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Original article

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A R T I C L E   I N F O

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A B S T R A C T

Objective: This study sought to determine the association between social support and stigma experienced by HIV-positive patients and presence of subclinical cardiovascular disease. Methods: We implemented a cross sectional study in 67 HIV-positive patients and 52 controls from a community health care center in central India. The participants underwent an in-depth survey and a clinical and laboratory assessment of cardiovascular risk. Carotid-intimal thickness (CIMT) was used as a marker of subclinical cardiovascular disease. Results: On comparing the HIV and age and sex-matched control population, HIV patients had lower body weight (P = 0.001), and lower systolic blood pressures (P = 0.002). Despite the lack of higher cardiac risk factor prevalence and lower lipid abnormalities, HIV patients had higher right, left and average CIMT values than controls (P < 0.001 for all). HIV patients also showed higher prevalence of abnormal CIMT (≥ 0.9 mm) than controls (32% vs. 0%, P < 0.001). HIV patients with increased CIMT (n = 37) in comparison with those with normal CIMT (n = 30) were more frequently males (P = 0.023), had higher systolic blood pressures (P = 0.002), lower CD4 counts (P = 0.033) and experienced higher enacted stigma (P = 0.044). On multivariable stepwise logistic regression, systolic blood pressure (odds ratio: 1.06, P = 0.002) and stigma score > 25th percentile value (odds ratio: 3.84, P = 0.037) were independent predictors of the abnormal CIMT.

Conclusions: HIV-positive patients from central India have a higher prevalence of abnormal CIMT as a marker of subclinical cardiovascular disease than the general population. This predisposition to increased cardiovascular risk may be related to complex interactions between HIV disease and stigma-related healthcare inequities.

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1. Introduction

Lower economic countries across the world are going through an epidemiological transition with the decline of infectious and nutritional disorders and emergence of a pandemic of non-communicable diseases, including those related to health habits such as diet and exercise. However, slow-smoldering infections like HIV show paradoxical relationships with the growing epidemiology of non-communicable diseases; On one side, challenging socio-economic environments coupled with barriers to accessing treatment has heightened the prevalence of HIV globally. On the other side, HIV-positive people already on therapies in their 30 s and 40 s are more prone to the premature development of chronic diseases like diabetes and cardiovascular or atherosclerotic disease.¹ Not enough is understood about the impact of existing cultural and social barriers, which are associated with altered disease expression and increase the risk of development of non-communicable diseases in people surviving with HIV.

Understanding the factors associated with altered disease expression like HIV is particularly relevant for South Asian countries such as India, where the social and economic environment is rapidly changing and nearly 2.4 million individuals are living with HIV.² At its core, HIV stigma is grounded in cultural...
2. Materials and methods

2.1. Participants

The data for this cross sectional study was collected between January 2016 and January 2017 at a tertiary health care center in central India (Sengupta Hospital and Research Institute, Nagpur). We recruited a convenience sample of HIV patients who were registered and followed at Community Care Centre, Lata Mangeshkar Hospital, Nagpur. Patients were randomly selected during their clinic visit and given the opportunity to opt in or out of the study. A total of 67 HIV positive patients were recruited for the study. Exclusion criteria for the HIV-positive subjects were being HIV-positive and over the age of 18 years. We further categorized the cohort into groups on the basis of their treatment status and virologic control at the baseline visit.

Control subjects were also recruited from Sengupta Hospital and Research Institute, with inclusion criteria including being no known diseases and over the age of 18 years. Total 52 control participants were recruited. Exclusion criteria for the controls included having known heart disease and being over the age of 60. All participants were not preselected with respect to cardiovascular risk factors or coronary artery disease. The Institutional Committee on Human Research approved this study, and all individuals provided written informed consent before study enrollment.

2.2. Clinical and Socio-Demographic Characteristics

Patients received a uniform questionnaire conducted by a nurse fluent in English, Hindi, and Marathi. The survey focused on the patient’s medical history, medication usage, symptoms of cardiovascular disease and presence of cardiovascular risk factors as well as questions that explored the patient’s perceived stigma and level of social support. HIV disease characteristics including duration of HIV infection and current and prior antiretroviral medication were assessed in the HIV-infected individuals.

2.3. Laboratory Assays

Blood was drawn in the fasting state and used to measure hemoglobin, blood sugar, serum creatinine, total cholesterol, LDL and HDL cholesterol, and triglycerides.

Carotid Artery Intima-Media Thickness: The participants were imaged supine with their head rotated 45° away from the side being imaged, and the images were recorded digitally using the GE Vivid 9 system and a 10-MHz linear array probe. Intima-media thickness (IMT) was measured in 12 segments that included the near and far walls of the common carotid bifurcation region and internal carotid region on both the left and right sides. The right and left carotid arteries were studied with the head in the midline position and tilted upward. The probe was then adjusted to obtain the near and far walls in a parallel orientation and then positioned to obtain the maximal luminal diameter in the longitudinal plane.

Images were recorded digitally using a cine-loop format for subsequent analysis using manual caliper assessment of the digital images. Within each segment (common, internal, bifurcation region), IMT was calculated as the average of the near and far walls of the left and right carotid arteries. A single experienced technician who was blinded to the subjects’ HIV status performed all the IMT studies and caliper measurements of the digital images. Abnormal carotid intima-media thickness (CIMT) was defined as a CIMT greater than 0.9 mm15 while increased CIMT was defined as age-matched value exceeding 97.5 percentile of the normal control population.

The survey (see Supplemental Data) created for this study combined 3 previously validated surveys: 1) the India HIV-related Stigma Scales,13 2) the Multidimensional Scale of Perceived Social Support,14 and the 3) NIAID AIDS Clinical Trials Group Adherence Barriers Questionnaire.15 There were a total of 155 questions asked in 8 groups:

1) Lab measures included those taken from the patient’s medical record and measures taken on the day, such as weight, blood pressure and blood draw.
2) There were six additional sections with a mix of measures:
3) Health Related Questions: answered as Yes or No.
4) Barriers to Adherence: answered using a scale of Never = 1, Rarely = 2, Sometimes = 3, Frequently = 4.
6) Enacted Stigma: answered as Yes or No.
7) Vicarious Stigma: answered using a scale of Never = 1, Rarely = 2, Sometimes = 3, Frequently = 4.
8) Felt Normative Scale: answered using a scale of No one = 1, Very Few = 2, Some People = 3, Most People = 4.
9) Internalized Stigma: answered using a scale of Not at All = 1, A Little = 2, A Fair Amount = 3, A Great Deal = 4.

3. Statistical analysis

We conducted descriptive statistics to calculate means and standard deviations of continuous variables and frequencies of categorical variables. Scale items were summed in order to calculate total scale scores. Non-missing responses were included in data analyses. We conducted independent sample t-tests for continuous variables. Chi-square or Fisher exact test, where appropriate, was computed to assess differences in categorical variables. A stepwise multivariate logistic regression was performed to identify independent predictors of abnormal CIMT in HIV patients. A P < 0.05 was considered significant. Statistical analysis was performed using MedCalc software (version 9.3.6.0, Belgium). Scatterplot visualization for multidimensional attributes of interest was performed using a machine-learning algorithm, VizRank Orange 2.7.16

4. Results

The 67 HIV patients (mean age of 40 ± 7 years and 42% male) had been diagnosed with HIV for a mean of 10 ± 4 years and were
receiving highly active antiretroviral therapy (HAART) for 8 ± 4 years. On comparing the HIV and age and sex-matched control population (Table 1), HIV patients had lower body weight (P<0.001), and lower systolic blood pressures (P=0.002). A total of 29 (42%) HIV patients reported clinical symptoms with lower daily time spent in exercise than controls (P<0.001).

HIV patients and controls had no differences in prevalence of diabetes, hypertension, tobacco use or a family history of coronary artery disease. On comparing the laboratory investigations, HIV patients had lower hemoglobin (P=0.075), serum creatinine values (P=0.016), lower LDL (P=0.014), and higher HDL (P=0.013) values. Despite the lack of a higher risk factor prevalence and lower lipid abnormalities, HIV patients had higher right, left and average CIMT values than controls (P<0.001 for all). HIV patients also showed higher prevalence of abnormal CIMT (≥ 0.9 mm) than controls (32% vs. 0%, P<0.001).

For understanding the differences in clinical features associated with higher CIMT, we divided the CIMT patients into groups: with normal (<0.7 mm) and increased (>0.7) CIMT values. Patients with higher CIMT were more frequently males (P=0.023), had increased frequency of medical illness (P=0.048), and more frequently experienced chest pain (P=0.087) (Table 2). Patients with increased CIMT also had higher systolic and diastolic blood pressures (P=0.002 and 0.022), and lower absolute and percentage CD4 counts (P=0.033 and 0.011, respectively) (Table 3). There were no differences in perceived social support between the two groups (Table 2). Similarly, there were no differences in vascicular stigma and felt normative stigma scores reported by the two groups. However, enacted stigma scale reported by patients with increased CIMT was significantly higher than those with normal CIMT (P=0.044). Fig. 1 shows the distribution of HIV patients with normal CIMT and high CIMT as per intervals of enacted stigma index score. The proportion of HIV positive individuals with a total enacted stigma score above 25th percentile was significantly higher in the high CIMT group (60% vs. 86%, P=0.013).

Fig. 2 is a linear projection graph showing the relationship between CIMT, CD4 values and Enacted stigma. We subsequently performed a stepwise logistic regression model including gender, systolic blood pressure, CD4 cell count and the presence of stigma score >25th percentile value (dichotomized). Systolic blood pressure (odds ratio: 1.06, P=0.011) and the presence of stigma score > 25th percentile value (odds ratio: 3.84, P=0.037) were the only independent predictors of the presence of abnormal CIMT value (Table 3).

5. Discussion

The burden of coronary artery disease (CAD) continues to rise globally, as developing nations, including India, are adopting to lifestyle changes that increase predisposition to cardiovascular diseases. With the introduction of HAART, HIV has been transformed to a chronic disease and infected people are living longer and therefore experiencing the development of secondary chronic disease such as cardiovascular diseases (CVD).10 In this cross-sectional study, we measured carotid-intimal thickness (CIMT) as a marker of subclinical cardiovascular disease in HIV positive patients from central India. The principal findings were:

1) Relatively young HIV-positive subjects had significantly higher CIMT values in comparison with age- and sex-matched healthy general population who served as controls.
2) Patients with HIV felt lower perceived social support compared to controls.
3) Presence of high CIMT values (>0.7 mm) in HIV patients was associated with several high risk demographic, laboratory, and social features like male gender, low CD4 cell counts and increased enacted stigma scores respectively, and
4) A total of 16% of the HIV patients were not on HAART therapy and 64% of these people had evidence of subclinical CVD and experienced increased enacted stigma.

6. The need for screening in HIV patients

Compared to uninfected people, individuals with HIV are at a 1.5- to 2-fold greater risk of developing CVD.17 The presence of chronic inflammation associated with HIV disease has been correlated with risk of increased CVD.18,19 Despite compelling evidence that there is increased risk of CVD in HIV-positive populations, there are no specific screening and assessment plans for HIV populations.17 A recent European study found that stress testing in addition to medication with stress testing and

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV (n=67)</th>
<th>Control (n=52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), Mean (SD)</td>
<td>40.4(6.56)</td>
<td>37.78(9.81)</td>
<td>0.0851</td>
</tr>
<tr>
<td>Male, Number (%)**</td>
<td>28(41.79%)</td>
<td>28(53.84)</td>
<td>0.1300</td>
</tr>
<tr>
<td>Height (cm), Mean (SD)</td>
<td>160.72(9.37)</td>
<td>160.83(8.08)</td>
<td>0.9481</td>
</tr>
<tr>
<td>Weight (Kg), Mean (SD)</td>
<td>53.34(10.36)</td>
<td>58.95(7.76)</td>
<td>0.0020</td>
</tr>
<tr>
<td>Current smokers Number (%)**</td>
<td>0(0.0)</td>
<td>2(3.8)</td>
<td>0.1888</td>
</tr>
<tr>
<td>Exercise Measure, Number (%) *</td>
<td>4.02 x 10^-14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 hours</td>
<td>1 (1.49)</td>
<td>29 (55.77)</td>
<td></td>
</tr>
<tr>
<td>≥5 - &lt;10 hours</td>
<td>3 (4.48)</td>
<td>11 (21.15)</td>
<td></td>
</tr>
<tr>
<td>≥2 - &lt;5 hours</td>
<td>8 (11.94)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>&lt;2 hours</td>
<td>55 (82.09)</td>
<td>12 (23.08)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), Mean (SD)</td>
<td>115.54(13.80)</td>
<td>123.14(12.24)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), Mean (SD)</td>
<td>74.36(11.10)</td>
<td>77.05(11.54)</td>
<td>0.2110</td>
</tr>
<tr>
<td>Hemoglobin (gm/dl), Mean (SD)</td>
<td>11.87(1.56)</td>
<td>18.67(26.71)</td>
<td>0.1422</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl), Mean (SD)</td>
<td>0.78(0.16)</td>
<td>0.86(0.1)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl), Mean (SD)</td>
<td>155.17(49.36)</td>
<td>140.65(11.74)</td>
<td>0.0463</td>
</tr>
<tr>
<td>LDL (mg/dl), Mean (SD)</td>
<td>72.31(41.98)</td>
<td>98.84(12.24)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL (mg/dl), Mean (SD)</td>
<td>46.31(12.28)</td>
<td>40.7(3.15)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Right Carotid IMT (mm), Mean (SD)</td>
<td>0.77(0.16)</td>
<td>0.47(0.1)</td>
<td>1.18 x 10^-21</td>
</tr>
<tr>
<td>Left Carotid IMT (mm), Mean (SD)</td>
<td>0.77(0.16)</td>
<td>0.48(0.13)</td>
<td>1.07 x 10^-17</td>
</tr>
<tr>
<td>Average CIMT (mm), Mean (SD)</td>
<td>0.77(0.16)</td>
<td>0.48(0.11)</td>
<td>7.14 x 10^-21</td>
</tr>
<tr>
<td>Total perceived social support, Mean (SD)</td>
<td>5.63(1.00)</td>
<td>6.05(0.24)</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

All measures are expressed as mean (standard deviation) except when identified as n(%). * chi-square test, ** means Fisher’s exact test, all continuous variables were analyzed using the t-test
intervention, coronary CT angiogram with medication, and coronary CT angiogram with intervention strategies were found to be clinically beneficial and cost-effective when compared to no screening.\textsuperscript{20} However, developing countries like India pose several challenges; the use of screening coronary CT angiogram or echocardiographic stress testing may not be feasible for population-wide screening since these tests are not easily available and require specialized expertise. Hence the search for simple, cost-effective strategies and identification of high risk features associated with subclinical CVD is of paramount importance for prevention of CVD progression in HIV-positive patients.

### 7. The role of CIMT as screening technique

One of the widely used and best-validated atherosclerosis imaging techniques is the ultrasonographic measurement of carotid intima media thickness (CIMT) – a safe, noninvasive and cost effective method to detect subclinical and asymptomatic atherosclerotic vascular diseases.\textsuperscript{21,22} In healthy adults the range in distance is 0.6–0.7 mm and increases with age and is typically greater in men.\textsuperscript{23,24} Therefore we used a threshold of >0.7 mm for defining increased CIMT. A threshold value of >0.9 has been used in guidelines documents for defining abnormal CIMT and was seen in 12(18\%) patients.

In the present study, HIV positive patients had significantly higher CIMT values with nearly 37 (55\%) patients having CIMT values > 0.7 mm and 15 (22\%) patients having values over 0.9 cm. CIMT may be well suited for screening risk of CV disease in HIV patients. Over more than two decades, CIMT has been extensively researched and established. Moreover, several large, research-based cohort studies have clearly indicated a relationship between CIMT and CV events.\textsuperscript{21–23} Carotid plaque, defined as a focal abnormal wall thickness (CIMT > 1.5 mm) or a focal thickening of >50\% of the surrounding CIMT has been shown to be a more powerful predictor of CV risk compared with CIMT alone. Interestingly, however, plaque formation was seen in only 2 cases in the present study, perhaps related to the relatively young cohort of patients where the average age was 40 years.

The findings in this study are consistent with previous reports of increased CIMT in HIV patients compared with age-matched control subjects.\textsuperscript{30–34} Interestingly, we observed that patients with increased CIMT also had lower CD4 counts. This finding is also
coherent with previous reports in which carotid IMT was shown to be associated with classic coronary risk factors and CD4 count \( < 200 \), suggesting an interaction of immunodeficiency and traditional coronary risk factors in contributing to atherosclerosis.\(^3^4\)

The reason for low CD4 counts may also be related to compliance with HAART. It has been determined that for antiretroviral therapy to be effective adherence is required to be \( > 95\% \).\(^3^5\) An analysis of 569 studies found that 75.2% of HIV positive people were optimally adherent to drug therapy.\(^3^6\) In three Indian studies, adherence was determined to be 76–93%,\(^3^7\)–\(^3^9\) compared to only 55% of people in North America.\(^4^0\) Moreover, despite optimal adherence there may not be a significant relationship between adherence and viral suppression.\(^4^1\) This may be related to immunological non-responders in whom the CD4 counts fail to rise optimally despite adequate therapy.\(^4^2\) Irrespective of the mechanism, the increased CIMT in HIV patients and low CD4 counts suggest ongoing unsuppressed infection, which leads to enhanced endothelial activation and inflammation despite antiretroviral therapy.\(^4^3\)

8. Stigma as a risk feature

The current study measured four types of stigma:

1) **Internalized Stigma Scale**, which refers the acceptance of negative stereotypes about HIV as being true.\(^4^4\)\(^4^5\)

2) **Felt Normative Scale**, which refers perceptions of the prevalence of HIV stigma.\(^4^6\)

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Fig. 1. Distribution of total enacted stigma index subgroups. The frequency of HIV patients with normal CIMT (group 0, blue color) and increased CIMT (group 1, red color) is shown as bar graphs.

Fig. 2. 2D-Linear projection graph. Lines originating from the graph origin are projections of features’ base vectors and circles represent data instances. Blue color represents HIV patients with normal CIMT. Red represents HIV patients with increased CIMT. Size of the circle represents the %CD4 cell counts.
3) Vicarious Stigma, hearing about other people's discrimination or stigma, 46 and
4) Enacted Stigma, describing direct negative actions, including but not limited to verbal harassment, discrimination or physical assault.47

In our study, HIV-positive participants felt lower perceived social support when compared to the healthy control population, which is consistent with previous studies.48–51 Moreover, patients with increased CIMT reported higher Enacted Stigma. Previous reports have suggested improving positive social support including self-reported social support could reduce perceived HIV-related stigma.52–54 The effects of such interventions in reducing sense of stigma can increase one’s ability to seek care. The result of such therapeutic interventions and their possible impact on CIMT progression would need to be investigated in future studies. Specifically, current guidelines suggest statins should be used by all those with established vascular disease and among those with type 2 diabetes or at high risk of CVD, irrespective of lipid levels.55 Moreover, existing guidelines from India recommend an aggressive LDL target of < 50 mg/dl.56 Future studies should address the value of incorporating CIMT has a potential tool for justifying intensive lipid therapies and evaluating the impact of such interventions in reducing the high cardiovascular morbidity and mortality seen in HIV-positive patients.

Stigma in Indian patients with HIV has been an area of intense investigation, since it impacts overall disease progression. For example, a study in West Bengal found that even without a stigma reduction program HIV-positive people seeking care at a medical institution felt moderate to low levels of stigma.57 In another South Indian study it was found that 72% of people experienced severe forms of stigma resulting into a poor quality of life.58 In another South Indian study stigma was experienced by a higher proportion of females than males; that study found that perceived stigma was widespread and was suggested to be more disruptive to people's lives than enacted stigma.59 A relationship between enacted stigma and felt stigma (in our study referred to as “felt normative stigma”) that influences health care utilization, treatment adherence, and overall health and well being of people with HIV has also been reported.57 Moderate levels of stigma have also been associated with the lack of adherence to HAART. It was found that a reduction in stigma resulted in an increase of 5% in adherence to HAART for men and 7% in women.60

9. Limitations and future directions

The data from the present study suggests that patients with HIV in central India are at increased risk for premature CVD and need to be screened and aggressively treated. Moreover, HAART need to be optimized with close monitoring of therapeutic compliance and responsiveness. In our study, 10 patients were not prescribed HAART, which suggests need for wider educational programs amongst physicians for following the recommended therapeutic guidelines. Despite a small number of subjects, data from this pilot study will be useful for designing larger intervention studies. Moreover, longitudinal follow-up would be desirable to understand the incremental value of interventions on clinical outcomes. Caution needs to be also applied in interpreting the control population. Since HIV test was not ethnically possible to be administered in the control population, the estimates from the control group represent crude data for the general population. Finally, we did not assess inflammatory markers, lipoprotein subfraction analysis, subjects’ economic and educational status and the information or the limitations of the self-reported survey, which would need to be addressed in future investigations.

10. Conclusions

Relatively young HIV patients from central India have a higher prevalence of abnormal CIMT as a marker of subclinical cardiovascular disease than healthy general population. This predisposition to increased cardiovascular risk is not explained by the prevalence of traditional risk factors, and may be related to complex interactions between chronic HIV disease and stigma-related healthcare inequalities. These results emphasize the need for interventions to address the stigma and promote screening programs with positive health behavior interventions among the high-risk HIV population in South Asian countries.

Conflict of interest

Authors declare no conflicts of interests or funding sources

References

23. Evesnes K, Sarvari SL, Renning OM, Edwardsen T, Russell D. Carotid artery intima-media thickness is closely related to impaired left ventricular function