patients enrolling in an ART service in Mumbai, India (Pathai *et al.* 2009), and have since implemented the same study protocol, using the same study personnel, in a comparable cohort of patients starting treatment in a well-characterised ART service in Cape Town, South Africa (Lawn *et al.* 2006, 2007). The aim of this paper was to directly compare the profile of HIV ocular manifestations in these two populations.

Data collection comprised demographic information, standardised ocular symptom screening and a full

\*Re-use of this article is permitted in accordance with the Terms and Conditions set out at [http://wileyonlinelibrary.com/onlineopen#OnlineOpen\\_Terms](http://wileyonlinelibrary.com/onlineopen#OnlineOpen_Terms).

S. Pathai *et al.* Differing spectrum of HIV-associated ophthalmic disease

ophthalmic examination among patients starting ART as previously detailed (Pathai *et al.* 2009). Prevalence of HIV ocular disease was estimated, and factors associated with disease were compared between sites using the chi-squared test. Multiple logistic regression analysis was used to examine associations between retinal OIs and demographic/clinical characteristics. Three hundred and six patients were studied (157 in Cape Town and 149 in Mumbai). Patients from the African and Indian study sites had similar demographic and clinical characteristics although the Cape Town cohort had a lower median CD4 cell count (Table 1).

The prevalence of overall HIV-related eye disease was higher in the Mumbai (17.5%) than in the Cape Town cohort (12.1%; Table 2). The evidence for a difference was strongest among those with CD4 count <200 cells/ $\mu$ l and those with advanced WHO clinical stage. When stratifying by specific diagnoses, it was clear that the overall difference was largely because of the higher prevalence of retinal OIs in the Mumbai cohort, specifically CMVR (Table 2).

The difference in the risk of retinal OI between sites persisted after adjusting for age, gender and other *a priori* confounders (CD4 count, WHO clinical stage, visual impairment and ocular symptoms), with an adjusted odds ratio = 11.32, 95% confidence interval (CI): 2.67–48.13 (Table 3). In addition, low CD4 cell counts and advanced WHO clinical stages of disease were also independently associated with the prevalence of retinal OIs (Table 1).

Our data confirm that the spectrum of HIV-related eye disease differs between these two study sites in India and Africa. The use of identical study protocols and study personnel, as well as demographically and clinically similar study populations, suggests that these findings can be reliably compared. The low prevalence of retinal OIs within the Cape Town cohort (2.6%) is consistent with other data from the region (Lewallen *et al.* 1994; Jaffar

*et al.* 1999; Kestelyn 1999). Similarly, our prevalence estimate of CMVR in Mumbai is in agreement with other reports from Asia (Biswas *et al.* 2000; Ausayakhun *et al.* 2003; Gharai *et al.* 2008; Shah *et al.* 2008).

A previously proposed hypothesis for this difference is that patients with advanced immunodeficiency in the African region have high mortality and do not survive to develop CMVR and other complications (Jaffar *et al.* 1999). However, this would not explain our findings whereby the geographical location was a strong independent predictor of the prevalence of ophthalmic disease after adjustment for CD4 cell count and WHO stage of disease. Previous studies have shown that CMV seroprevalence is similar in the two populations (Kothari *et al.* 2002; Cannon *et al.* 2010; Chakraborty *et al.* 2010; Rabenau *et al.* 2010), suggesting lack of exposure to CMV within the Cape Town cohort is an unlikely reason for this difference. The disparities in prevalence are unclear but could potentially be related to genetic differences at the host or virus level (Jabs 1995; Jaffar *et al.* 1999). There are no reports to date of geographical differences in the epidemiology of non-ocular systemic CMV disease, possibly suggesting that host ophthalmic factors may also be involved. The prevalence of HIV retinopathy was similar in both groups, and these non-infectious retino-vascular pathological processes may occur independently of CMV-mediated mechanisms.

In conclusion, the higher prevalence of HIV-associated ophthalmic disease in the Indian study population was largely because of the higher prevalence of CMVR. Further studies are needed to document other geographical variations in ocular HIV epidemiology and investigate the underlying mechanisms. Most cases of CMVR in the Indian population were not detectable with symptom screening (Pathai *et al.* 2009), and this indicates the need for careful retinal screening in this patient population in

**Table 1** Summary characteristics of the two cohorts of patients enrolling for anti-retroviral therapy

Variable	Cape Town ( <i>n</i> = 157)	Mumbai ( <i>n</i> = 149)	<i>P</i> -value
Age (years) median $\pm$ SD	34 $\pm$ 10.1	36 $\pm$ 8.3	0.12
CD4 count (cells/ $\mu$ l) median (IQR)	143 (59–199)	180 (106–253)	0.01
History of past or current TB <i>n</i> , % (95% CI)	80 50.1% (42.8–59.0)	79 53.0% (44.7–61.2)	0.72
WHO clinical stage 3 or 4 <i>n</i> , % (95% CI)	99 63.1% (55.0–70.6)	83 55.7% (47.3–63.8)	0.19

SD, standard deviation; *n*, number; IQR, interquartile range; 95% CI, 95% confidence interval.

**Table 2** Prevalence of HIV-related eye disease within different risk groups in Cape Town and Mumbai populations

Prevalence % (95% confidence interval), n	Overall study population		Participants with CD4 count <200 cells/ $\mu$ l		Participants staged at WHO clinical stage 3 or 4				
	Cape Town (n = 157)	Mumbai (n = 149)	P	Cape Town (n = 120)	Mumbai (n = 84)	P	Cape Town (n = 99)	Mumbai (n = 83)	P
Overall HIV	12.1% (7.4–18.3)	17.5% (11.7–24.5)	0.19	13.3% (7.8–20.7)	23.8% (15.2–34.3)	0.05	15.5% (8.7–23.8)	27.2% (18.4–38.6)	0.05
ocular disease	19	26		16	20		15	23	
Overall retinal opportunistic infections†	2.6% (0.7–6.4)	11.4% (6.8–17.6)	0.003	2.5% (0.5–7.1)	15.5% (8.5–25.0)	0.001	4.0% (1.1–10.0)	19.3% (11.4–29.4)	0.001
	4	17		3	13		4	16	
Cytomegalovirus retinitis (CMVR)	1.3% (0.1–4.5)	8.7% (4.7–14.4)	0.003	0.8% (0.02–4.5)	11.9% (5.8–20.8)	0.001	2.0% (0.2–7.1)	14.4% (7.7–23.9)	0.002
	2	13		1	10		2	12	
Ocular TB and toxoplasmosis	1.3% (0.1–4.5)	2.7% (0.7–6.7)	0.38	1.6% (0.2–5.9)	3.6% (0.7–10.0)	0.39	2.0% (0.2–7.1)	4.8% (1.3–11.8)	0.29
	2	4		2	3		2	4	
Other conditions									
Optic neuropathy	3.8% (1.4–8.1)	2.0% (0.4–5.8)	0.5	4.2% (1.4–9.5)	0 (0)	0.08	4.0% (1.0–10.0)	2.4% (0.3–8.4)	0.69
	6	3		5	0		4	2	
HIV retinopathy	5.1% (2.2–9.8)	4.7% (1.9–9.4)	0.87	5.0% (1.9–10.6)	8.3% (3.4–16.4)	0.34	5.1% (1.7–11.4)	6.0% (2.0–13.5)	0.77
	8	7		6	7		5	5	

\*NB – participants could have more than one condition, so values within subsets may not reflect overall total.

†Retinal opportunistic infections: CMVR, choroidal TB, toxoplasmosis.

**Table 3** Multivariable analysis to investigate relationship between HIV-associated vitreo-retinal opportunistic infections and demographic, clinical and ophthalmic factors

Variable	Multivariable model* Odds ratio (95% confidence interval)	P-value (Wald test)
Gender		
Male	1	
Female	0.71 (0.22–2.35)	0.57
Age group (years)		
16–30	1	
31–35	1.12 (0.28–4.45)	0.5
36–40	0.65 (0.15–2.78)	
41–45	0.14 (0.01–1.52)	
>46	0.83 (0.17–3.93)	
Geographical location		
Cape Town	1	
Mumbai	11.32 (2.67–48.13)	0.001
CD4 count (cells/ml)		
>200	1	
51–200	1.39 (0.38–5.07)	0.02
0–50	6.98 (1.93–31.72)	
WHO clinical stage		
1 or 2	1	
3 or 4	17.39 (2.21–137.14)	0.007
Visual impairment		
None	1	
Present	3.80 (0.89–16.17)	0.07
Ocular symptoms		
No	1	
Yes	1.49 (0.29–7.57)	0.63

\*Adjusted for all other factors in model.

those with low CD4 cell counts. Routine retinal screening by ophthalmologists may not be easily available within all settings, and alternative cost-effective strategies to detect retinal OIs within this population may need to be devised.

**Acknowledgements**

The authors thank the staff at both study sites and particularly the staff of the Desmond Tutu HIV Centre and the Hannan Crusaid Treatment Centre (study site), Professor Colin Cook and the Ophthalmology Department of Groote Schuur Hospital who kindly provided ophthalmic clinical support. Professor Kovin Naidoo (University of KwaZulu Natal) provided technical assistance at the Cape Town study site. Appasamy Associates (India) provided ophthalmic equipment for both studies. SP and SDL are funded by the Wellcome Trust, UK.

## References

- Ausayakhun S, Watananikorn S, Ittipunkul N, Chaidaroon W, Patikulsila P & Patikulsila D (2003) Epidemiology of the ocular complications of HIV infection in Chiang Mai. *Journal of the Medical Association of Thailand*, **86**, 399–406.
- Biswas J, Madhavan HN, George AE, Kumarasamy N & Solomon S (2000) Ocular lesions associated with HIV infection in India: a series of 100 consecutive patients evaluated at a referral center. *American Journal of Ophthalmology*, **129**, 9–15.
- Cannon MJ, Schmid DS & Hyde TB (2010) Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Reviews in Medical Virology*, **20**, 202–213.
- Chakraborty N, Bhattacharyya S, De C *et al.* (2010) Incidence of multiple Herpesvirus infection in HIV seropositive patients, a big concern for Eastern Indian scenario. *Virology Journal*, **7**, 147.
- Gharai S, Venkatesh P, Garg S, Sharma SK & Vohra R (2008) Ophthalmic manifestations of HIV infections in India in the era of HAART: analysis of 100 consecutive patients evaluated at a tertiary eye care center in India. *Ophthalmic Epidemiology*, **15**, 264–271.
- Jabs DA (1995) Ocular manifestations of HIV infection. *Transactions of the American Ophthalmological Society*, **93**, 623–683.
- Jaffar S, Ariyoshi K, Frith P *et al.* (1999) Retinal manifestations of HIV-1 and HIV-2 infections among hospital patients in The Gambia, west Africa. *Tropical Medicine and International Health*, **4**, 487–492.
- Karavellas MP, Lowder CY, Macdonald C, Avila CP Jr & Freeman WR (1998) Immune recovery vitritis associated with inactive cytomegalovirus retinitis: a new syndrome. *Archives of Ophthalmology*, **116**, 169–175.
- Kestelyn P (1999) The epidemiology of CMV retinitis in Africa. *Ocular Immunology and Inflammation*, **7**, 173–177.
- Kestelyn PG & Cunningham ET Jr (2001) HIV/AIDS and blindness. *Bulletin of the World Health Organization*, **79**, 208–213.
- Kothari A, Ramachandran VG, Gupta P, Singh B & Talwar V (2002) Seroprevalence of cytomegalovirus among voluntary blood donors in Delhi, India. *Journal of Health, Population, and Nutrition*, **20**, 348–351.
- Lawn SD, Myer L, Bekker LG & Wood R (2006) CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. *BMC Infectious Diseases*, **6**, 59.
- Lawn SD, Myer L, Bekker LG & Wood R (2007) Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*, **21**, 335–341.
- Lewallen S, Kumwenda J, Maher D & Harries AD (1994) Retinal findings in Malawian patients with AIDS. *British Journal of Ophthalmology*, **78**, 757–759.
- Pathai S, Deshpande A, Gilbert C & Lawn SD (2009) Prevalence of HIV-associated ophthalmic disease among patients enrolling for antiretroviral treatment in India: a cross-sectional study. *BMC Infectious Diseases*, **9**, 158.
- Price P, Mathiot N, Krueger R, Stone S, Keane NM & French MA (2001) Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. *Journal of Clinical Virology*, **22**, 279–287.
- Rabenau HF, Lennemann T, Kircher C *et al.* (2010) Prevalence- and gender-specific immune response to opportunistic infections in HIV-infected patients in Lesotho. *Sexually Transmitted Diseases*, **37**, 454–459.
- Shah SU, Kerkar SP & Pazare AR (2008) Evaluation of ocular manifestations and blindness in HIV/AIDS patients on HAART in a tertiary care hospital in western India. *British Journal of Ophthalmology*, **93**, 88–90.

**Corresponding Author** Sophia Pathai, International Centre for Eye Health, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK. Tel.: +44-20-7958 8343; Fax: +44-20-7958 8325; E-mail: Sophia.Pathai@lshtm.ac.uk