

Effect of antiretroviral therapy on cardiac risk markers in people living with HIV/AIDS

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Abstract

Introduction: Chronic HIV infection and antiretroviral therapy (ART) are the major causes of cardiovascular diseases (CVDs) and mortality in HIV patients. This study was conducted to look upon the effect of ART on CVD risk markers in patients on different ART regimens and ART-naïve patients. **Methods:** It was a cross-sectional, observational study done on 120 HIV-infected patients. CV risk markers were assessed and correlated with disease-specific factors within individual subgroups differentiated as Group A (ART naïve), Group B (first-line ART), and Group C (second-line ART). Carotid intimal medial thickness (CIMT) and high-sensitivity C reactive protein (hsCRP) were done to classify cases as having CVD. **Results:** CVD risk parameters were found to be significantly higher in cases on ART, as compared to ART-naïve cases. The mean CIMT among cases in Group C, Group B, and Group A was 0.072 ± 0.01 cm, 0.063 ± 0.01 cm, and 0.055 ± 0.01 cm, respectively ($P < 0.01$). 95%, 65% and 25% cases in Group C, Group B, and Group A, respectively, had high CIMT (>0.06 cm) and were seen to be directly correlated with disease-related factors, i.e., duration of disease and ART, type of ART, and low CD4 cell counts. hsCRP was significantly increased in 65 out of total 120 cases. The mean hsCRP in Group A, Group B, and Group C was 3.69 ± 3.37 , 4.21 ± 3.4 , and 5.72 ± 3.54 mg/L, respectively ($P < 0.01$), which corresponds to the high risk of CVD. **Conclusion:** CVD risk parameters of CIMT and hsCRP are seen to be higher in patients on ART than ART-naïve subjects.

Key words: Antiretroviral therapy, carotid intimal medial thickness, HIV, high-sensitivity C reactive protein

Introduction

India has one of the highest numbers of HIV-infected individuals (2.1 million) in the world. HIV infection-associated mortality till date has been attributed mainly to opportunistic infections (OIs); however, in recent years, after the advent of highly active antiretroviral therapy (HAART), people are dying more with the complications of antiretroviral therapy (ART), especially cardiovascular diseases (CVDs) rather than OIs.^[1] Increased incidence of CVD in patients with HIV might be due to the direct consequence of infection or a complication of HAART^[2] or known classical CV risk factors.

Methods

It was a cross-sectional, observational study done on 120 HIV-infected individuals in a tertiary care center at New Delhi. Pregnant or lactating females, patients

with known history of coronary artery disease, any other cardiac illness, hypertension, diabetes, chronic kidney or liver disease, hypothyroidism, or on any other medications (except ART) especially those on steroids, statins, antiepileptic medications, or aspirin were excluded. The ethical clearance and institutional review board permission were obtained from the appropriate authority. All 120 cases underwent thorough clinical assessment, laboratory investigations, and radiological investigations by a single observer. BECTON-DICKINSON FACS flow cytometer was used to obtain CD4 cell counts.

The list of ART administered to Indian patients with HIV (till mid-2020) is shown in Table 1.

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CV risk was interpreted according to the AHA/ACC guidelines with high-sensitivity C reactive protein (hsCRP) <1 mg/L = low risk, 1–3 mg/L = intermediate risk, and >3 mg/L = high risk.^[3]

Carotid intimal medial thickness (CIMT) (a surrogate marker of atherosclerosis and CVD) was done by a single observer to look for subclinical CVD.

CIMT was measured by carotid color Doppler ultrasound. Ultrasonographic scanning of the carotid arteries was performed by the HD 11 machine (Philips, USA) equipped with color flow imaging and pulse Doppler, with an electrical linear transducer (mid-frequency of 7.5 MHz). CIMT was calculated as the mean of four measurements for both the arteries, and a common carotid artery IMT ≥ 0.60 mm was regarded as a marker of atherosclerosis.^[4] Data were analyzed using IBM SPSS software for Windows version 20. Armonk, NY: IBM Corp. Quantitative variables were reported as mean \pm standard deviation. For continuous variables, statistical correlation was done by using correlation test and Chi-square test, and other appropriate statistical tests were used for analyzing categorical variables. A $P < 0.05$ was considered statistically significant.

Observations and Results

A total of 120 HIV-infected individuals were recruited as cases in the present study. The study group was further subdivided into three subgroups:

1. Group A: 40 HIV-infected individuals not on antiretroviral therapy (ART naive)
2. Group B: 40 HIV-infected individuals on first-line antiretroviral therapy (ART1)
3. Group C: 40 HIV-infected individuals on second-line antiretroviral therapy (ART2).

The demographic and laboratory characteristics of all the cases (in different subgroups) are depicted in Table 2.

The mean CD4 cell counts in Group A, Group B, and Group C was 505.25 ± 268.97 , 341.5 ± 240.7 , and 370.25 ± 199.72 cells/ μ l, respectively. Approximately 60% of the cases in all groups were males. CIMT was found to be higher in 72 out of total 120 cases.

The mean CIMT among cases in Group A was 0.055 ± 0.01 cm, ranging between 0.040 cm and 0.078 cm, while the mean CIMT in cases in Group B was 0.063 ± 0.01 cm (range 0.049–0.087 cm) and in Group C was 0.072 ± 0.01 cm (range 0.057–0.092 cm), respectively. Comparison of different subgroups revealed significantly higher CIMT in Group C as compared to both Group B and Group A [Figure 1] ($P < 0.001$ and $P < 0.0001$, respectively). Similarly, significantly higher CIMT was found in Group B compared to Group A ($P < 0.001$), implying the effect of ART and specifically ART2 (i.e., protease inhibitors) on higher occurrence of subclinical CVD in these individuals. Surprisingly, majority of cases (95%) in Group C had CIMT ≥ 0.06 cm, suggestive significantly of greater CVD

Table 1: The list of antiretroviral treatment administered to Indian patients with HIV (till mid-2020)

First line ART (mg)	Second line ART (mg)
Tenofovir (300)	Tenofovir (300)
Lamivudine (300)	Lamivudine (300)
Efavirenz (600)	Atazanavir/ritonavir (300/100)

ART=Antiretroviral treatment

risk in almost all individuals on protease inhibitors-based regimen [Table 3].

CIMT was found to have a noteworthy significant direct correlation with duration of disease ($P = 0.02$), duration of ART ($P = 0.01$), type of ART ($P = 0.001$), and low CD4 cell counts ($P = 0.02$), respectively. Among the classical CV risk factors, it was seen to be associated with high fasting blood glucose ($P = 0.04$), triglyceride levels ($P = 0.034$), microalbuminuria (MAU, $P = 0.01$), and high Waist Hip Ratio (WHR) ($P = 0.02$). No association of CIMT was seen with age, sex, body mass index, low-density lipoprotein, and systolic or diastolic blood pressure.

Fasting glucose levels were found to be significantly higher (97.3 ± 7.5 mg/dl) in cases having high average CIMT (0.06 cm or above) as compared to 84.8 ± 8.7 mg/dl in cases with normal CIMT ($P = 0.04$, t -test value of 2.124). Similarly, triglyceride levels were found to be significantly raised (98.8 ± 33.8 mg/dl) in cases with high CIMT (>0.06 cm) as compared to 84.8 ± 8.7 mg/dl in cases with normal CIMT ($P = 0.034$, t -test value of 2.204). Similarly, MAU was observed to be high in only 10% of cases with normal CIMT (<0.06 cm) as compared to 25% of cases with high CIMT ($P = 0.01$).

hsCRP which is considered as a CV risk marker was found to be significantly increased in 65 (17 in Group A, 21 in Group B, and 27 in Group C) out of total 120 cases as shown in Table 4. The mean hsCRP in Group A, Group B, and Group C was 3.69 ± 3.37 , 4.21 ± 3.4 , and 5.72 ± 3.54 mg/L, respectively ($P < 0.01$). 67.5%, 52.5%, and 42.5% of cases in Group C, Group B, and Group A had a high risk of CVD as per criteria according to the values of hsCRP.

Discussion

CVDs are now the most common cause of mortality after OIs in people infected with HIV/AIDS. Not only the traditional risk factors, but HIV *per se* and on top of that, ART has been implicated in increased frequency of CV risk and deaths in these patients.^[5] This study was done to specifically see the effect of ART on CV risk in HIV-positive Indian subjects.

120 HIV-infected individuals were recruited in the present study and subdivided into Group A (ART naive), Group B (patients on ART1), and Group C (patients on ART2) and were evaluated for CV risk by measuring CIMT and hsCRP and comparing them with other known traditional CV risk markers and HIV-related parameters.

In our study, out of the total 120 HIV-infected cases, 72 (60%) were found to have raised CIMT. CIMT was found to be significantly higher in cases on ART2 (0.072 ± 0.01 cm), which includes protease inhibitors, than those who were on ART1, i.e., Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI) (0.063 ± 0.01) and patients who were ART naive (0.055 ± 0.01 cm) ($P < 0.001$). So it can be inferred that the patients on ART2 have higher risk of cardiovascular disease followed by those on ART1 and ART naive Group respectively.

Although duration of ART as such was not included in the current study, it may be assumed that the patients on ART2 must have a longer duration of HIV infection in comparison to patients on ART1 and ART-naive cases. This is because according to the National AIDS

Table 2: Laboratory and demographic characteristics of all cases included in the study

Demographic & lab parameters	Mean±SD		
	ART naïve (Group A) (n=40)	ART 1 (Group B) (n=40)	ART 2 (Group C) (n=40)
Age (years)	33.85±8.84	37.8±3.3	36.38±7.95
Waist hip ratio	0.83±0.03	0.9±0.02	0.9±0.02
Body mass index (kg/m ²)	21.87±2.84	23.4±3.5	25.95±2.22
Systolic blood pressure (mmHg)	131.75±7.72	131.8±8.9	131.75±8.88
Diastolic blood pressure (mmHg)	81.1±6.90	82.3±6.6	82.3±6.7
Urea (mg %)	24.35±25.49	33.5±50.4	23.35±7.94
Creatinine (mg %)	0.86±0.86	1.2±1.8	0.79±0.28
Uric acid (mg %)	5.27±1.81	5.5±2	4.3±1.62
Aspartate aminotransferase (IU/L)	48.13±30.52	52.1±32.3	37.35±11.61
ALT (IU/L)	49.6±41.71	57.9±48.2	49.28±30.21
Alkaline phosphatase (IU/L)	131.4±128.63	158.5±147.8	161.75±78.87
Fasting blood sugar (mg %)	86.4±8.80	88.9±18.2	90.48±21.98
Post prandial blood sugar (mg %)	125±43.76	135±38.9	143.43±42.69
Creatine phosphokinase (IU/ml)	99.58±124.24	103.5±83.7	116.92±121.36
Creatine phosphokinase-MB (IU/L)	16.33±13.85	19.5±10.3	29.53±18.41
hsCRP	3.69±3.37	4.2±3.4	5.72±3.54
CHOL (mg %)	138.13±36.88	145.3±44.4	164.08±47.56
HDL (mg %)	49.30±26.64	34.9±13.1	33.4±11.95
LDL (mg %)	81.65±23.13	88.2±26.6	92.4±28.75
VLDL (mg %)	27.75±13.55	29.7±15.4	30.1±18.44
Serum triglycerides (mg %)	144.98±80.18	150.7±93.1	157.82±143.47
Mean CIMT (cm)	0.055±0.01	0.063±0.01	0.072±0.01
CD4 cell counts (cells/mm ³)	505.25±268.97	341.5±240.7	373.25±199.72

SD=Standard deviation; ART=Antiretroviral treatment; ALT=Alanine transaminase; hsCRP=High-sensitivity C reactive proteins; CHOL=Cholesterol; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; VLDL=Very low-density lipoprotein; CIMT=Carotid intimal medial thickness

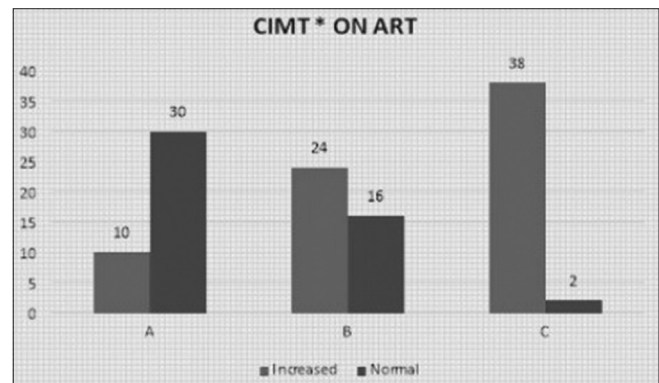
Table 3: Prevalence of carotid intimal medial thickness (average) in different HIV groups

CIMT average (cm)	Risk for CV events	A (n=40), n (%)	B (n=40), n (%)	C (n=40), n (%)
<0.06	Low	30 (75)	16 (40)	2 (5)
≥0.06	High	10 (25)	24 (60)	38 (95)

CIMT=Carotid intimal medial thickness; CV=Cardiovascular

Control Organization guidelines, ART2 starts after ART1 failure. In a study done by Hsue *et al.*,^[6] ART exposure was associated with higher CIMT and the rate of progressive increase of CIMT was found to be greater in HIV-positive patients (0.055 mm/year) compared to healthy controls (0.024 mm/year), the difference being statistically significant ($P = 0.016$). Thus, it can be concluded that not only HIV-positive patients have a higher CIMT than HIV-negative individuals, but with increasing duration of HIV infection, CIMT also increases. On top of that with universal access and early start of ART, this risk increases linearly as can be seen in our study.

A multitude of factors have been associated with greater CIMT and development of CV risk in HIV-infected patients, including HIV-related risk factors such as HIV viremia, immune activation and cART, and classical CV risk factors such as smoking, hypertension, and dyslipidemia.^[7-10] In our study also, cases in Group C showed the highest CIMT among all the three groups, and this can be explained by the fact that these cases were on protease inhibitors, which are shown to have an adverse effect on arterial wall and endothelial function and inflammation as seen in previous studies.^[11] Endothelial dysfunction and reduced flow-mediated dilatation in association with increased atherogenic lipoproteins reported among HIV-infected adults receiving protease inhibitors^[12]

**Figure 1: Increased carotid intimal medial thickness in different HIV groups**

can explain the significantly higher CV risk seen in our cases in Group C (protease inhibitors based).

hsCRP was found to be significantly higher in Group C followed by Group B and Group A (5.72 ± 3.54 , 4.21 ± 3.4 , and 3.69 ± 3.31 gm/L, respectively). 67.5%, 52.5%, and 42.5% cases in Group C, Group B, and Group A had elevated hsCRP. Serum hsCRP among our cases showed a direct correlation with high CIMT. Previous studies have also proved hsCRP as a useful marker for predicting CV risk.^[3] Higher level of hsCRP was present in our patients on ART2. This may be attributed to the HIV-induced inflammatory process or due to the effect of ART itself. Even in the absence of traditional CV risk factors, high hsCRP in our HIV-infected individuals was seen to be independently associated with high CIMT, i.e., CVD risk. De Luca *et al.* estimated that elevated hsCRP was associated with increased CVD risk in HIV-positive patients receiving cART (8-fold risk increase in patients with hsCRP levels >3.3 mg/L compared to those with <0.9 mg/L) and

Table 4: Prevalence of cardiovascular risk as calculated by high-sensitivity C reactive proteins in different HIV subgroups

hsCRP value (mg/L)	Risk for CV events	A (n=40), n (%)	B (n=40), n (%)	C (n=40), n (%)
<1	Low risk	11 (27.5)	10 (25)	7 (17.5)
1-3	Intermediate risk	12 (30)	9 (22.5)	6 (15)
3-10	High risk	17 (42.5)	21 (52.5)	27 (67.5)

CV=Cardiovascular; hsCRP=High-sensitivity C reactive proteins

reported 30% of patients receiving long-term ART to have hsCRP levels 3.0 mg/L, the highest being observed in those who were currently treated with ART.^[13] Similarly, in spite of excluding all traditional CV risk markers, we found hsCRP to be significantly higher in more than 50% of cases and this may be attributed to ART.

CIMT and hsCRP were also observed to have a significant correlation with the level of immunodeficiency (i.e., low CD4 cell counts ($P < 0.02$)). This can simply be explained by the fact that most of the cases in ART naïve Group A were still in asymptomatic state and did not manifest any AIDS-related features, hence with higher CD4 cell counts, whereas, all cases with recent OIs history were excluded as a part of protocol. Contrary to that, most of our cases in Group B and Group C were patients with long duration disease and had some overt or covert OI as a part of natural history of disease.

However, few limitations also were there in our study. The gold standard for the diagnosis of CAD is coronary angiography, which was not done in our study. Apart from that, adding control would have been a feather in the cap because CIMT is known to vary according to races and communities. However, it would have been impossible to do this extensive workup in similar number of controls. Studies in future with greater number of patients and controls can be done to corroborate with the findings of our study.

Conclusion

Health professionals have to step up their health advocacy with respect to policies to find out early CV risk in HIV-positive patients. There is strong need of creating awareness about the problems associated with the use of ART, and their association with increasing CV events. HIV in our country is affecting almost every age group and primarily the earning population of the nation. With ART, the longevity has increased and so has the duration of exposure to ART which has led to increasing risk of CVD substantially. We recommend counseling and rehabilitation centers to be established in every hospital, for providing proper evaluation of cardiovascular risk assessment to the patients on ART. In addition, the recent changes in national guidelines regarding switch to dolutegravir-based regimen are an appreciable move ahead in reducing these complications and expected to reduce this CV risk in these individuals.

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Conflicts of interest

There are no conflicts of interest.

References

- HIV and AIDS in India | AVERT Accessed on Site. Available from: <https://www.avert.org>. Last accessed on 05.08.2021.
- Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: Associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. *Diabetes Care* 2007;30:113-9.
- Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, *et al*. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499-511.
- Belcaro G, Nicolaidis AN, Ramaswami G, Cesarone MR, De Sanctis M, Incandela L, *et al*. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: A 10-year follow-up study (the CAFES-CAVE study(1)). *Atherosclerosis* 2001;156:379-87.
- Friis-Møller N, Weber R, Reiss P, Thiébaud R, Kirk O, d'Arminio Monforte A, *et al*. Cardiovascular disease risk factors in HIV patients – Association with antiretroviral therapy. Results from the DAD study. *AIDS* 2003;17:1179-93.
- Hsue PY, Hunt PW, Schnell A, Kalapus SC, Hoh R, Ganz P, *et al*. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS* 2009;23:1059-67.
- Baker JV, Henry WK, Patel P, Bush TJ, Conley LJ, Mack WJ, *et al*. Progression of carotid intima-media thickness in a contemporary human immunodeficiency virus cohort. *Clin Infect Dis* 2011;53:826-35.
- Ross AC, Rizk N, O'Riordan MA, Dogra V, El-Bejjani D, Storer N, *et al*. Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis* 2009;49:1119-27.
- Merlini E, Luzi K, Suardi E, Barassi A, Cerrone M, Martínez JS, *et al*. T-cell phenotypes, apoptosis and inflammation in HIV+ patients on virologically effective cART with early atherosclerosis. *PLoS One* 2012;7:e46073.
- Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, *et al*. T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. *J Infect Dis* 2011;203:452-63.
- de Saint Martin L, Vandhuick O, Guillo P, Bellein V, Bressollette L, Roudaut N, *et al*. Premature atherosclerosis in HIV positive patients and cumulated time of exposure to antiretroviral therapy (SHIVA study). *Atherosclerosis* 2006;185:361-7.
- Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, *et al*. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation* 2001;104:257-62.
- De Luca A, de Gaetano Donati K, Colafigli M, Cozzi-Lepri A, De Curtis A, Gori A, *et al*. The association of high-sensitivity C-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: A nested case-control study. *BMC Infect Dis* 2013;13:414.