

Comparable carotid intima-media thickness among long-term virologically suppressed individuals with HIV and those without HIV in Thailand

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Abstract

Objectives: This study compared the carotid intima-media thickness (cIMT) among well suppressed adult participants living with HIV and adults without HIV, aged >45 years.

Methods: A cross-sectional, age and sex-matched study was conducted at two sites in Thailand: King Chulalongkorn Memorial Hospital (KCMH) and HIV-NAT. All participants had no evidence of coronary artery disease (CAD). Ultrasonography of the carotid artery was measured by one well-trained neurologist who was blinded to the participants' care. The primary endpoint was the difference in cIMT between participants with HIV and controls without HIV. Prevalence and predictive risk of cIMT \geq 0.9 mm were determined.

Results: Of 90 individuals, 60 were living with HIV. The overall median (IQR) age was 54.1 (52–60) years and 53.3% were male. For the group with HIV, the median duration of ART was 15 years and 33% were on boosted PIs. Compared to controls without HIV, the group with HIV had a higher proportion of hypertriglyceridaemia (48.3% vs 26.7%, $P=0.049$) but the median overall cIMT of the common carotid arteries (0.665 mm vs 0.649 mm, $P=0.277$) and serum high-sensitivity C-reactive protein (hs-CRP) (1.59 mg/dL vs 1.46 mg/dL, $P=0.325$) were not different. Hs-CRP was not correlated with cIMT \geq 0.9 mm. However, carotid plaques ($n=6$) were found only among the group with HIV. From the multivariate analysis, only male sex and hypertension were significantly associated with cIMT \geq 0.9 mm.

Conclusions: Well-controlled and long-term treated participants living with HIV had comparable cIMT to Thai adults without HIV. Monitoring for progression of cIMT, carotid plaques and cardiovascular disease in this population is warranted to guide continued management.

Keywords: cIMT, participants living with HIV, controls without HIV, antiretroviral therapy, Thailand

Introduction

The success of combination antiretroviral therapy (cART) in the past two decades has been responsible for the significant decline in not only AIDS-related mortalities, but also the incidence of serious non-AIDS events [1]. Life expectancies of people with HIV who adhere to cART approaches those of people without HIV [2], and as a result, the incidence of non-communicable diseases (NCDs) such as hypertension, diabetes, cancer, cardiovascular disease (CVD) in people living with HIV is expected to rise [3–6]. People with HIV have higher rates of atherosclerosis and CVD than matched populations without HIV [5–8]. They are also at risk of CVD partly due to HIV-related chronic inflammation, which could promote insulin resistance and increase atherosclerosis [9–11]. Some antiretroviral (ARV) agents have metabolic side effects, for example protease inhibitors (PI) can cause dyslipidaemia that indirectly increases CVD risk [12,13]. Indeed, increased prevalence of myocardial infarction among those on long-term cART and, especially in those treated with PIs are observed [14,15]. However, the direct causality of HIV and cART on increased rates of CVD have not been confirmed owing to short duration of observation and the presence of other risk factors such as smoking and hypertension [7,16].

There is much interest in identifying surrogate biomarkers to predict CVD in people with HIV. High-sensitivity C-reactive protein (hs-CRP) is predictive of the first atherothrombotic event in the general population [17]. Previous studies have demonstrated that people with HIV had higher hs-CRP levels compared to the general population [18,19]. Additionally, elevated hs-CRP and HIV are independently associated with increased acute myocardial infarction (AMI) risk [20]. One study showed a strong association of cIMT and hs-CRP with all-cause mortality in people with HIV on the same cART [21]. Therefore, measurement of hs-CRP may be useful in assessing the risk for CVD among individuals living with HIV.

Carotid intima-media thickness (cIMT) is a surrogate marker of atherosclerosis that has been associated with risks for CVD and mortality in the general population [22–24]. cIMT measurement is a reliable, non-invasive procedure, suitable for longitudinal assessment [25]. People with HIV had a higher rate and magnitude of increased cIMT over time compared to those without HIV [26–28]. Suppressing HIV replication to undetectable levels reduced the risk for atherosclerosis [29]. Increased cIMT was more pronounced in PI-treated participants with HIV than that in people on a non PI-based regimen, and in those who did not have HIV [30]. cIMT increased over time may, however, be associated with conventional rather than HIV-associated cardiovascular risk factors, but confirmation is needed [31].

The prevalence of coronary atherosclerosis may differ by ethnicity. There are few data on cIMT from Asia. One study from Thailand

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found that cIMT was similar among adolescents with perinatally acquired HIV and controls without HIV [32]. There are no data in Thai adults with HIV who are likely to possess a higher traditional CVD risk than adolescents. We therefore investigated the cIMT and hs-CRP levels among virologically suppressed people with HIV and their matched controls without HIV.

Methods

Patient population

A cross-sectional study was conducted at the King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand, from 1 December 2016 to 26 February 2017. Sixty people with HIV at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), and 30 controls without HIV seeking an annual health check-up were also enrolled. Consecutive cases who visited regular HIV care were approached. All were >45 years of age and those with HIV had to be on cART for at least 6 months and without a change in their regimen in the previous 3 months. Exclusion criteria included any known CVD (e.g. myocardial infarction, silent myocardial infarction, myocardial ischaemia, stable and unstable angina pectoris), having a history of coronary procedures (coronary angioplasty and coronary artery surgery), ischaemic or haemorrhagic stroke, currently treated for opportunistic infection or hyperlipidaemia (using statins or any lipid-lowering agents) and pregnancy. Controls without HIV underwent HIV testing. They had to be without a history of CVD or clinically suspicious CVD. All eligible participants with and without HIV were referred to a cIMT unit without identifying their HIV status. This study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. All participants provided informed consent to participate in the study.

Study design

Physical examination was performed. Heart rate, blood pressure measurements, weight and height measurements, and waist and hip circumferences were assessed. Blood was collected for complete blood count, fasting plasma glucose, lipid profiles, and hs-CRP (Roche Diagnostics GmbH, Mannheim, Germany). CD4 cell counts and HIV-1 RNA were measured only in the group with HIV. The participants then underwent a cIMT measurement. Case record forms were completed by extracting the data from medical records for demographic data, medical history and HIV-related treatments.

Carotid intima-media thickness measurement

Carotid Doppler ultrasound was performed by one trained neurologist who was blinded to the HIV status of the participants. A GE LOGIQ 9 model ultrasound machine equipped with a 9MHz linear probe was used. Images of the bilateral proximal, mid, distal common carotid arteries (CCAs) were separately obtained longitudinally. The means of three measurements of each side (right and left) were used to calculate the mean for all proximal, mid and distal CCAs to provide an overall cIMT measurement.

Sample size calculation

Based on a study reporting the mean baseline cIMT of 0.91 ± 0.33 mm in people with HIV and 0.74 ± 0.17 mm in those without HIV ($P < 0.0001$) [27], the 2:1 sample size to detect differences between groups with a confidence level of 95%, power of 80%, type I error 0.05 was 59 participants in the group with HIV versus 29 participants in the group without HIV. The sample size was calculated using G*Power programme version 3.1.9.2.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (version 22.0, SPSS, USA). The results were expressed as medians and interquartile ranges (IQR) for continuous data. For categorical data, the results were expressed as number and percentages. Comparisons of age within and between the two groups were completed using the Wilcoxon rank-sum test for continuous data and chi-squared test for categorical data. The cIMT was compared between those with HIV and those without HIV, and participants living with HIV but without PI exposure. A multivariate linear regression model was used to assess factors associated with cIMT; factors with P -values ≤ 0.10 in univariate analysis, or those with evidence of clinical significance were adjusted for in a multivariate model. The coefficients from the regression models represent the change in cIMT for a one-unit change in a continuous covariate, or relative to the reference group for a categorical covariate. The level of significance for all other analyses was set at $P=0.05$.

Results

Baseline characteristics

Among 90 adult participants enrolled, 60 were living with HIV. Baseline demographics and clinical characteristics are shown in Table 1. The overall median (IQR) age was 54 (52–60) years, and the male-to-female ratio was 1.1:1. People with and without HIV were similar in age and sex ratio. Smoking was significantly higher in people with HIV (25% vs 6.7%). Nineteen (32%) people with HIV and six (20%) controls had hypertension. Diabetes mellitus was found in seven (12%) people with HIV and three (10%) people without HIV. The history of CVD in a first-degree relative was 24% in people with HIV and 26% in people without HIV. The median body mass index (BMI) for people with HIV (22.7 kg/m^2) and people without HIV (24.4 kg/m^2) groups was comparable ($P=0.069$). There also was no median body weight difference among the participants with HIV (59 kg) versus people without HIV (63 kg) ($P=0.124$). Similarly, the waist:hip ratio was comparable: 0.90 in people with HIV versus 0.89 in people without HIV ($P=0.236$).

Among people with HIV, the median duration of cART was 15.4 years. The median nadir CD4 cell counts were 206 and 602 cells/ mm^3 . One-third had CD4 cell count >500 cells/ mm^3 , and 59 (98.3%) individuals had HIV-1 RNA <40 copies/mL. Non-nucleoside reverse transcriptase (NNRTI) based regimens ($n=29$, 48%) were the most common treatments, followed by PI-based ($n=20$, 33%) and integrase inhibitor-based regimens ($n=4$, 6.7%).

Fasting glucose, lipid abnormality and hs-CRP

Individuals with HIV had higher fasting glucose (94 vs 89 mg/dL, $P=0.043$) and higher triglyceride (145 vs 100 mg/dL, $P=0.002$) levels compared to controls (Table 2). There was a significantly higher proportion of people with HIV with hypertriglyceridaemia (triglycerides >150 mg/dL) than the controls (48.3 vs 26.7%, $P=0.049$). The proportions with hypercholesterolaemia (cholesterol >200 mg/dL), high LDL (LDL >130 mg/dL) and low HDL (HDL <40 mg/dL) were not significantly higher in people with HIV versus people without HIV (31.7 vs 23.3%, $P=0.414$).

Moreover, there was no difference in the median hs-CRP between the two groups (1.59 in people with HIV vs 1.46 mg/dL in people without, $P=0.325$). Eleven (18.3%) individuals with HIV and three (10%) in the control group had high hs-CRP levels of >5.0 mg/dL ($P=0.304$).

Table 1. Demographic and clinical characteristics of the group with HIV and the control group without HIV

Characteristics	Group with HIV (Total=60)	Group without HIV (Total=30)	P-value
Median age (years, IQR)	54.9 (52–60)	53 (50–60)	0.226
Male gender (<i>n</i>)	34 (56.7%)	14 (46.7%)	0.370
Median body weight (kg, IQR)	59.00 (53–66)	63 (56–70)	0.124
Median BMI (kg/m ² , IQR)	22.70 (20.6–24.3)	24.41 (21.3–25.7)	0.069
Median waist circumference (cm, IQR)	84.25 (79–89)	85.75 (81–90)	0.413
Median hip circumference (cm, IQR)	92.25 (89–98)	96 (93–98)	0.016
Median waist:hip ratio (IQR)	0.90 (0.86–0.94)	0.89 (0.85–0.91)	0.236
Smokers (<i>n</i>)	15 (25%)	2 (6.7%)	0.046
Ex-smokers (<i>n</i>)	5 (8.3%)	2 (6.7%)	–
Current smokers (<i>n</i>)	10 (16.7%)	0 (0%)	–
Diabetes mellitus (<i>n</i>)	7 (11.7%)	3 (10%)	0.813
Hypertension (<i>n</i>)	19 (31.7%)	6 (20%)	0.244
Median nadir CD4 cell count (cells/mm ³ , IQR)	206 (91–322.5)	N/A	–
Median current CD4 cell count (cells/mm ³ , IQR)	602.5 (487–811.5)	N/A	–
Current HIV-1 RNA <40 copies/mL (<i>n</i>)	59 (98.3%)	N/A	–
Cumulative duration of antiretroviral therapy (years, range)	15.39 (10.92–18.38)	N/A	–
Experience of antiretroviral drugs (<i>n</i>)			
PI	50 (83.3%)	N/A	–
NNRTI	50 (83.3%)	N/A	–
Current regimen (<i>n</i>)			
NNRTI-based (<i>n</i>)	29 (48.3%)	N/A	–
PI-based (<i>n</i>)	20 (33%)	N/A	–
Integrase inhibitors (<i>n</i>)	4 (6.7%)	N/A	–
Combination PI + NNRTI (<i>n</i>)	4 (6.7%)	N/A	–
Combination PI + Integrase inhibitors (<i>n</i>)	3 (5%)	N/A	–

BMI: body mass index; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; N/A: not applicable

Table 2. Lipid profile and biomarkers in the group with HIV and the control group without HIV

Characteristics	Group with HIV (Total=60)	Group without HIV (Total=30)	P-value
Median fasting plasma glucose (mg/dL, IQR)	94 (87–106.5)	89 (82–99)	0.043
Median total cholesterol (mg/dL, IQR)	211.5 (191.5–216.5)	203.5 (168–222)	0.070
Median triglycerides (mg/dL, IQR)	145 (111–205)	100 (70–153)	0.002
Median LDL (mg/dL, IQR)	134.2 (113.8–155.9)	130 (102–148)	0.210
Median HDL (mg/dL, IQR)	44 (37.5–54)	48.5 (41–55)	0.438
Impaired fasting glucose (mg/dL, IQR) (FPG>100) (<i>n</i>)	19 (31.7%)	7 (23.3%)	0.414
Hypercholesterolemia (total cholesterol >200 mg/dL) (<i>n</i>)	38 (63.3%)	15 (50%)	0.226
Hypertriglyceridemia (triglycerides >150 mg/dL) (<i>n</i>)	29 (48.3%)	8 (26.7%)	0.049
High LDL (LDL >130 mg/dL) (<i>n</i>)	34 (56.7%)	15 (50%)	0.549
Low HDL (HDL <40 mg/dL) (<i>n</i>)	17 (28.3%)	7 (23.3%)	0.613
Hs-CRP (g/dL, IQR)	1.59 (0.66–4)	1.46 (0.74–2.17)	0.325
Hs-CRP >5.0 g/dL (<i>n</i>)	11 (18.3%)	3 (10%)	0.304

BMI: body mass index; LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; VL: viral load; FPG: fasting plasma glucose

Predictors of cIMT

The cIMT was similar between the two groups (Table 3). Median cIMT was 0.665 mm in people with HIV and 0.649 mm in the control groups ($P=0.277$). However, plaques were only observed in participants with HIV (10%). In the univariate analysis for all of the participants, sex, waist–hip ratio, smoking and hypertension correlated with overall cIMT. HIV infection was not correlated with the overall cIMT with a coefficient of 0.035 ($P=0.110$).

In the multivariate regression analysis, of the HIV group only, by the stepwise method, only male sex and hypertension were correlated with the overall cIMT, with a coefficient of 0.041 ($P=0.046$) and 0.047 ($P=0.037$), respectively (Table 4).

Discussion

A current inactive lifestyle, living with HIV and using ARVs may contribute to higher risks for CVD. cIMT is one of the markers

Table 3. The carotid intima-media thickness in group with HIV and the control group without HIV

Characteristics	Group with HIV (Total=60)	Group without HIV (Total=30)	P-value
Median proximal CCA IMT (mm, IQR)	0.650 (0.580–0.728)	0.635 (0.577–0.690)	0.362
Median mid CCA IMT (mm, IQR)	0.673 (0.605–0.748)	0.646 (0.595–0.692)	0.114
Median distal CCA IMT (mm, IQR)	0.698 (0.645–0.793)	0.675 (0.625–0.715)	0.180
Median overall cIMT (mm, IQR)	0.665 (0.613–0.743)	0.649 (0.612–0.743)	0.277
Plaque detected (n)	6 (10%)	0 (0%)	0.073

CCA: common carotid artery; cIMT: carotid intima-media thickness; IMT: intima-media thickness,

Table 4. Multivariate regression analysis for factors associated with overall cIMT in the group with HIV

Factor	Univariate			Multivariate		
	Coefficient of overall cIMT	95% CI	P-value	Coefficient of overall cIMT	95% CI	P-value
HIV	0.035	–0.008–0.079	0.110	-	-	
Age (years)	0.003	–0.001–0.007	0.130	-	-	
Male gender (%)	0.040	–0.001–0.081	0.055	0.041	0.001–0.081	0.046
BMI (kg/m ²)	–0.003	–0.009–0.004	0.441	-	-	
Waist:hip ratio	0.354	–0.017–0.725	0.061	-	-	
Smoking	0.031	–0.003–0.066	0.074	-	-	
Hypertension	0.047	0.001–0.092	0.044	0.047	0.003–0.092	0.037
Diabetes mellitus	0.045	–0.020–0.111	0.173	-	-	
Hypercholesterolaemia	0.011	–0.031–0.053	0.611	-	-	
Hypertriglyceridaemia	0.012	–0.030–0.054	0.568	-	-	
High LDL	0.019	–0.022–0.061	0.360	-	-	
Low HDL	0.018	–0.029–0.064	0.457	-	-	
Hs-CRP	1.003	0.986–1.021	0.701	-	-	
Nadir CD4 cell count (per 100)	–0.006	–0.024–0.012	0.507	-	-	
Current CD4 cell count (per 100)	0.004	–0.007–0.016	0.460	-	-	
Nadir HIV VL	1.023	0.955–1.096	0.510	-	-	
Current HIV VL	0.879	0.067–1.148	0.339	-	-	

BMI: body mass index; LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; VL: viral load

that can predict cardiovascular risk, and is currently accepted for risk assessment for CVD. It is unclear whether HIV is correlated with changes in cIMT. Risk of developing CVD among participants with HIV may also be higher in certain ethnic groups [33]. Asians (Chinese and Japanese) exhibit high rates of stroke but not coronary heart disease compared to individuals of white, African and Hispanic ethnicity. In the present study we observed similar cIMT between 60 adults with HIV and 30 adults without HIV. This is likely to be because our participants were healthy with high CD4 cell counts and viral suppression after long-term cART for a median of 15 years. Very few were smokers. Whether the carotid plaque in 10% of the group with HIV were due to their HIV status is difficult to interpret in this small study

The lack of difference in cIMT between groups in our adult participants is consistent with those from a study of Thai adolescents with perinatally acquired HIV [32]. In that study, diastolic blood pressure and duration of a PI-based regimen were correlated with the overall cIMT [32]. Consistent with other reports [34], our data suggest that traditional risk factors for CVD such as hypertension and male sex, and not HIV were correlated with increased

cIMT. We postulated that any potential negative effects of HIV infection on cIMT would have resolved during long-term successful cART. We did not find a correlation between ARV and cIMT despite one-third of our participants being treated with a boosted PI regimen.

Our study had several limitations: the small sample size meant that we may have missed small differences between groups. It was also cross-sectional and there was no follow-up period to monitor the progression of cIMT. We also only measured cIMT of the common carotid artery and could have failed to detect atherosclerosis at other locations. However, a larger US study observed more extensive atherosclerosis measured by cIMT in people with HIV [35]. After adjusting for traditional risk factors, HIV was significantly associated with the internal carotid artery and bulb region compared to the common carotid artery [35]. Another large study found an independent association of HIV infection with cIMT at the bifurcation (HIV=+0.250 mm, 95% CI 0.198–0.303, $P<0.0001$) and the common carotid artery (HIV=+0.044 mm, 95% CI 0.021–0.066, $P=0.0001$) [35,36]. These studies suggest cIMT measurement locations should not be

limited to the common carotid artery, but also include measurements of the internal carotid and the bulb region. Suppression of HIV viraemia with cART can slow the progression of atherosclerosis [29]. A longitudinal follow-up is needed to adequately assess the risk of cardiovascular problems in people living with HIV.

High hs-CRP in the general population is consistently correlated with CVD, especially myocardial infarction [20]. In people with HIV, elevated hs-CRP levels can be due to HIV or other infections, which can be resolved with successful treatment [19]. Both hs-CRP and cIMT were associated with all-cause mortality in one study [21]. Yet in our study, there was no significant difference in hs-CRP between Thais with and without HIV, and hs-CRP was not correlated with cIMT. The study in Thai adolescents with perinatal HIV infection observed a higher proportion with hs-CRP level >3.0 g/dL, and no association of hs-CRP with cIMT. These results suggest that hs-CRP may not be useful in predicting CVD risk among Thais living with HIV [32].

In conclusion, we found no differences in cIMT between people with well-controlled and long-term treated HIV and those without HIV. However, cIMT was correlated with hypertension and male sex that are the traditional risk factors for CVD. A future longitudinal study to evaluate the progression of cIMT and the correlation of cIMT with CVD is warranted to guide management.

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Conflict of interest

OP is a recipient of the Research Chair Grant, the National Science and Technology Development Agency, Thailand. KR has received the Senior Research Scholar from Thailand Research Fund. KR also received honoraria or consultation fees from Merck, Roche, Jensen-Cilag, Tibotec, Mylan and Governmental Pharmaceutical Organization, Thailand. He has also participated in company-sponsored speakers' bureaux from Abbott, Gilead, Bristol-Myers Squibb, Merck, Roche, Jensen-Cilag, GlaxoSmithKline and Governmental Pharmaceutical Organization. AA participated in company-sponsored speakers' bureaux from Jensen-Cilag, Gilead and Bristol-Meyers Squibb. All other authors declare no conflict of interest.

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