

# Study of Retinal Nerve Fibre Layer Thickness and Visual Contrast Sensitivity in HIV Positive Individuals

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## ABSTRACT

**Introduction:** Measurement of Retinal Nerve Fibre Layer Thickness (RNFLT) by Optical Coherence Tomography (OCT) is a sensitive, non invasive and cheap method of detecting early retinal changes in a variety of diseases. In HIV infection, RNFLT is altered and this may have effect on other visual functions like Contrast Sensitivity (CS) and visual acuity. Such ocular pathology can affect the daily life and profession (especially driving) of HIV infected individuals. However, studies on this topic in HIV infected population are rare from India.

**Aim:** To study RNFLT, CS and their correlation in a sample of HIV positive Indian population.

**Materials and Methods:** The present cross-sectional study was done in a tertiary care medical college hospital of Eastern India between May 2016 and September 2016. We did this study on HIV positive subjects with no clinically apparent ocular infection or other pathology. In this study, we have measured the RNFLT using the HRA-OCT Spectralis machine. The CS was tested using a smartphone version of the Pellie-Robson chart.

CD4 count, visual acuity and colour vision were also tested. The data was analysed using SPSS version 20.0 for any correlation between these parameters. Pearson coefficient was used for continuous data and Spearman rank correlation was used for categorical data. A p-value <0.05 was considered significant.

**Results:** We had 17 patients, that is 34 eyes. RNFLT loss was found in 21% of the eyes and borderline thinning was found in a further 26%. Predominantly, the temporal quadrant was involved. The mean of log CS was 1.33±0.38. Taking 1.5 as the cut-off value for normalcy, 47% of the eyes tested showed decreased CS. Log CS showed significant correlation with RNFLT of the temporal quadrant only ( $r=0.37$ ; 95% C.I. 0.041 to 0.631;  $p=0.02$ ). Temporal RNFLT also showed statistical correlation with the CD4 count. The low CS was also significantly correlated with low visual acuity ( $r=0.5$ ).

**Conclusion:** In HIV infected persons, subtle ocular changes may occur and this may affect visual functions quite early. Hence, a comprehensive eye check-up should include parameters like CS and OCT.

**Keywords:** CD4 count, HIV infection, Optical coherence tomography

## INTRODUCTION

Measurement of RNFLT is a novel test in ophthalmology, useful in a variety of conditions. It is done using a technique called OCT. OCT is a computerized technique which measures the RNFLT in vivo [1]. A near-infrared beam is passed into the eye and its reflectivity pattern is studied [2]. This technique is easy to operate, reproducible, non-invasive and gives an objective measurement [1]. It produces a high-resolution cross-sectional image of the retina in the posterior pole which can be used to determine localized thinning or thickening [1]. Thus, it is a sensitive technique for early detection of incipient retinal changes in a variety of diseases [1].

Visual abnormalities form an important comorbidity in HIV infection [3]. Earlier, opportunistic infections were the commonest ophthalmologic manifestation in HIV. But now-a-days, with improvement in immune status due to early therapy, such infections are rare. Still, other more subtle manifestations in the eye are common in HIV infected persons. Damage to the Retinal Nerve Fibre Layer (RNFL) with associated secondary peripapillary changes are thought to be the main pathological process which causes the early optic changes in HIV [3]. Knowledge about the pathophysiology of retinal lesions is still evolving [4]. The most consistent finding till date has been cotton wool spots caused by direct nerve fibre damage [4]. There is increased phagocytosis by retinal pigment epithelium [4]. There is also specific down regulation of cone-specific genes in the retina, which may be a factor in decreased contrast sensitivity [4].

Significant thinning of the RNFL has been documented in HIV infection [3]. Clinically, this can cause symptoms like decreased contrast sensitivity, colour vision and/or decreased visual acuity [3]. Such defects may interfere with the daily livelihood of the patient. In the Indian context, this factor may have even greater significance [5], as in India, a large portion of HIV positive persons belong to professions like driving. Some studies have shown that RNFL thinning in HIV infection correlates with more driving errors [6]. Hence, visual impairment will have a greater impact on their occupation or may mean loss of their jobs.

The thinning of the retina in HIV progresses with time and decline in CD4 count [6,7]. Hence, if early diagnosis and treatment of HIV is instituted, this decline in visual functions can be thwarted. Early diagnosis of the visual impairments can also help in future career planning for the patients.

There are only a few studies on RNFLT in HIV patients from India [8,9]. However, since India has a very large HIV positive population group, such studies are important [5]. They will help in quantifying the level of public health burden due to visual problems in HIV. The OCT technique is ideally suited to the Indian context as it is cheap and done very quickly in a busy clinic. In this study, we have analysed the RNFLT and its correlation with other clinical visual parameters in HIV infection in a sample population from Eastern India. This study is a continuation of our earlier works on the same subject [8].

## MATERIALS AND METHODS

The present cross-sectional study was done in a tertiary care medical college hospital of Eastern India between May 2016 and September 2016. This particular institution has the separate regional referral centres for ophthalmology as well as HIV infection in Eastern India. Hence, a large patient pool was potentially available. The Institutional Ethical Committee was informed of the detailed study protocol and full ethical permission was obtained prior to embarking on the study. The ethical guidelines for study on human subjects, laid down by ICMR, were strictly followed [10].

Sampling was done from the registered HIV patients of the ART centre of the institution. People <60 years of age only were considered to avoid the confounding effect of age related retinal changes. The names of the registered patients were arranged in serial order. Then, random numbers were generated using Microsoft Excel and the corresponding patients were selected. The potential subjects were explained about the study in their own language. Only those who chose to take part voluntarily were selected. The patients were examined clinically first and direct ophthalmoscopy was done to rule out any retinal infection or other pathology. Patients with ocular disorders like glaucoma or any congenital ocular disease were excluded. Also, anyone with systemic disorders like diabetes, hypertension or recent use of oculotoxic drugs like chloroquine was excluded from the study. Our exclusion criteria also included anyone with prior history of posterior segment surgery or laser therapy.

RNFLT was measured using the HRA-OCT Spectralis machine (Heidelberg Engineering, Germany, 2011). Software for analysis was the Heidelberg Eye Explorer, available with the machine. All the study subjects were examined by the same machine operator. The testing was done on undilated eye. A circular area of 3.4 mm diameter around the optic nerve head was analysed. The angle of infra-red rays and the depth of analysis were auto-adjusted by the machine. Each reading was an average of three consecutive readings by the machine. Average resolution was 3  $\mu$ m. All the output cross-sectional images were inspected by the authors and only those images which were free of significant artefacts or distortion were included in the study.

Based on normative Indian data, the output from the analysing software automatically classified the RNFLT ordinarily as normal (green), borderline (Yellow) and thin (Red).

Contrast sensitivity was examined using Pellie-Robson chart. However, in this study, we used a smartphone version of the chart, as available in the free application, EyeHandbook™. We made this improvisation as the original Pellie Robson chart is very costly. The chart was displayed full screen in a 7-inch smartphone with maximum background illumination and was held at the near point of vision of the subject. The near point was first determined by suitable clinical examination. In this chart, the logarithm of the contrast sensitivity is recorded and a higher value equates with better sensitivity. A cut off of  $\geq 1.5$  was considered as normal [11].

Visual acuity was determined by Snellen chart (6 m) and colour vision was determined by Ishihara chart using standard procedures. All these examinations were done by the same investigator for all patients. For all the study subjects, each eye was tested separately.

The CD4 count was done at the ART centre in the same machine for all patients.

## STATISTICAL ANALYSIS

The data was entered into SPSS version 20.0 software. Suitable analyses were done using appropriate statistical tests. For continuous variables, Pearson coefficient was calculated in correlation analyses. For discrete variables or ordinal data, Spearman coefficient was used. The  $p < 0.05$  was considered significant.

## RESULTS

We initially selected 32 patients. After considering the exclusion criteria, 21 patients were finally taken for the OCT [Table/Fig-1]. But in four cases, the output images were distorted. Thus, finally in our study, we had 17 patients, which is 34 eyes. The average age of the study subjects was  $33.5 \pm 11.6$  years with a range of 14 to 56 years. Male: female ratio was 12: 5. The CD4 count of the subjects ranged from 181 to 1256/ $\mu$ L with a mean CD4 count of  $527 \pm 290$ / $\mu$ L. All of the patients were on suitable ART.

The mean of log CS was  $1.33 \pm 0.38$ . Taking 1.5 as the cut off, 16 eyes (47%;95% C.I. 30.2%,63.8%) were found to have low CS.

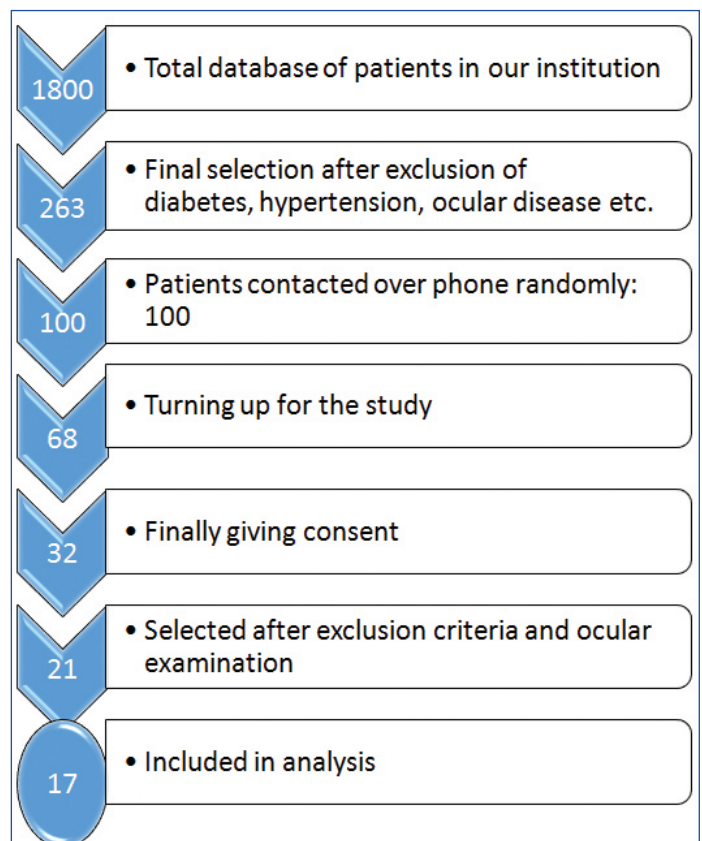
[Table/Fig-2] shows the visual acuity in the study subjects. As seen here, 50% of the eyes ( $n=17$ ) had normal (6/6) visual acuity. Significantly low visual acuity ( $\geq 6/18$ ) was present in only 23.5% of the eyes ( $n=8$ ). However, in all cases with less than normal visual acuity, vision was correctable with suitable lenses.

As [Table/Fig-3] shows, frank RNFLT thinning was found in 21% of the eyes ( $n=7$ ) and "borderline" thinning was present in 26%. Out of the 17 patients in the study, two had bilateral RNFLT thinning and three had unilateral thinning. Out of the seven eyes which showed RNFLT thinning, 5 (71.4%) showed only temporal quadrant thinning, one showed nasal quadrant thinning and one showed both temporal and nasal quadrant thinning. Out of the nine eyes where borderline thinning was present, 7 (77.8%) showed a temporal quadrant lesion.

The average RNFLT in the right eye was  $98.7 \pm 9.6$   $\mu$ m and that in the left eye was  $96.2 \pm 11.2$   $\mu$ m ( $p > 0.05$  by Student t test).

All the study subjects showed normal colour vision except two male subjects with red-green blindness.

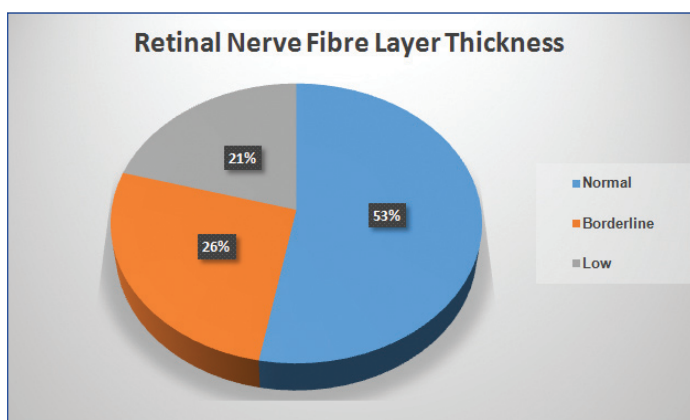
Correlation study showed that there was no statistical correlation between the CD4 count and log contrast sensitivity (LCS) ( $r=0.178$ ;  $p=0.49$ ). LCS showed a negative correlation with age ( $r=-0.37$ ) but did not reach statistical significance ( $p=0.14$ ). Pearson rank correlation coefficient analysis showed that the LCS had a positive correlation only with absolute RNFLT of the temporal quadrant



[Table/Fig-1]: Flow diagram showing the selection of patients for our study.

Visual Acuity	Number of Eyes
6/6	17
6/9	6
6/12	3
6/18 and higher	8

**[Table/Fig-2]:** Table showing the visual acuity of the study subjects.



**[Table/Fig-3]:** Pie chart showing the distribution of RNFLT in study eyes.

Area	Average RNFLT In $\mu\text{m}$	Mean log CS	Correlation coefficient	p-value
Temporal	66.6 $\pm$ 17.8	1.33 $\pm$ 0.38	0.37	0.02
Nasal	75.1 $\pm$ 20.6		0.13	0.47
Superior	127.8 $\pm$ 13.5		-0.08	0.62
Inferior	120.5 $\pm$ 22.8		0.09	0.6
Average of all	97.5 $\pm$ 10.4		0.24	0.16

**[Table/Fig-4]:** Table showing the correlation coefficients of log CS with RNFLT in different quadrants.

Test used: Pearson correlation coefficient

( $r=0.37$ ; 95% C.I., 0.041 to 0.631;  $p=0.02$ ) [Table/Fig-4]. Thus, lower the RNFLT in temporal quadrant, lower the LCS. However, the correlation between average peripapillary RNFLT and LCS ( $r=0.24$ ) was not statistically significant ( $p=0.16$ ).

When the RNFLT is expressed as ordinal data (normal, borderline, low in that order) the correlation coefficient between LCS and this ordinal RNFLT is  $-0.29$  (95% C.I.,  $-0.57$  to  $0.056$ ).

The absolute RNFLT of the temporal quadrant of the eyes also showed a significant correlation with CD4 count ( $r=0.36$ ; 95% C.I.,  $0.024$ ,  $0.621$ ;  $p=0.03$ ).

There was significant correlation between LCS and visual acuity (expressed as ordinal data) ( $r=-0.5$ ; 95% C.I.,  $-0.79$ ,  $-0.03$ ;  $p=0.04$ ). There was no statistical correlation between visual acuity and RNFLT, either average or of individual quadrants.

## DISCUSSION

In our study, we found that a large proportion of the eyes in HIV positive persons had low contrast sensitivity. Also, a large proportion of the subjects had RNFLT thinning. This was predominantly localized to the temporal quadrant of retina. CS was significantly correlated with temporal RNFLT and visual acuity. The temporal RNFLT showed a weak correlation with CD4 count. However, CS did not show any correlation with the CD4 count.

In a similar study from South Africa, a significant proportion (43.5%) of HIV infected individuals was found to have low CS [12]. However, in that study, the authors had used a cut-off of 1.65 by Pellie-Robson chart to categorise as "poor CS". In our study, we used a cut-off of 1.5, as is more commonly used [13]. Study of the predictors of low CS in HIV has yielded varying results. While some studies have found a significant correlation between the CS and HIV viral load, other studies failed to find any correlation with any factor [12,13].

Using other methods of measuring CS, also showed a similar trend of low CS in HIV infected individuals [14]. In this latter study, low CS was correlated to a falling CD4 count. In our case, there was no correlation between the CS and CD4 counts.

Thinning of the RNFL is a known ocular complication in HIV infection [15]. This is said to occur due to axonal degeneration [15]. Some authors have marked this as a manifestation of wider neuro-retinal degeneration that occurs in HIV [12]. Certain host factors, besides the virus related damage, may also be responsible for these degenerative changes [15]. In a study from USA, 17.6% of the eyes studied showed RNFL thinning. In our study, thinning was present in 21% of the eyes with a further 26% showing borderline values. The authors of the USA study found a significant correlation between temporal RNFLT ( $r=0.295$ ) and log CS [15]. In our study, a similar result has been obtained. Since, temporal quadrant contains the macula, alterations in the RNFL of this area will, logically, have effect on essential visual functions like CS.

The predilection for RNFL thinning to affect the temporal quadrant has been found in other studies too. In our previous study too, a significant proportion of subjects with borderline or low values had temporal quadrant involvement [8]. The exact reason for this asymmetry is not fully known. But, some authors have hypothesized that the papillomacular bundle and its surrounding area in the temporal quadrant may be more susceptible to damage due to the low volume to surface area ratio of the axons there [15]. Thus, they may be more susceptible to energy deficits and eventual cell death [16]. This theory was first applied to Leber hereditary optic neuropathy, but is now thought to be applicable for HIV retinopathy as well [15].

But, some other studies have found low RNFLT in all quadrants of retina [15]. This is particularly true for children with HIV [17]. Since our study is only on adults, we cannot comment on this difference. A recent study found a generalized decrease in photoreceptor density in the retina of HIV infected subjects [3].

These results show that instead of the commonly used visual acuity testing, a more comprehensive testing protocol should be adopted for HIV positive individuals, especially when screening for occupations like driving. In a recent study, where HIV positive individuals were divided into four groups based on low/high CD4 count and low/high RNFLT, the group with low CD4 and low RNFLT had the worst visual performance [6]. Thus, as a practical guide, for professions like drivers, both CD4 count and RNFLT should be used as predictors of poor performance.

Visual field is another parameter that is found to be affected in HIV infection [15]. However, the pathophysiology of that disorder is likely to be different from that of alteration in CS as visual field is affected in peripheral retinal degeneration. Hence, we did not include it as a study variable.

In our study, we found a significant correlation between CS and visual acuity. A similar result has been obtained from studies done in other continents too [14,18]. Usually disorders of visual function occur concurrently and this may be a part of the greater problem of silent neurodegeneration in HIV infection.

There are some limitations in our study. As this is a cross-sectional study, we can only establish an association. But, a true cause-effect relationship can only be established after a longitudinal study. Also, the sample size is quite small. Finally, there is also scope for improvement in the method of testing CS and colour vision. However, in a resource limited setting like ours, such criteria are often difficult to meet.

## CONCLUSION

Significant ocular damage can occur in HIV infection before clinically apparent manifestations or opportunistic infections. This may have dire consequences for the subject and lead to considerable handicap. Hence, eye testing in HIV infection should include modalities like CS and OCT from an early stage.

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