OCULAR DISEASES AMONG HIV/AIDS PATIENTS IN JAKARTA, INDONESIA

Yeni Dwi Lestari[1], Ratna Sitompul[1], Lukman Edwar[1] and Zubairi Djoerban[2]

[1]Department of Ophthalmology, [2]Department of Internal Medicine,
Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Abstract. We conducted a survey of ocular diseases among HIV/AIDS outpatients in Jakarta, Indonesia. This cross sectional study was conducted among 311 HIV/AIDS patients presenting to three referral hospitals in Jakarta, Indonesia from September 2008 to May 2009. All subjects underwent ophthalmological examination, including visual acuity, intraocular pressure, eye movement, Schirmer's test and anterior and posterior segment evaluation. Most subjects (86%) were aged 20-40 years; and 77% were male. Intravenous drug use was the most common risk factor (48.9%) for HIV infection. At the time of enrollment, 85% of subjects were receiving anti-retroviral therapy (ART); the median CD4+ T cell count prior to ART was 56 (0-757) cells/ l. The most common ocular manifestations were dry eye syndrome (54%), followed by toxoplasma retinochoroiditis (8.4%) and cytomegalovirus (CMV) retinitis (5.8%). Risk factors associated with ocular diseases were late HIV clinical stage (OR= 4.35 for clinical stage 4 *vs* 1; p= 0.001), co-infection (OR= 2.67 for 2 co-infections *vs* no co-infection; $p = 0.009$) and low CD4+ T cell count prior to ART (<50 cells/ l *vs* ≥ 200 cells/ l; $p = 0.003$). The CD4+ count at the first visit (p=0.041) and clinical stage (p=0.049) were associated with dry eyes. This study shows dry eyes were the most prevalent ocular disease among HIV/AIDS patients in Jakarta. HIV clinical stage 3 or 4, co-infection with tuberculosis and hepatitis C infection and a CD4+ T cell count of <50 cells/ l were risk factors for ocular disease in HIV/AIDS patients.

Keywords: ocular manifestations, HIV/AIDS, dry eye, toxoplasma retinochoroiditis, CMV retinitis, Indonesia

INTRODUCTION

Indonesia has the fastest growing number of HIV cases in Southeast Asia. The Department of Health, Republic of Indonesia has reported 26,483 cumulative cases of AIDS as of July 2011 with the highest number being found in Jakarta (UNAIDS, 2007; Department of Health, 2011). Intravenous drug injection is the primary mode of transmission followed by sexual transmission. New infections among intravenous drug users (IDUs) are projected to decrease from 40% to 28% while sexual transmission is projected to increase from 43% to 58% by 2014 (USAID, 2008).

The use of antiretroviral therapy (ART) has prolonged the life expectancy of HIV/AIDS patients; HIV/AIDS-related

Correspondence: Dr Ratna Sitompul, Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia, Jl Salemba Raya no. 6, Jakarta, Indonesia.
Tel/Fax: 62 21 31934878
E-mail: ratna_sitompul@yahoo.com

ocular diseases have become more frequent (Kestelyn *et al*, 1985; Lewallen *et al*, 1994; Lewallen and Courtright, 1997). Ocular problems are reported by 78-80% of HIV/AIDS patients (Schuman *et al*, 1987; DeGrezia and Robinson, 2001; Moraes, 2002; Vrabec, 2004; Jeng *et al*, 2007). The life time cumulative risk of developing at least one ocular disease among HIV patients ranges from 52% to 100% (Hodge *et al*, 1998).

The epidemiology of ocular disease among HIV/AIDS patients may differ between developing and developed countries due to different socioeconomic conditions, basic health care availability, different patterns of endemic disease present, CD4+ count, mode of transmission and co-infection (Kestelyn *et al*, 1985; Lewallen *et al*, 1994; Lewallen and Courtright, 1997). In contrast to the abundant number of studies in developed countries, studies of HIV/AIDS-related ocular diseases are limited in developing countries. This is disproportionate to the fact that 90% of HIV-infected patients reside in developing countries (Biswas *et al*, 1999; Department of Health, 2009; Shah *et al*, 2009).

This study was conducted to determine ocular diseases among HIV/AIDS patients in Jakarta, Indonesia. The association between HIV/AIDS-related ocular diseases and demographic, clinical, and laboratory characteristics were explored.

MATERIALS AND METHODS

Selection of patients

This cross sectional study was conducted from September 2008 to May 2009 among HIV/AIDS presenting as outpatients to Cipto Mangunkusumo, Dharmais and Kramat 128 Hospitals: referral hospitals providing care for HIV/AIDS patients and free anti-retroviral therapy (ART). Subjects were HIV positive or adult AIDS patients. We excluded HIV/AIDS patients who did not have a CD4+ cell count taken at the first visit. Informed consent was obtained from each subject prior to participation in this study. This study was reviewed and approved by the ethics committee of the Faculty of Medicine, University of Indonesia.

Interventions and measurements

Each subject underwent a thorough ophthalmologic examination consisting of visual acuity, measurement of intraocular pressure, evaluation of eye movement, a Schirmer's test, an anterior segment evaluation using a slit lamp biomicroscope and a posterior segment evaluation with a dilated pupil. Demographic data, history of present illness, other systemic diseases, baseline and follow-up CD4+ count were collected by a combination of direct interview, review of medical records and laboratory examination.

Statistical analysis

Statistical analysis was conducted using SPSS 11. The association between HIV/AIDS-related ocular manifestations and demographic, clinical and laboratory characteristics were analyzed using a chi-square test, Fisher's exact test or Kolmogorov-Smirnov test where appropriate; a $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the subjects (Table 1)

A total of 311 subjects (622 eyes) were examined in our study. They consisted of 150 subjects (48%) from Cipto Mangunkusumo Hospital, 138 subjects (44%) from Dharmais Hospital and 23 subjects (8%) from Kramat 128 Hospital. Most of the subjects were male (76.8%) aged 30-39 years (51.1%). The median age of all the

Table 1
Characteristics of subjects (N = 311).

Variable	n (%)
Sex	
Female	72 (23.2)
Male	239 (76.8)
Age (years)	
< 30	113 (36.3)
30-39	159 (51.1)
40-49	30 (9.7)
≥ 50	7 (2.9)
Route of transmission	
Homosexual	4 (1.3)
Heterosexual	127 (40.8)
IVDU	152 (48.9)
Blood transfusion	0 (0)
> 2 modes	26 (8.4)
Unknown	2 (0.6)
HIV clinical stage at the first visit	
1st stage	31 (10.0)
2nd stage	35 (11.3)
3rd stage	140 (45.0)
4th stage	105 (33.8)
Co-infection[a]	
None	72 (23.2)
TB	192 (61.7)
Hepatitis C	114 (36.7)
Hepatitis B	18 (5.8)
Anti-retroviral therapy	
None	44 (14.1)
Using ART	265 (85.2)
History of ART use	2 (0.6)
Visual acuity (n=622)	
≥ 6/18	583 (93.7)
4/60-6/20	7 (1.1)
≤ 3/60	32 (5.1)
Intraocular pressure (mmHg) (median)	18 (8-34)
CD4+ count (cells/ l)	
Baseline	
≥ 200	55 (17.7)
100-199	59 (19.0)
50-99	52 (16.7)
< 50	145 (46.6)
Lowest level	
≥ 200	25 (8.0)
100-199	57 (18.3)
50-99	60 (19.3)
< 50	169 (54.3)
At the time of study	
≥ 200	155 (49.8)
100-199	88 (28.3)
50-99	29 (9.3)

IVDU, intravenous drug use; [a]Subject may have more than one co-infection; TB, tuberculosis; ART, antiretroviral therapy

subjects was 31 (18-61) years old.

Intravenous drug injection was the main route of HIV transmission (48.9%). Median duration from HIV diagnosis to the time of the study was 24 (1-159) months and the median duration since the diagnosis of AIDS to the study was 24 (0-136) months. Eighty-five point two percent of subjects had received ART for a median time of 21 (1-121) months. Approximately 80% of subjects were classified as WHO HIV clinical stage 3 or 4. Seventy-six point eight percent of subjects had a history of co-infection, mainly tuberculosis (TB) or hepatitis C. Ninety-three point seven percent of subjects had a visual acuity of 6/18 or better. The rates of unilateral and bilateral blindness among subjects were 7.7% and 1.3%, respectively.

The median CD4+ T cell count among all subjects was 56 (0-757) cells/ l. Eighty-two point three percent of subjects had a baseline CD4+ count of < 200 cells/ l. Ninety-two percent of subjects had their lowest CD4+ count of < 200 cells/ l. At the time of the study, 49.8% of subjects had a CD4+ count ≥ 200 cells/ l.

Distribution of ocular diseases (Table 2)

Ocular diseases were present in 198 subjects (63.67%). One hundred fifty subjects had more than one ocular disease. The most common ocular problem was dry eyes (54.0%), followed by oxoplasma chorioretinitis (8.4%) and CMV retinitis (5.8%). The neuro-ophthalmological disorders seen in this study were optic neuropathy (1.9%) and cranial nerve paresis (2.2%). Unilateral and bilateral CMV retinitis was found in 15 and 3 subjects, respectively. One subject with CMV retinitis had a CD4+ count of 376 cells/ l.

Risk factors for ocular diseases of HIV/ AIDS (Table 3)

There were no significant differences

Table 2
Ocular diseases (*N*=311).

Ocular diseases	Unilateral	Bilateral	Total *n* (%)
No reduction in visual acuity	24	172	196 (63.0)
Xerophthalamia	8	159	167 (53.7)
Conjunctival microvasculopathy	1	8	9 (2.9)
HIV retinopathy	5	2	7 (2.2)
Cranial nerve paresis	7	-	7 (2.2)
Conjunctivitis	1	3	4 (1.3)
Molluscum contagiosum	1	-	1 (0.3)
Hordeolum	1	-	1 (0.3)
With reduction in visual acuity	45	11	56 (18.0)
Toxoplasma chorioretinitis	21	5	26 (8.4)
CMV retinitis	15	3	18 (5.8)
Optic neuropathy	3	3	6 (1.9)
Uveitis	5	-	5 (1.6)
Keratitis	1	-	1 (0.3)

between the subjects with and without ocular diseases in sex, age, route of transmission or the use of ART. There was significant association between WHO clinical stage 3 or 4 at the first visit and ocular disease. Having 2 co-infections was associated with eye disease (p = 0.009). Subjects with two co-infections had a 2.67 times greater risk of having ocular disease. Having a baseline CD4+ count <50 cells/ l was significantly associated with the presence of ocular disease (p = 0.003); having twice the risk of ocular disease compared to those with a baseline CD4+ count ≥ 200 cells/ l.

There was no significant association between dry eyes and age (p=0.594), co-infection (p=0.323), or the use of ART (p=0.461). CD4+ count at the first visit (p=0.041) and HIV clinical stage (p=0.049) were associated with dry eyes. Multivariate logistic regression analysis gave as OR=1.4 (95% CI 1.108-1.823) for HIV clinical stage and 0.765 (95% CI 0.63-0.92) for CD4+ count. Clinical stage and CD4+ level were analyzed separately.

DISCUSSION

This was the first study in Indonesia determining ocular diseases among HIV/AIDS patients with or without eye complaints. Jakarta has the highest number of HIV/AIDS patients in Indonesia (Department of Health, 2011). Our subjects were taken from the three hospitals in Indonesia with the largest number of HIV/AIDS patients. The sex and age of subjects are similar to HIV/AIDS patients throughout Indonesia based on reports by the Department of Health (2011) and similar to HIV/AIDS populations throughout the world (Biswas *et al*, 1999; Jabs *et al*, 2007a,b; Shah *et al*, 2009). The most common modes of transmission of HIV/AIDS among subjects in this study, as well as throughout Indonesia, are intravenous drug use and heterosexual transmission. In India and

Table 3
Association between ocular disease and demographic, clinical, and laboratory characteristics.

Variable	Without ocular disease (*n*=113)	With ocular disease (*n*=198)	*p*-value	OR	95% CI
Sex					
Female	22 (19.5%)	50 (25.3%)		1.00	reference
Male	91 (80.5%)	148 (74.7%)	0.246	1.40	0.79-2.46
Age (years)					
< 30	41 (36.3%)	72 (36.4%)		1.00	Reference
30-39	54 (47.8%)	105 (53.0%)	0.692	1.11	0.67-1.83
40-49	15 (13.3%)	15 (7.6%)	0.174	0.57	0.25-1.28
≥ 50	3 (2.7%)	6 (3.0%)	0.859	1.54	0.27-4.80
Route of transmission					
Blood transfusion	0 (0.0%)	0 (0.0%)			
Homosexual	2 (1.8%)	2 (1.0%)		1.00	reference
Heterosexual	50 (44.2%)	77 (38.9%)	0.671	1.54	0.21-11.29
IVDU	49 (43.4%)	103 (52.0%)	0.464	2.10	0.29-15.37
> 2 modes	12 (10.6%)	14 (7.1%)	0.886	1.17	0.14-9.59
Unknown	0 (0.0%)	2 (1.0%)			
HIV clinical stage at the first visit					
1st stage	19 (16.8%)	12 (6.1%)		1.00	reference
2nd stage	15 (13.3%)	20 (10.1%)	0.137	2.11	0.79-5.65
3rd stage	51 (45.1%)	89 (44.9%)	0.013	2.76	1.24-6.15
4th stage	28 (24.8%)	77 (38.9%)	0.001	4.35	1.88-10.11
Co-infection					
None	31 (27.4%)	41 (20.7%)		1.00	reference
TB	48 (42.5%)	71 (35.9%)	0.712	1.12	0.62-2.02
Hepatitis C	16 (14.2%)	28 (14.1%)	0.477	1.32	0.61-2.86
Hepatitis B	1 (0.9%)	2 (1.0%)	0.740	1.51	0.13-17.44
2 co-infections	15 (13.3%)	53 (26.8%)	0.009	2.67	1.28-5.59
3 co-infections	2 (1.8%)	3 (1.5%)	0.894	1.13	0.18-7.21
Anti retroviral therapy					
Using ART[c]	98 (86.7%)	167 (84.3%)		1.00	reference
History of ART use	0 (0%)	2 (1.0%)			
None	15 (13.3%)	29 (14.6%)	0.713	1.14	0.58-2.22
CD4+ cell counts (cells/ l)					
Baseline					
≥ 200	29 (25.7%)	26 (13.1%)		1.00	reference
100-199	26 (23.0%)	33 (16.7%)	0.356	1.42	0.68-2.96
50-99	15 (13.3%)	37 (18.7%)	0.013	2.75	1.24-6.12
< 50	43 (38.1%)	101 (51.5%)	0.003	2.65	1.40-5.01
Lowest level					
≥ 200	13 (11.5%)	12 (6.1%)		1.00	reference
100-199	26 (23.0%)	31 (15.7%)	0.594	1.30	0.50-3.31
50-99	21 (18.6%)	39 (19.7%)	0.148	2.01	0.78-5.19
< 50	53 (46.9%)	116 (58.6%)	0.046	2.37	1.01-5.54
At the time of study					
≥ 200	67 (59.3%)	87 (44.2%)		1.00	reference
100-199	27 (23.9%)	61 (31.0%)	0.050	1.74	1.00-3.03
50-99	8 (7.1%)	21 (10.7%)	0.115	2.02	0.84-4.85
< 50	11 (9.7%)	28 (14.2%)	0.085	1.96	0.91-4.22

OR, odds ratio; CI, confidence interval; TB, tuberculosis; ART, antiretroviral therapy; IVDU, intravenous drug user

many countries in Africa where HIV/AIDS transmission is common heterosexual transmission is a common mode of transmission, which is different from America where homosexual transmission is more common (Humphry *et al*, 1987; Biswas *et al*, 2000; Jabs *et al*, 2007a,b).

Antiretroviral therapy prolongs the life expectancy of HIV/AIDS patients. Although non-infectious ocular diseases have lower morbidity, they can have a negative impact on the quality of life. Ophthalmologists should be aware of the non-infectious ocular diseases found in HIV/AIDS patients, such as dry eyes, since they may be underdiagnosed.

Eye diseases were found in 63.7% of the subjects in this study compared with 8-45% of subjects from several countries (Biswas *et al*, 2000; Jabs *et al*, 2007a,b; Gharai *et al*, 2008; Shah *et al*, 2009). In our study the Schirmer's test was performed as a screening method to diagnose dry eyes; this is something not found in other studies of eye diseases among HIV/AIDS patients. Dry eyes was the most common ocular disease found in our study. If we exculde dry eye disease, ocular diseases were found in 28% of our subjects with HIV/AIDS.

A decrease in tear production among HIV/AIDS patients has been reported previously (Lucca *et al*, 1990; Geier *et al*, 1995; Biswas and Sudharshan, 2008). Geier *et al* (1995) reported a decrease in tear production occurred in 20-25% of HIV patients. Ali *et al* (2007) found the prevalence of dry eyes among HIV/AIDS patients to be 20-38.8%, compared with 1% of the general population. In our study, dry eyes was observed in nearly 54% of subjects. The dry eyes are thought to be due to lymphocytic infiltration of the lacrimal glands (Lee *et al*, 1999; Biswas and Sudharshan, 2008). HIV-mediated inflammation of the lacrimal gland results in lacrimal gland deficiency and eventually dry eye syndrome (Zoukhri, 2006). Indeed, the exact mechanism of dry eyes among HIV/AIDS patients remains unknown.

The prevalence of CMV retinitis in this study was 5.8%, below the percents reported by Biswas *et al* (2000) (17%) and Jabs *et al* (2007a,b) (22.1%); who reported the median CD4+ counts in their studies of 83 cells/ l and 30 cells/ l, respectively. Biswas *et al* (2000) used a different sampling method in their study; therefore, the difference in prevalence was not surprising; Jabs *et al* (2007a,b) used the same sampling method as our study and reported similar median CD4+ count and use of ARV, but a higher percent of patients with CMV retinitis. The high mortality among AIDS patients during infection, before development of CMV retinitis may explain this finding (Lewallen and Coutwright, 1997). Another reason for this difference in prevalence CMV retinitis is the subjects in their study were in-patients, whereas our subjects were only obtained from outpatient clinics.

Hoover *et al* (1996) found that HIV/AIDS patients in their study had an approximately 30% probability of developing CMV retinitis during their lifespan. Thirty percent of the subjects in the study by Hoover *et al* (1996) had a CD4+ cell count <50 cells/ l. In our study, the rate of blindness in both eyes was 1.3%, most of which was caused by CMV retinitis.

In our study we found an association between ocular disease and: HIV clinical stage, co-infection and CD4+ cell count at the first visit (Table 3). Ocular disease was usually seen in patients with severe systemic conditions and poor immune

status. We encountered more ocular disease among AIDS patients than those who were only HIV positive. Ocular disease was found more often among patients with a 3rd or 4th HIV clinical stage, which have a poor clinical condition and immune status.

Poor immune increases the risk for co-infection. Co-infection also causes morbidity which lowers the immune status of HIV/AIDS patients (Aditama *et al*, 2007). A study of HIV/AIDS patients with tuberculosis and hepatitis C co-infections and those without a co-infection and found those with a co-infection generally had a poorer clinical status, a higher rate of hospital stays, a lower CD4+ count at the first visit and lower immunological response (Djoerban Z *et al*, unpublished preliminary report, 2007).

Patients with HIV/AIDS are more prone to tuberculosis infection (Zhou *et al*, 2009). Not surprising, tuberculosis was the most common co-infection in our study. Kumarasamy *et al* (1995) studied 100 AIDS patients and found tuberculosis in 61% and pulmonary tuberculosis in 46% There is a high prevalence of tuberculosis in Indonesia and India (Kumarasamy *et al*, 1995; Aditama *et al*, 2007). Vilarino *et al* (1992) found HIV patients exposed to *M. tuberculosis* had a 113 times greater risk of contracting tuberculosis and AIDS patients had a 170 times greater risk of contracting tuberculosis. Whalen *et al* (1995) found AIDS patients with tuberculosis co-infection had a lower survival rate. Tuberculosis co-infection can increase HIV replication, both at the tissue and systemic levels, and can accelerate the progression of HIV infection (Goletti *et al*, 1996). Prevention of contracting tuberculosis is needed in HIV/AIDS patients not only to prevent tuberculosis but to prevent an increase in HIV replication (Goletti *et al*, 1996).

We found no ocular diseases caused by tuberculosis or hepatitis viruses in this study but did find a significant association between co-infection with these organisms and ocular disease in general. This might be due to the difficulty of diagnosing ocular tuberculosis. Most studies found the prevalence of ocular tuberculosis is low (0.6-7.9%) but varies by country (Bodaghi and LeHoang, 2000; Babu *et al*, 2006; Tabbara, 2007). Tuberculosis can cause great variation in manifestations in the anterior and posterior segments of the eye and may appear similar to other inflammatory diseases of the eyes (Sheu *et al*, 2001; Ali *et al*, 2007). There are no reports of ocular diseases caused by hepatitis B or C viruses. The association between co-infection and ocular disease is probably due to a worsening in immune status making HIV/AIDS patients more prone to ocular disease.

The CD4+ cell count is an indicator of immune status in HIV/AIDS patients. Nearly 50% of our subjects had a CD4+ cell count <50 cells/ l on their first visit and more than half had a lowest CD4+ count <50 cells/ l. Generally, the subjects first came to the hospital with their lowest CD4+ cell count. Ocular disease were found mostly among subjects with a CD4+ cell count of <50 cells/ l; more than 90% of ocular disease in our study were found among subjects with a CD4+ cell count ≤200 cells/ l. Among subjects with a CD4+ count <50 cells/ l, the ocular diseases seen were mostly infections, such as molluscum contagiosum, hordeolum, keratitis, toxoplasma chorioretinitis, CMV retinitis and ophthalmologic disorders caused by cerebral infection. Ocular diseases found among subjects with a CD4+ cell count >200 cells/ l were dry eyes, conjunctival microvasculopathy and uveitis; these three are inflammatory disorders.

Eight-five percent of subjects in our study were on ART. This number is higher than the Indonesian national average for ART among HIV/AIDS patients of approximately 25% (National AIDS Commission, 2007). This is understandable since the locations of this study was conducted provide free ART (National Aids Comission Republic of Indonesia, 2007). ART decreases morbidity and mortality (Hogg *et al*, 1998; Mocroft *et al*, 2003). The prevalence of ocular diseases among HIV/AIDS patients has decreased from 70-80% to 8-45% (Hogg *et al*, 1998). We still found ocular disease among subjects on ART. Unfortunately, our study did not differentiate whether the ocular disease occurred before or after beginning ART; therefore we could not determine the effect of ART on ocular disease. A prospective cohort study needs to be conducted to determine such an effect.

In this study only the Schirmer's test was used to screen for dry eyes. Since HIV/AIDS can cause abnormalities of the lacrimal system, further studies are needed. This study did not exclude an eye problem present before the patient was diagnosed with HIV/AIDS. Early detection of HIV in Indonesia is still limited; therefore, the length of time a patient has been infected with HIV is difficult to determine. There were differences in the modes of transmission of HIV/AIDS in this study compared to those in Papua, Indonesia (Barraclough *et al*, 2008); therefore, this study cannot be applied to the population of Papua, Indonesia.

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