

# The Evaluation of Carotid Atherosclerosis in Patients with the HIV-1 Infection: The Role of the Antiretroviral Therapy

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## ABSTRACT

**Background and Objective:** The recognition and the assessment of the carotid intimal thickness helps in predicting the risk of the cardiovascular events in Human Immunodeficiency Virus (HIV) infected patients who are on Antiretroviral Therapy (ART). The objective of this study was to assess and compare the carotid intimal thickness in HIV positive individuals who were on anti-retroviral therapy with HIV positive individuals who were not on anti-retroviral therapy.

**Subjects and Methods:** All the HIV positive individuals who were 20 years old and above, who had been diagnosed by the National AIDS Control Organization (NACO) guidelines were included in the study. The HIV positive individuals who were diagnosed with diabetes mellitus and hypertension were excluded from the study. The study subjects were divided into 2 groups i.e. HIV patients who were on anti-retroviral therapy and HIV patients who were not on anti-retroviral therapy. The patients had to be on anti-retroviral therapy for a minimum of 6 months for them to be included in the first group. The data was collected by using a semi structured, pre-tested proforma,

which included the demographic details, the duration of the HIV infection, details of the antiretroviral treatment, a history of smoking/ alcohol consumption and details on the assessments of the metabolic syndrome.

**Results:** A total of 42 patients were included in the study. Among them, 28 were males (66.7%) and 14 were females (33.3%). Twenty six patients were on ART and the remaining patients were treatment naïve. There were significant differences with regards to their age and the duration of the HIV infection, which was longer in the patients who were on ART ( $p=0.049$ ,  $p=0.003$  respectively). The Body Mass Index (BMI), the waist: hip ratio, the mid-arm circumference, the waist circumference, the skin fold thickness and the carotid intimal-media thickness were higher in the HIV patients who were on ART as compared to those in the treatment naïve patients, though the difference was statistically insignificant.

**Conclusion:** The carotid intimal thickness was higher in the HIV patients who were on ART as compared to those in the treatment naïve HIV infected patients.

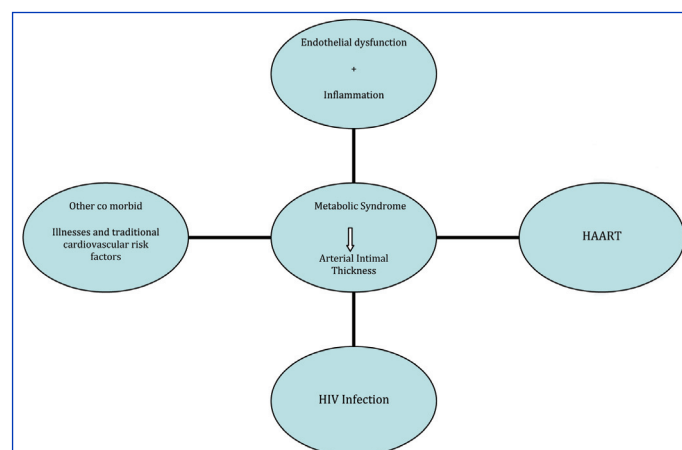
**Key Words:** HIV, Carotid atherosclerosis, Antiretroviral therapy

## INTRODUCTION

Since the introduction of highly potent anti-retro viral drugs, the clinical outcome of the human immunodeficiency virus infection has significantly improved and this has increased the patients' survival rate. This increased longevity and the associated dyslipidaemias place them at a risk of developing cardiovascular disease. The metabolic and the morphological changes which are collectively referred to as lipodystrophy, are prevalent amongst the individuals who are treated with the anti-retroviral therapy. The morphological changes cannot only be highly stigmatizing, but they can also affect the adherence to the treatment of the patients. The metabolic manifestations contribute to the risk of developing cardiovascular diseases. These changes manifest as dyslipidaemia, insulin resistance and abnormal fat accumulation. These complications may further increase the risk for cardiovascular disease [1]. Once established, the metabolic syndrome is a vicious cycle that is hard to break. Thus, avoiding the syndrome is of particular relevance for the control of this aspect of lipodystrophy [Table/Fig-1].

Extensive functional and structural arterial changes have been observed in the HIV positive patients. It has been documented that these vascular changes are closely associated to the Highly Active Antiretroviral Therapy (HAART) induced metabolic syndrome

and to the HIV infection itself. The sub-clinical carotid lesions have a highly significant association with all the cardiovascular risk predictors [2]. Thus, the recognition and assessment of the carotid intimal thickness would further help in predicting the risk of the cardiovascular events among these patients and addressing these



**[Table/Fig-1]:** showing mechanism of arterial intimal thickness among HIV positive patients on HAART

factors as well as the therapy optimization with lipid lowering agents and an antiretroviral therapy modification will improve the outcome.

The objective of our study was to assess and compare the carotid intimal thickness in the HIV positive individuals who were on anti-retroviral therapy, with that in the HIV positive individuals who were not on anti-retroviral therapy.

## SUBJECTS AND METHODS

This cross sectional observational study was conducted at a tertiary care hospital in Mangalore. This hospital has an infectious disease cell where a complete and a comprehensive care (diagnoses, counseling and management of opportunistic infections) is provided to the HIV AIDS patients. This study was approved by the institutional ethics committee and a written informed consent was taken from all the patients. All the HIV positive individuals who were 20 years old and above, who had been diagnosed by the NACO guidelines for a minimum duration of 6 months, were included in the study. The HIV positive individuals who were diagnosed with diabetes mellitus and hypertension were excluded from the study. The study subjects were divided into 2 groups i.e the HIV patients who were on anti-retroviral therapy and the HIV patients who were not on anti-retroviral therapy. The patients had to be on anti-retroviral therapy for a minimum of 6 months for them to be included in the first group.

The data was collected by using a semi structured, pre-tested proforma which included the demographic details, duration of the HIV infection, details of the antiretroviral treatment, a history of smoking/ alcohol consumption and details on the assessments of the metabolic syndrome.

The mid-arm circumference was measured at the mid-point of the acromian process of the clavicle and at the olecranon process of the ulna. Assessment of the lipodystrophy was done by measuring the waist circumference; the waist-hip ratio and the skin fold thickness. The waist circumference was measured at the patient's bare midriff, after he/she exhaled, while he/she stood without shoes and with both his/her feet touching and his/her arms hanging freely. The measuring tape was made of a material that could not be easily stretched. The waist circumference was measured at the mid-point between the lowest rib and the iliac crest. The hip circumference was measured, with the measuring tape being positioned at the maximum circumference of the buttocks.

The skin fold thickness was measured by using Lange's skin fold calipers. The measurement was made at the triceps site, at the point where the mid circumference was measured; a pinch of skin to raise a double layer of skin and the thickness is measured.

The carotid intimal thickness was measured by the Doppler ultrasound technique in the B-scan mode. Three measurements of the intimal thickness of the common carotid artery at the proximal, the mid and the distal parts of the common carotid artery were taken and the average of the three was noted down in millimetres.

## STATISTICAL ANALYSIS

A non-random sampling was done. The sample size was calculated, based on the expected proportion of the HIV positive individuals who developed plaque as 44% (based on previous studies) [1] and the absolute precision as 15% and at a confidence interval of 95%, the sample size was found to be 42.

The data was collected was analyzed by using the SPSS, version 11.5. For the qualitative analysis, the Chi square test was used and for quantitative analysis, the Students 't' test was used. A 'p' value of less than 0.05 was considered to be statistically significant.

## RESULTS

A total of 42 patients were included in the study. Among them, 28 were males (66.7%) and 14 were females (33.3%). Among these patients, 11.9% were professional workers, 2.4% were semi-professional workers, 14.4% were clerical workers, 19% were skilled workers, 2.4% were semi-skilled workers, 7.1% were unskilled workers, 26.2% were unemployed workers and in 16.7% of the patients, the occupation details were not available. None of the study subjects had given a history of smoking and consuming alcohol.

Twenty six patients were on ART and the remaining patients were treatment naive. Among these 26 patients, 21 patients (80.7%) were on the category A treatment [2 Nucleoside Reverse transcriptase Inhibitors + 1 non nucleoside reverse transcriptase inhibitor] (2NRTIs+1 NNRTI) and 5 patients (19.3%) were on the category B treatment [2 Nucleoside Reverse transcriptase Inhibitors + Protease Inhibitor] (2NRTIs+PI) regimens. Around 12 (28.6%) patients were underweight, 24 (57.1%) were in the normal range and 6 (14.3%) were overweight.

[Table/Fig-2] shows the comparative characteristics of the patients who were on/not on ART. There were significant differences with regards to the ages of the patients and the duration of the HIV infection, which was longer in the patients who were on ART ( $p=0.049$ ,  $p=0.003$  respectively). There were no significant differences between the 2 groups with regards to the monthly income, the BMI, the waist: hip ratio, the mid-arm circumference, the waist circumference, the skin fold thickness and the carotid intima-media thickness.

Patient Characteristics	Patients on ART	Patients not on ART	P value
Age (years)	38.6±7.015	34.13±6.90	0.049
Income/month (INR)	5012.5±5752.8	4656.2±3170.5	0.87
Duration of HIV infection	6.43±4.11	2.2±2.24	0.003
CD <sub>4</sub> count	437.62±227.99	387.33±317.9	0.56
BMI (kg/mt <sup>2</sup> )	20.59±3.2	20.76±4.2	0.88
Waist:Hip ratio	.87±0.06	0.82±0.07	0.05
Mid-arm circumference	25.77±3.53	25.25±3.37	0.64
Waist circumference	76.42±8.89	74.38±11.25	0.51
Skin-fold thickness	9.81±4.82	11.31±4.77	0.33
Carotid intima media thickness	0.63±0.23	0.59±0.17	0.46

**[Table/Fig-2]:** Comparative characteristics patients with or without ART

## DISCUSSION

The main objective of our study was to measure the carotid intimal thickness, which is a main marker for sub-clinical atherosclerosis [3] in the HIV patients, and to compare it between the patients who were on the antiretroviral therapy and the naive patients. It has been proven from previous studies that HIV is a pro-inflammatory disease, which can lead to a vascular thickening [4]. The anti-retroviral therapy has an additive effect on the pro-

inflammatory process and it can further lead to the formation of arterial plaques [5].

The measurement of the carotid intimal thickness with B-mode high-resolution ultrasound is a well-accepted, non-invasive method of assessing atherosclerosis. Because the carotid intimal measurements correlated satisfactorily with the pathological measurements and as they were potent predictors of myocardial infarction and stroke, even after the adjustment for the other risk factors, carotid B-mode high-resolution ultrasound imaging has been used in several studies to evaluate the cardiovascular risk in HIV infected patients [6].

Many studies have shown an increased prevalence of subclinical atherosclerosis in the patients who were on ART [7-11]. The carotid intimal thickness of the patients who were on ART was not statistically significant ( $p = 0.46$ ) as compared to that of the treatment naïve patients. This can be attributed to the shorter duration of the ART therapy in our study. Though the data was not statistically significant, the mean value of the carotid intimal thickness was higher in the patients who were on ART (0.63mm) than that of those who are not on ART (0.59mm). In the present study, 14.3% of the patients were overweight, which is an additional risk for cardiovascular disease. The waist: hip ratio of the patients who were on ART was higher ( $0.87 \pm 0.06$ ) as compared to that of the patients who were not on ART ( $0.82 \pm 0.07$ ). In accordance to our results, Calza L et al., also reported a higher prevalence of carotid atherosclerosis in the treatment experienced patients than in the treatment naïve patients [5]. Highly active antiretroviral therapy regimens, especially those which include protease inhibitors, have been shown to cause the iatrogenic metabolic syndrome in HIV infected patients [12]. The adipose tissue pathology and the lipotrophic fat loss are highly prevalent among the recipients of a stavudine or zidovudine based HIV treatment.

The role of a highly active antiretroviral therapy and the separate effect of HIV on the patients who survived longer may contribute to the increased incidence of the development of the metabolic syndrome, as was concluded in a study which was conducted by Feigenbaum K et al., [13] Our study also showed a longer duration of the HIV infection in the patients who were on ART, in whom the carotid intimal thicknesses as well as other parameters of lipodystrophy were higher. In a study which was conducted by Seaberg EC et al., in a span of 2 years, it was shown that the HIV related immunosuppression was associated with an increased carotid arterial stiffness which was independent of other traditional atherosclerosis risk factors [4]. A carotid arterial stiffness of lesser than  $500/\text{mm}^3$  is an independent risk factor for cardiovascular disease [2]. In the present study, the mean value of the CD4 count was higher in the patients who were on ART as compared to that in the naïve patients.

The limitations of the present study included the cross sectional design in which it is difficult to draw a causality. The shorter duration

of the ART treatment was also a limitation, as lipodystrophy was associated with a prolonged duration of the treatment. The sample size also was smaller to make a valid conclusion. The data on the lipid profile was also not collected.

To conclude, the findings our study suggest the role of ART in the development of carotid atherosclerosis in HIV patients. ART has dramatically reduced the morbidity and the mortality in HIV infected patients, which clearly outweigh the possible complications which are associated with ART. But we should be aware that with the prolonged survival rate of the HIV infected patients who are on ART and the expected long term use of ART, these long term adverse effects which are related to the metabolic syndrome and lipodystrophy, should be addressed appropriately. Hence, a long term follow up and a periodical screening of all the HIV patients who are on ART should be done, to assess the early risks of cardiovascular disease.

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