



COMPARISON OF CIMT AMONG HIV SEROPOSITIVE AND HIV SERONEGATIVE SUBJECTS: A CASE-CONTROL STUDY

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ABSTRACT

Background: CVD is an emerging cause of increased morbidity and mortality in HIV positive patients. Studies have demonstrated an increase in carotid intimal-medial thickness in HIV-infected individuals. Because of limited studies on relative contribution of HAART and HIV infection, per se, on the spectrum of cardiovascular health of the patients, we conducted this study in terms of CIMT assessment in HIV subjects, to generate more evidence on the subject.

Aims and Objectives: To compare Carotid Intimal Medial Thickness (CIMT) among HIV Sero-positive (Pre-ART/On ART) individuals with HIV Sero-negative controls and to analyze the association of HAART and CD₄ cell count on CIMT.

Material and Methods: 75 patients infected with HIV and 45 healthy controls were enrolled in this case-control study, done between 1st July, 2015 to 30th June, 2016, from the ART (Anti-Retroviral Treatment) center, outpatient department of Indira Gandhi Medical College & Hospital, Shimla.

Results: All the three groups (Group A- HIV Seropositive, ART Positive, Group B - HIV Seropositive, ART Negative & Group C – HIV Seronegative Controls) were identical when compared for sex distribution, smoking and alcohol intake, however they differed according to Age and BMI distribution across various groups ($p < 0.05$). Left carotid IMT, Right carotid IMT, Mean CIMT, and Maximum CIMT were evaluated. Among all the three groups, the difference between the CIMTs was significant when evaluated ($p < 0.05$).

Conclusion: We observed that HIV positive patients had a significantly higher carotid intima media thickness at the level of common carotid artery as compared to HIV negative patients. CIMT in HIV positive patients was mainly determined by the duration of HIV infection and the CD₄ counts of the patient after adjusting for factors like age and smoking.

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INTRODUCTION

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is an established global pandemic with a total of 36.7 million People Living with HIV/AIDS (PLHIV), out of which nearly 17 million have been put on ART since then¹. As per the National AIDS Control Organisation (NACO) Annual Report 2015 – 2016, the estimated adult HIV prevalence has shown a steady decline in India from 0.32 percent (0.26% – 0.41%) in 2008 to 0.26% (0.22%-0.32%) in 2015². CVD is an emerging cause of increased morbidity and mortality in HIV positive patients.

HIV infection itself that causes damage to arterial wall and (3) also to the adverse metabolic effects of some anti-retroviral drugs^{3,4}.

Previous studies have demonstrated an increase in carotid intimal-medial thickness in HIV-infected individuals as compared to controls. However, the reason for this increased level of subclinical vascular disease is unknown⁵. One study also reported an increased rate of progression in CIMT in HIV infected individuals⁶.

Measures obtained from the arterial wall thickness have been used as a surrogate of extent, severity and progression of atherosclerosis in numerous studies of cardiovascular health involving diverse health populations.⁷

Because of limited studies on relative contribution of HAART and HIV infection, per se, on the spectrum of cardiovascular health of the patients, we conducted this study in terms of

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CIMT assessment in HIV subjects, to generate more evidence on the subject.

Aims and Objectives

1. To compare Carotid Intimal Medial Thickness (CIMT) among HIV Sero-positive (Pre-ART/On ART) individuals with HIV Sero-negative controls.
2. To analyze the association of HAART and CD₄ cell count on CIMT.

MATERIAL AND METHODS

75 patients infected with HIV and 45 healthy controls were enrolled in this case-control study, done between 1st July, 2015 to 30th June, 2016, from the ART (Anti-Retroviral Treatment) center, outpatient department of Indira Gandhi Medical College & Hospital, Shimla. All study participants signed a written consent form to participate in the study. The cases were selected after satisfying all the exclusion/ inclusion criteria of the study.

Inclusion Criteria

1. HIV sero-positive patients (defined as per NACO guidelines) registered at ART Clinic, IGMC, Shimla who have Age between 18-50 years.
2. Patient are labelled as HIV positive if blood/plasma/venous sample is reactive by one E(Elisa)/ R(Rapid)/ S(Simple) screening test, subjected to an additional supplemental(or confirmatory) test and again reconfirmed by third reactive ELISA⁸.
3. Hospital controls from the ICTC centre, which tested negative for HIV and were free of any systemic disease age between 18-50 years.

Exclusion Criteria

1. Clinical/Biochemical/Electrocardiographic features suggestive of Ischemic Heart Disease (myocardial infarction, unstable ischemic heart disease, coronary revascularization procedure) stroke.
2. Congestive heart failure, Type 2 diabetes mellitus, Hypertension, Chronic kidney disease, Serious/life threatening acute opportunistic infections, Psychosis/neurosis
3. Patients not willing to participate in the study.

For HIV status

HIV test was done using 3 different kits:

1. SD BIOLINE HIV-1/2 3.0 Test
2. COMBAIDS- RS HIV 1+2 Immunodot test kit
3. AIDSCAN HIV-1/2 TRISPOT Test Kit

CD4 cell count

flow cytometer was used to obtain CD₄ counts.

Diabetes Mellitus

The World Health Organization definition of diabetes is for a single raised glucose reading with symptoms otherwise raised values on two occasions, of either⁹:

Fasting plasma glucose \geq 126 mg/dl Or With a glucose tolerance test, two hours after the oral dose a plasma glucose \geq 200 mg/dl. Or HbA_{1c} \geq 6.5 %

Hypertension

Defined as any one of the following: systolic blood pressure \geq 140 mmHg, diastolic blood pressure \geq 90 mmHg, OR taking antihypertensive medications¹⁰.

Chronic Kidney Disease

CKD to be defined as per KDIGO guidelines. Patient having CKD stage \geq 3 to be excluded from the study¹¹.

History

A detailed history included: Age, Sex, H/o Smoking, and Alcohol intake, Symptoms of coronary artery disease, a history of CABG or PTCA, previous myocardial infarction and Rose questionnaire were used to evaluate for the presence of angina. Any history suggestive of thyroid, kidney and liver disease was also taken.

Clinical examination

A detailed general physical and systemic examination was conducted.

Measurement of blood pressure

Indirect auscultatory arterial blood pressure was measured using a standard clinical sphygmomanometer and stethoscope by the same observer. Precautions were taken for creating standard conditions of blood pressure recording as per WHO recommendations.

Height (in cm)

Standing height was measured without shoes, the back placed squarely against the wall tape, eyes looking straight ahead (visual axis being horizontal with the top of the external auditory meatus level with the inferior margin of the bony orbit), with a set square resting on the scalp and against the wall.

Weight (in kg)

Weight was measured in normal indoor clothing and without shoes.

Body Mass Index

Weight(Kg)/[Height(m)]²

ECG

12 lead electrocardiograms will be recorded on BPL-Cardiart 6108 T for identification of coronary artery disease. Coding of ECG shall be done using the Minnesota Code Manual of Electrocardiographic findings and all subjects with a Diagnostic ECG (category D1 D2) and equivocal ECG (category E1 E2 E3 E4) shall be excluded as per exclusion criteria¹².

Laboratory investigations

An overnight fasting 10 ml venous blood sample was taken for measuring Haemoglobin concentration, Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), Platelet Count, peripheral blood smear, fasting blood sugar, kidney function tests (Urea, Creatinine, Uric acid), liver function tests (Bilirubin, SGOT, SGPT, Alkaline Phosphatase), lipid profile (Total Cholesterol, LDL, VLDL, HDL, S. Triglyceride). Investigations were done using Beckman coulter bioanalyser AU-680. Patients would also be tested for VDRL, HBsAg and Anti-HCV.

Carotid Intima Media Thickness Measurement

It was measured by the technique of carotid Colour Doppler Ultrasound. Ultrasonographic scanning of the carotid arteries was performed by the Philips i33 X-Matrix (Philips, USA) equipped with colour flow imaging and pulse Doppler, with an electrical linear transducer (mid frequency of 7.5 MHz). The scanning session lasted for an average of 30 minutes.

Statistical Analysis

We compared the baseline demographic and other characteristics to see the distribution of these across different groups. We compared proportions by Chi-square tests, means by One way ANOVA or Kruskal –Wallis test, depending upon the type of distribution. To see the type of distribution (normal/ non-normal), we performed Shapiro-Wilk test where a p>0.05 was considered indicative of normal distribution of the variable. We calculated correlation co-efficients between CIMT and Duration of HIV, Duration of ART and CD₄ counts. We applied pearson’s correlation coefficient, if the variables were normally distributed and spearman’s correlation coefficient, if one of the variables were non-normal. Except for Shapiro-Wilk test, p≤0.05, were treated as statistically significant. We performed stratified analysis on the variables which were found to be potential confounders at the baseline.

We analysed data using EpiInfo version 7.0.9 for Windows and SPSS version 16.0 for Windows.

RESULTS

We studied 120 participants in our study, which were stratified into following study groups

- Group A- HIV Seropositive, ART Positive (n=45)
- Group B - HIV Seropositive, ART Negative (n=30)
- Group C – HIV Seronegative Controls (n=45)

Evaluation of Baseline Characteristics in Different Groups

All the three groups were evaluated on the basis of their baseline characteristics, including both qualitative and quantitative variables to look for baseline differences and potential confounders in the study groups.

Evaluation on the basis of QUALITATIVE characteristics

All the three groups were identical when compared for sex distribution, smoking and alcohol intake, however they differed according to Age and BMI distribution across various groups (p<0.05). (Table1)

All the three groups’ subjects were evaluated on the basis of their usage of smoking in terms of people who have never smoked, current smoker and ex-smoker (those who have not smoked more than 1 year). The difference between the three groups regarding smoking has not been found to be statistically significant, p = 0.143. (Table 1)

All the three groups’ subjects were evaluated on the basis of their usage of alcohol in terms of people who are current user, those who have never used, past user (those who have left more than 1 year). The relationship between the three groups has not being found to be statistically significant, in terms of alcohol usage, p>0.05. (Table 1)

Patient’s were stratified into different groups according to their BMI. All the patients were found to be similar according

to their BMI stratification, and there was no statistically significant difference found between the three groups, p>0.05. (Table 1)

Table 1 Comparison of Some Baseline Qualitative Characteristics Across Different Study Groups

Variable/Charateristic	ARTGroup (n=45)		ART Negative (n=30)		HIV Seronegative (n=45)		p-value
	No.	%	No.	%	No.	%	
Sex							
Men	23	51.1	19	63.3	27	60	0.526
Women	22	48.9	11	36.7	18	40	
Age							
18-30	2	4.4	7	23.3	21	46.7	<0.001
31-40	28	62.2	16	53.3	13	28.9	
41-50	15	33.3	7	23.3	11	24.4	
Smoking							
Smoker	5	11.1	5	16.7	3	6.7	0.143
Ex-smoker	2	4.4	3	10.0	9	20.07	
Non-smokers	38	84.4	22	73.3	33	73.3	
Alcohol consumption							
Current users	2	4.4	1	3.3	2	4.4	0.267
Past users	3	6.7	1	3.3	8	17.8	
Never used	40	88.9	28	93.3	35	77.8	
Obesity							
Obese (BMI≥25)	4	8.9	4	13.3	7	15.6	0.018
Overweight (BMI=23-24.9)	11	24.4	3	10.0	4	8.9	
Normal (BMI=18-22.9)	23	51.1	14	46.7	32	71.1	
Underweight (BMI<18)	7	15.6	9	30.0	2	4.4	

Evaluation on the basis of QUANTITATIVE characteristics

When the three groups were evaluated on the basis of quantitative characteristics, significant correlation found between age distribution, total cholesterol, triglyceride, HDL cholesterol, and BMI values among them p<0.05. However, LDL cholesterol distribution among the three groups was not found to be significant p>0.05. (Table 2)

Table 2 Comparison of Some Baseline Quantitative Characteristics Across Different Study Groups

Variable/Charateristic	ART Group (n=45)		ART Naive (n=30)		HIVSeronegative(n=45)		p-value
	Mean	s.d.	Mean	s.d.	Mean	s.d.	
Age (Years)	39.2	5.3	35.5	7.2	32.5	8.5	0.001
Lipid Profile (mg/dL)							
Total cholesterol	190.4	49.0	178.4	40.1	136.9	32.1	<0.001
Triglycerides	192.0	113.3	159.0	230.6	116.0	47.6	<0.001
HDLCholesterol	53.7	19.6	46.7	8.4	39.2	9.2	<0.001
LDL Cholesterol	101.7	53.8	87.8	23.9	82.6	22.2	0.060
BMI (Kg/M ²)	21.4	3.3	20.4	4.2	22.4	2.2	0.005
Duration since HIV diagnosis(yrs)	5.6	3.3	1.9	1.6	N/A	N/A	<0.01
Duration of ART(yrs)	4.7	2.7	N/A	N/A	N/A	N/A	N/A
CD ₄ COUNT	443	225	566	207	N/A	N/A	0.019

CIMT Evaluation among Different Groups

CIMT was calculated among the three groups and further evaluated across the three groups. Left sided CIMT among Group A was 0.62 + 0.09 mm, Group B was 0.53 + 0.05 mm and Group C was 0.48 + 0.06 mm, and the difference was statistically significant, p<0.05. Right sided CIMT among Group A was 0.62 + 0.08 mm, Group B was 0.54 + 0.06 mm and Group C was 0.49 + 0.08 mm, and the difference was statistically significant, p<0.05. Mean CIMT among Group A was 0.62 + 0.08 mm, Group B was 0.53 + 0.05 mm and Group C was 0.48 + 0.07 mm, and the difference was statistically significant, p<0.05. Maximum CIMT among

Group A was 0.65 + 0.08 mm, Group B was 0.55 + 0.06 mm and Group C was 0.50 + 0.07 mm, and the difference was statistically significant, $p < 0.05$. (Table 3)

Table 3 Comparison of CIMT among Different Groups

Measurement	ART Group (n=45)		ART Negative (n=30)		HIV Seronegative (n=45)		p-value
	Mean	s.d.	Mean	s.d.	Mean	s.d.	
	Left carotid artery int	0.62	0.09	0.53	0.05	0.48	
Right carotid artery int	0.62	0.08	0.54	0.06	0.49	0.08	<0.001
Mean cimt (l+r)	0.62	0.08	0.53	0.05	0.48	0.07	<0.001
Max Cimt(L+R)	0.65	0.08	0.55	0.06	0.50	0.07	<0.001

CIMT relation with Duration of HIV

The average duration of HIV infection in Group A patients was 5.6 + 3.3 years, whereas in the group B, the average duration of HIV infection was 1.9 + 1.6 years. When CIMT was evaluated with respect to duration of HIV among both groups, it showed significant correlation $p < 0.05$. Duration of HIV showed positive correlation with both Left sided, Right sided, and Mean carotid intimal medial thickness (Pearson's correlation coefficient (r) of +0.35, +0.30 and +0.35 respectively). (Table 4, Fig.1)

CIMT relation with HAART

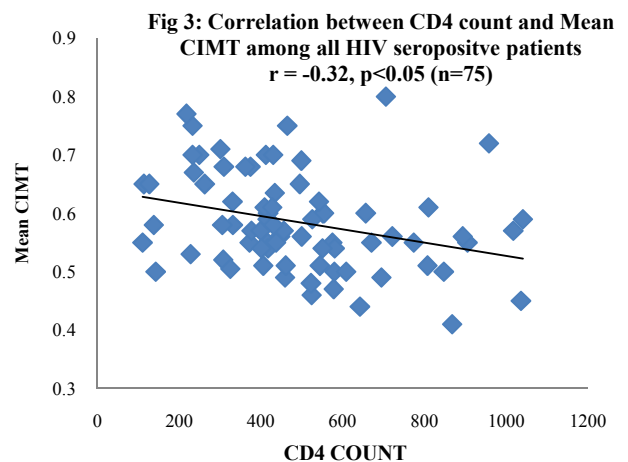
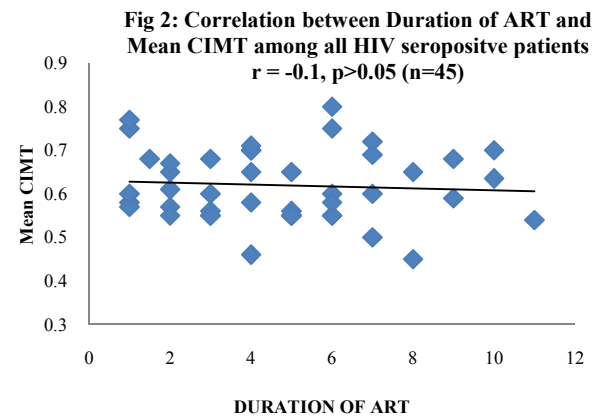
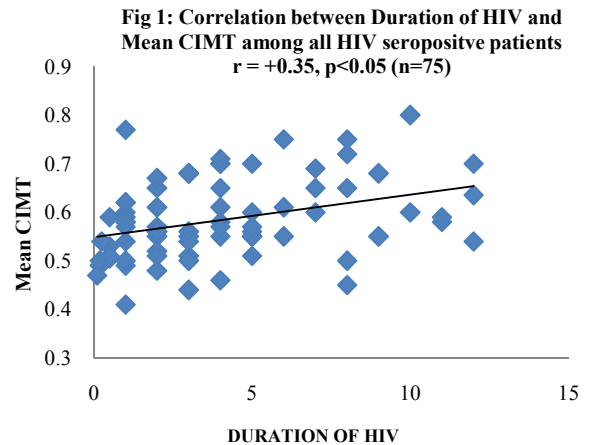
In all the above mentioned groups, on the basis of regimens(ART as per NACO), the mean and standard deviations were calculated of Left CIMT, Right CIMT, Mean CIMT, and Maximum CIMT. The average duration of ART consumption was 4.7 + 2.7 years in Group A patients. CIMT was evaluated in Group A patients with respect to their duration of ART usage. Duration of HIV showed negative correlation with both Left sided, Right sided and Mean carotid intimal medial thickness (Pearson's correlation coefficient (r) of -0.02, -0.13 and -0.1 respectively). However, the relationship was not statistically significant ($p > 0.05$). (Table 4, Fig.2)

CIMT relation with CD4 count

CIMT was evaluated among the HIV seropositive patients with respect to CD4 counts. The mean CD4 count of the 75 HIV seropositive patients was 493 + 226 / μ l. The mean CD4 count of the 45 patients in the patients taking ART, i.e., Group A was 443 + 225 / μ l, whereas, in ART naïve HIV seropositive Group B, the mean CD4 count of the 30 patients was 566 + 207 / μ l. The difference of CD4 counts between the two groups was found to be statistically significant, $p < 0.05$. CD4 counts in group A + B patients has a significant inverse correlation ($p < 0.05$) with left sided, right sided and mean carotid intimal medial thickness (Pearson's correlation coefficient (r) of -0.33, -0.25 and -0.32 respectively). (Table 4, Fig.3)

Table 4 Pearson's Correlation coefficient (r) and p-value analysis comparing Left CIMT and Right CIMT with different variables

Variable/Characteristic	Left cimt		Right cimt		Mean cimt	
	R	p-value	r	p-value	r	p-value
Duration of HIV (Years) (Group A + B)	+ 0.35	0.002	+ 0.30	0.009	+ 0.35	0.002
Duration of ART (Years) (Group A)	- 0.02	0.141	- 0.13	0.387	- 0.1	0.625
CD4 COUNT (/ μ l) (Group A + B)	- 0.33	0.004	- 0.25	0.031	- 0.32	0.007



Evaluation of CIMT according to confounding factors determined at baseline

Once the baseline characteristics were evaluated, the confounding factors were screened, that might affect the outcome of CIMT evaluation. Between the three groups, Age stratification and BMI were unevenly distributed, which might confound the CIMT findings. For expulsion of confounding among the groups, they were again stratified according to-

1. Age - ≤ 37 years and >37 years, after calculating median age across all the study population.
2. BMI - overweight/obese and normal/underweight.

Left carotid IMT, Right carotid IMT, Mean CIMT, and Maximum CIMT were evaluated after stratification. Among all the three groups, the difference between the CIMTs was significant when evaluated ($p < 0.05$), thus nullifying the effect of potential confounders. (Table 5)

ART naïve group could be because of HIV infection itself. This emphasizes that HIV infection per se, is a cardiovascular risk factor in these patients, independent of other cardiac risk factors and exposure to antiretroviral therapy.

Jerico *et al*¹³, who also studied CIMT at the level of common carotid artery found that the CIMT value was 5.70% (95% confidence interval [3.08-8.38%], $p < 0.0001$) or 0.044 mm [0.021-0.066 mm] ($p = 0.0001$) higher in HIV-positive subjects than the HIV negative controls. A study done by Bajaj *et al*¹⁴ found mean CIMT of 0.65 mm in HIV positive patients and 0.68 mm in HIV negative healthy subjects with no statistical significance between the two.

In the present study the mean duration of HIV infection in 75 HIV positive patients was 4.1 + 3.3 years which showed significant positive correlation with the patients CIMT, both Left and Right CIMT, on pearson’s correlation($p < 0.05$).

Table 5 Stratified analysis to compare CIMT across groups

Measurement	Stratum	ART Group		ART Naive		HIV Seronegative		p-value
		Mean	s.d.	Mean	s.d.	Mean	s.d.	
Left carotid artery IMT	Men (n=69)	0.62	0.10	0.53	0.05	0.48	0.05	<0.001
	Women (n=51)	0.62	0.09	0.52	0.05	0.49	0.07	<0.001
	Age>37 yrs (n=58)	0.64	0.09	0.54	0.05	0.53	0.04	<0.001
	Age ≤ 37 yrs (n=62)	0.58	0.10	0.52	0.05	0.45	0.06	<0.001
	Overweight/Obese (n=33)	0.63	0.10	0.55	0.04	0.51	0.04	0.001
Right carotid artery IMT	Normal/Underweight (n=87)	0.61	0.09	0.52	0.05	0.47	0.07	<0.001
	Men (n=69)	0.62	0.10	0.53	0.07	0.47	0.08	<0.001
	Women (n=51)	0.62	0.07	0.54	0.04	0.50	0.08	<0.001
	Age>37 yrs (n=58)	0.62	0.09	0.55	0.07	0.54	0.06	0.004
	Age ≤ 37 yrs (n=62)	0.62	0.08	0.53	0.06	0.46	0.07	<0.001
Mean CIMT (L+R)	Overweight/Obese (n=33)	0.65	0.08	0.53	0.06	0.51	0.08	<0.001
	Normal/Underweight (n=87)	0.61	0.08	0.54	0.06	0.48	0.08	<0.001
	Men (n=69)	0.62	0.09	0.54	0.06	0.47	0.06	<0.001
	Women (n=51)	0.62	0.07	0.53	0.05	0.50	0.07	<0.001
	Age>37 yrs (n=58)	0.63	0.08	0.54	0.05	0.54	0.05	<0.001
Max CIMT(L+R)	Age ≤ 37 yrs (n=62)	0.60	0.08	0.52	0.05	0.45	0.06	<0.001
	Overweight/Obese (n=33)	0.64	0.08	0.54	0.04	0.51	0.06	<0.001
	Normal/Underweight (n=87)	0.61	0.08	0.53	0.06	0.48	0.07	<0.001
	Men (n=69)	0.65	0.09	0.55	0.06	0.49	0.06	<0.001
	Women (n=51)	0.64	0.07	0.54	0.04	0.52	0.07	<0.001
	Age>37 yrs (n=58)	0.66	0.08	0.56	0.06	0.55	0.05	<0.001
	Age ≤ 37 yrs (n=62)	0.63	0.08	0.53	0.05	0.47	0.06	<0.001
	Overweight/Obese (n=33)	0.67	0.08	0.56	0.05	0.53	0.07	<0.001
	Normal/Underweight (n=87)	0.64	0.08	0.55	0.06	0.49	0.07	<0.001

DISCUSSION

In the present study, we examined 75 HIV positive patients, including both ART negative and patients taking ART, along with age and sex matched 45 controls by measuring their CIMT and other laboratory and physical parameters.

In the present study mean CIMT in HIV positive patients has been found to be 0.59 + 0.08 mm, which was significantly higher than HIV negative healthy controls, having mean CIMT of 0.48 + 0.07 mm, ($p < 0.05$). The mean CIMT among ART positive and ART naïve patients was 0.62 + 0.08 mm and 0.53 + 0.05 mm respectively, which is significant, $p < 0.05$. Analysis of the data in the present study also revealed that HIV positive ART naïve patients also had a significantly higher CIMT as compared to the HIV negative group. When the mean CIMT was evaluated among ART group and ART naïve HIV positive patients, there was significant difference among CIMT, $p < 0.05$. The patients who were on ART also had increased duration of HIV infection. The increased duration of HIV infection became confounding factor, and difference in CIMT among ART group and HIV seropositive

In a study done by Hsue *et al*¹⁵ found that rate of progression of CIMT was greater in HIV positive patients (0.055 mm/year) as compared as compared to healthy controls (0.024 mm/year), the difference being statistically significant ($p < 0.05$).

In the current study we were not able to establish significant association between CIMT and anti-retroviral therapy, even though the CIMT has been found to be significantly higher in patients taking ART (0.62 + 0.08 mm) than those who were ART naïve (0.53 + 0.05 mm), $p < 0.05$. However, on pearson’s correlation analysis, there was negative association between use of ART and CIMT, but it was not statistically significant, $p > 0.05$. Higher CIMT in the ART group could be attributed to the increased duration of HIV infection itself.

There was significant association between low CD₄ count and higher CIMT in our study. Pearson’s correlation coefficient (r) for association between CIMT and CD₄ count was negatively correlated for both Left CIMT, Right CIMT and Mean CIMT, i.e., $r = -0.33$, $r = -0.25$ and $r = -0.32$ respectively, and it was significant, $p < 0.05$.

In a study done by Lebech AM *et al*¹⁶, patients receiving ART had no signs of accelerated atherosclerosis as assessed by IMT evaluation. Study done in Indian population by Bajaj *et al*¹⁴, also summarized that the duration of taking ART was the only significant predictor of CIMT in HIV positive patients in their study.

Limitations in the present study

Our study had several limitations. First, the cross-sectional design did not allow us to investigate progression of abnormalities in CIMT and other parameters like CD4 counts and serum lipid levels. Secondly, the sample size of patient subgroups, mainly ART-naïve patients may have been insufficient to detect smaller differences in parameters, as only 30 out of 75 HIV positive subjects were ART-naïve, most likely as the subjects were recruited from a well functioning ART centre of a tertiary care hospital. Thirdly, we could not estimate the viral load of the patients, even though the CD4 counts give a crude estimate for the same. More research is needed to understand the reasons, why subclinical vascular disease appears to be accelerated among those with HIV infection.

CONCLUSION

We observed that HIV positive patients had a significantly higher carotid intima media thickness at the level of common carotid artery as compared to HIV negative patients. In our study CIMT in HIV positive patients was mainly determined by the duration of HIV infection, as in, patients who had HIV infection for longer duration had a higher CIMT; and the CD4 counts of the patient, i.e., patients with low CD4 counts had a higher CIMT after adjusting for factors like age and smoking. No correlation was seen between duration of ART and type of ART with CIMT in HIV positive patients taking ART. Even though the CIMT was higher in the ART group among the three groups, which could be attributed to the longer duration of HIV infection in patients receiving ART.

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