

# Retinal manifestations of patients with human immunodeficiency virus, a multiethnics study in Malaysia

Loo A. V.P, Sujaya S, Peyman M, Florence S, Subrayan V

Department of Ophthalmology, University of Malaya, Kuala Lumpur, Malaysia

**Correspondence to:** Subrayan V. Department of Ophthalmology, University of Malaya, Kuala Lumpur, Malaysia.dvisva@hotmail.com  
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## Abstract

• **AIM:** To investigate the fundus findings of patients infected with human immunodeficiency virus (HIV) in correlation to Highly Active Antiretroviral Therapy (HAART) and CD4 count.

• **METHODS:** Two hundred and two patients of the three major races (Chinese, Malay and Indian) in Malaysia were recruited in this population-based cross-sectional study. This consisted of confirmed HIV sero-positive patients with HAART treatment (n=95) or without HAART therapy (n=107) from December 2007 to March 2008. They were further classified into the HIV infected group, AIDS related complex (ARC) group and AIDS group. Each group was then subdivided according to their CD4 count. Clinical fundus findings were recorded.

• **RESULTS:** Sixty six patients (32.7%) showed presence of fundus manifestation, majority of which was HIV microangiopathy (89%) and the rest being Cytomegalovirus (CMV) retinitis (11%). The most common fundus lesion was cotton wool spot (34%). There was a higher incidence of fundus manifestation in the non HAART group than the HAART group ( $P=0.04$ ) and in patients with CD4 count less than 200 cells/ml in both groups ( $P=0.01$ ). The HAART therapy had remarkably reduced the percentage of fundus manifestation by 20% but CD4 count remains the marker for fundus manifestations. There were no significant differences noted in the retinal manifestation among the different races. (ANOVA,  $P=0.25$ ).

• **CONCLUSION:** The fundus manifestations were higher in patients with CD4 < 200 cells/ml and in the non HAART group. Hence the HAART therapy is capable of reducing the incidence of fundus manifestations, however the CD4 count determines the occurrence of fundus manifestations.

• **KEYWORDS:** HIV; fundus manifestations; CMV retinitis; HAART; CD4 count

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## INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a morbid condition characterized by severe impairment of the immune system with the onset of a number of opportunistic infections and tumors. The etiology is human immunodeficiency virus (HIV), a retrovirus with elective tropism for the T-helper lymphocytes (CD4+). These cells play a role in modulating the immune response including fundus manifestation.

Highly Active Antiretroviral Therapy (HAART) has changed the clinical and prognostic outcome of fundus changes in the HIV seropositive patients<sup>[1]</sup>. However there is limited literature regarding the difference in retinal findings among patients of different races in Malaysia. The aim of this study is to determine the correlation between the fundus manifestations and total CD4 lymphocyte count in patients of different races either with or without HAART.

## MATERIALS AND METHODS

**Subjects** Two hundred and two patients of three major races (Malays, Chinese and Indians) irrespective of their age who attended the infectious clinic of three general hospitals in Malaysia from December 2007 to March 2008 were recruited in the study. They were confirmed HIV seropositive patients who were either on HAART regime or not, which was decided by the infectious disease physician. The study protocol was reviewed and approved by the local Research Ethical Committee of our hospital. The patients were divided into HAART group and non HAART group. Each treatment group was further assigned into three sub-groups according to CDC (Center for Disease Control) classification into patients with 1) HIV infection 2) AIDS related complex (ARC) and 3) AIDS. Each of these groups was then subdivided into those with CD4 count 1) more than 200 cells/ml or 2) less than 200 cells/mL based on the latest blood investigation. Informed consent was taken after the nature of the study was fully explained.

The exclusion criteria was 1) ward patients 2) patients on HAART regime less than three months 3) those with unconfirmed HIV status; 4) patients with treated ocular manifestations and 5) critically ill patients.

## Retinal changes in Malaysian HIV patients

**Methods** History was taken from each patient regarding their occupation, education level and mode of infection, ocular symptoms, current treatment and past history of systemic illnesses. Visual acuity was recorded and complete eye examination performed using a slit lamp. Fundus findings were recorded in a data sheet and later analyzed. Latest CD4 counts were also recorded. All the necessary precautions fulfilling the criteria of the conjoint committee of the American Academy of Ophthalmology and the National Society to Prevent Blindness, in consultation with the Contact Lens Association of Ophthalmologists were observed.

**Statistical Analysis** The analysis was done with a statistical package (SPSS). Chi-square test and the independent *t*-test were used to evaluate significant differences in terms of gender, age, race and mode of infection between HAART and NON-HAART groups. Comparison of fundus findings between the two groups was analyzed along with the fundus changes noted in relationship to CD4 count. A significance value of <0.05 were used in all analysis.

## RESULTS

The study showed differences of prevalence of HIV infection among the different ethnic groups. In the HAART group, the majority were Chinese (75%), followed by Malays (17%), Indians (4%) and Siamese (4%) and similarly, in the NON HAART group, majority were also Chinese (61%), followed by Malay (33.6%), Indians (4.6%) and Siamese (0.8%). Using the chi-square test to compare the patient gender, age, marital status, educational levels and mode of infection between HAART and NON HAART therapy group, there was no significant difference noted. Both groups (on HAART or no HAART) showed higher number of males (approximate female: male ratio of 1:3), age group among 30 to 39 (61% in HAART group and 51% in NON HAART group), married group rather than the unmarried (approximately 2:1), patients without secondary education level (94%) and patients infected through sexual intercourse (90% in HAART group and 80% in NON HAART group) rather than intravenous drug abuse (Table 1). There were 66 patients from the total population (*n*=202) of HIV seropositive patients of this study with presence of fundus manifestations (Table 2). 11% of patients (*n*=7) had CMV retinitis and 89% of patients (*n*=59) had microangiopathy. 16% of patients (*n*=1) in the HAART group and 84% of patients (*n*=6) in non HAART group had CMV retinitis. This showed a significant number of CMV retinitis patients in the NON HAART group (*P*=0.03) when compared to the HAART group. There was no significant difference noted among different races for retinal manifestation. (ANOVA, *P*=0.25).

Incidence of fundus manifestations among the HAART and NON HAART treatment groups are shown on Table 3.

**Table 1 Demographic characteristics of patients in HAART and NON HAART treatment groups**

Demographic Characteristics	HAART ( <i>n</i> =95)	NON HAART ( <i>n</i> =107)	Total ( <i>n</i> =202)	<i>P</i>
Male	70(74%)	82(77%)	152(75%)	0.62
Female	25(26%)	25(23%)	50 (25%)	0.74
Chinese	71(74.8%)	65(60.74%)	136(67.3%)	0.23
Malay	16(16.8%)	36(33.6%)	52(25.7%)	0.06
Indian	4(4.2%)	5(4.67%)	9(4.5%)	0.66
Siam	4(4.2%)	1(0.95%)	5(2.5%)	0.03
Married	55(58%)	72(67%)	127(63%)	0.16
Single	40(42%)	35(33%)	75(37%)	0.21
<i>Age</i>				
20-29	16(18%)	13(12%)	29(14%)	0.24
30-39	47(49%)	51(48%)	98(49%)	0.31
40-49	19(20%)	33(30%)	52(26%)	0.16
50-59	8(8%)	7(7%)	15(7%)	0.30
60-69	3(3%)	3(3%)	6 (3%)	0.35
70-79	2(2%)	0(0%)	2 (1%)	0.05
<i>Education level</i>				
Below secondary	89(94%)	100(94%)	189(94%)	0.40
Above secondary	6(6%)	7(6%)	13 (6%)	0.27
<i>Mode of infection</i>				
Sexual intercourse	86(91%)	84(79%)	170(84%)	0.35
IVDU	6(6%)	22(20%)	28(14%)	0.10
Both	3(3%)	1(1%)	4 (2%)	0.09

**Table 2 Fundus involvement in relation to CD4 count**

	HAART			NON HAART		
	AIDS	ARC	HIV	AIDS	ARC	HIV
CD4<200	26(11)	12(4)	13(0)	23(21)	9(7)	11(7)
Fundus involvement	42%	33%	0	91%	78%	64%
CD4>200	21(3)	11(2)	12(0)	5(1)	7(2)	52(8)
Fundus involvement	14%	18%	0	20%	29%	16%
<b>Total</b>	<b>47</b>	<b>23</b>	<b>25</b>	<b>28</b>	<b>16</b>	<b>63</b>

## DISCUSSION

In the late 20<sup>th</sup> century, AIDS has brought a great social change in the world including Malaysia. In fact Malaysia is home to one of the fastest growing AIDS epidemic in the East Asia and Pacific region. According to the reports from Ministry of Health in Malaysia, the epidemic is largely dominated by intravenous drug users (IVDU), however heterosexual transmission is on the rise. Also the prevalence is highest among the Malays, followed by the Chinese and the Indians. In this study the highest prevalence was noted among the Chinese, followed by the Malays and the Indians. The dissimilarity in the distribution of ethnic groups can be explained by the fact that this study was a cross-sectional study with limitation in regions, hospitals and duration. In this study, 86 (90.5%) of them contracted HIV infection through sexual intercourse, 6(6.3%) through IVDU and 3 via both routes (3.2%) were in the HAART group. In the non HAART group, 84 (78.5%) contracted through sexual

**Table 3 Fundus manifestations in relation to their CD4 count in both treatment groups**

Treatment Category	Number/percentage of patients	Positive fundus manifestations		P
		Number/percentage of patients with CD4 Count more or less then 200 cells/ mL		
		CD4<200	CD4>200	
HAART (n=95)	20(21%)	15(75%)	5(25%)	0.03
NON HAART (n=107)	46(43%)	35(76%)	11(24%)	0.01

intercourse, 22 (20.56%) through IVDU and 1 (0.94%) via both routes. The difference noted in the mode of spread of infection is in accordance with the data that spread of HIV through the sexual intercourse is on increase. Therefore there has been a possible change in the trend of mode of infection of HIV from IVDU to sexual intercourse in the past few years<sup>[2]</sup>. The most common fundus manifestation of HIV seropositive patients in the study was HIV microangiopathy and the rest had CMV retinitis<sup>[3]</sup>. A similar trend of the fundus manifestations has been noted in developing country, whereas the most common fundus manifestation in the developed world is CMV retinitis<sup>[4]</sup>.

The fundus manifestation of HIV and AIDS in the developed and developing countries will depend on several factors. The first factor is the overall availability of health care to the population. In some developing countries, patients may die in a relatively early phase of HIV infection before CMV retinitis can develop. The second factor is the regional variations in the disease patterns. The third being the understanding of the true prevalence of disease as it will always be hindered by a large degree of biasness, which is likely to accompany studies undertaken in clinics and hospital. In areas where ophthalmic manpower is extremely limited, any ocular conditions will simply go unrecognized. The fourth factor is the various drugs that have been used to prolong life and increase the quality of life for those with HIV and AIDS in the developed countries, are unavailable in some of the developing countries<sup>[5]</sup>. In the present study, cotton wool spots (34%) was the most frequently found lesion; it is asymptomatic and generally observed along the major vessel arcades. The cotton wool spots may resolve within a few weeks and are caused by retinal focal ischemia causing a stasis of axoplasmic flow inside the nerve fiber layer. The underlying cause of retinal ischemia seems to be a modification of the microcirculation, a common occurrence in patients with AIDS, possibly elicited by deposition of circulating immune complexes onto the vessel walls<sup>[6]</sup>. In conclusion, the study highlighted that the age group of HIV seropositive patients were between 20 to 50 years, which is also the productive age group of the country, causing a major drain on the economic status. There is also a change in the mode of spread of the disease. HAART therapy reduces the incidence of fundus lesions but CD4 count is still the major marker for fundus manifestations. The fundus manifestations among the HIV seropositive population were observed to be similar to those in developing countries.

Based on the current data and previous reports, ocular findings in Malaysia are comparable with those from eastern China<sup>[7]</sup>. HIV and its ocular manifestations are noted to be similar in other Asian countries as well<sup>[8-10]</sup>. Study of evaluation of ocular manifestations in HIV/AIDS patients on HAART in a tertiary care hospital in western India was done which shows results similar to Malaysian population<sup>[11]</sup>. Therapeutic strategies is also identical with western world meanwhile most of ocular findings are treatable.

In fact, the current findings suggest an important viewpoint that HAART has greatly suppressed the fundus manifestation in HIV-infected patients irrespective of CD4 counts and the patients should be aware of the risk of suffering the ocular complications even with CD4 count > 200.

Based on this study, a few recommendations can be made for future study. Firstly, detection of the change in mode of infection through the study of larger HIV seropositive population should be emphasized. Secondly a broader study is needed to get more information on the fundus manifestations between HAART and Non HAART groups in relation to the latest CDC classification.

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