

High Prevalence of Carotid Plaque Identified Using Standard Carotid Ultrasound Techniques in HIV-Positive Patients with Low to Moderate Vascular Risk

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Abstract

Background: People with HIV have an increased risk for developing atherosclerosis. The objective of our study was to measure the prevalence of carotid ultrasound abnormalities in HIV-positive patients receiving antiretroviral therapy using routine carotid ultrasound. We examined the association between abnormal carotid ultrasounds and traditional cardiovascular and HIV-related risk factors.

Methods: A cross-sectional study was carried out on male HIV-positive patients with low to moderate cardiovascular risk attending the HIV Metabolic Clinic in Vancouver, British Columbia (BC). Carotid ultrasounds were performed between January 1, 2002 and June 30, 2012, and this information was used to establish patients overall cardiovascular risk. Patient's charts were reviewed to obtain clinical data for traditional and HIV-related risk factors. Antiretroviral treatment information was obtained from the provincial Drug Treatment Program (DTP) data base. An abnormal carotid ultrasound was defined by the presence of carotid plaque(s) and was used as a surrogate marker for atherosclerotic cardiovascular disease. *Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation.*

Results: A total of 175 patients receiving antiretroviral therapy since 1996 were analyzed. The prevalence of carotid ultrasound abnormality was 47%. By multivariable analysis, the factors associated with carotid ultrasound abnormality included having history of high blood pressure (odds ratio 2.68, 95% confidence interval (CI): 1.17, 6.13) and a history of intravenous drug use (OR: 4.55, 95% CI: 1.40, 14.79). The odds ratios of carotid ultrasound abnormality for patients 46-55 years and ≥56 years old compared to ≤45 years old were 2.57 (95% CI: 1.08, 6.14) and 5.16 (95% CI: 2.02, 13.19) respectively. For every additional year on antiretroviral therapy, the odds ratio of abnormal carotid ultrasound increased by 1.10 (95% CI: 1.01, 1.19).

Conclusion: Our study suggests that HIV-positive patients assessed as having low cardiovascular risk have a high prevalence of atherosclerotic vascular disease at younger ages. Some traditional factors and longer exposure to ART were associated with carotid ultrasound abnormalities.

Keywords: HIV; Carotid ultrasound; Cardiovascular risk; Atherosclerotic cardiovascular disease; ART; HAART

Introduction

The introduction of highly active antiretroviral therapy (HAART) significantly improved the prognosis of people living with HIV [1]. As HIV-positive patients are living longer, it is becoming evident that this population has a greater prevalence of atherosclerotic cardiovascular disease than the general population [2,3]. Traditional risk factors such as hypertension, diabetes mellitus, dyslipidemia and smoking are highly prevalent among HIV-positive patients [4-6], which partly may explain the high rate of cardiovascular disease in this population. Another explanation relates to the fact that HAART may induce metabolic and anthropometric changes, which are risk factors for atherosclerotic cardiovascular disease [7,8]. HIV or HAART may accelerate atherosclerosis through unique pathways such as inflammation and endothelial dysfunction [9]. The relationship between HIV, HAART and atherosclerotic vascular disease is complex and has not been well defined.

Carotid plaque (CP) and carotid-intima-media thickness (CIMT) are validated surrogate markers of atherosclerotic cardiovascular disease that are measured by carotid ultrasound [10,11]. Previous observational studies that investigated the relationship between traditional and HIV-

related risk factors and carotid surrogate markers have shown conflicting results [12]. These studies used ultrasound-imaging techniques in a research setting and computer generated estimates of CIMT. However in one study, the prevalence of carotid artery abnormalities assessed in HIV-positive patients who were not previously exposed to HAART and with no overt cardiovascular disease (CVD) was 42% [13].

The objective of our cross-sectional study was to measure the prevalence of carotid ultrasound abnormality in HIV-positive patients using conventional carotid ultrasound imaging available in a large

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tertiary teaching hospital in Vancouver, Canada. We also examined the association of carotid US abnormality with traditional and HIV-related risk factors in patients receiving HAART.

Methods

Study design and population

This cross-sectional study was carried out at the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE). Clinical information was obtained from the files of patients attending the HIV Metabolic Clinic at St Paul's Hospital in Vancouver, Canada. This clinic is a medical referral center for the management of metabolic disorders in HIV-positive patients. These patients represent the HIV population in the greater Vancouver area and some areas of the province of British Columbia, Canada. As part of the standard care, patients were stratified according to cardiovascular risk during clinical evaluation. The modified Framingham Risk Score (FRS) was used to estimate the 10-year risk of developing CVD [14,15]. Those who fell under low- to moderate risk, defined as a 10-year modified FRS of <10%, or 10 to 20% respectively, were imaged with carotid ultrasounds scans to help determine cardiovascular risk assessment and to guide medical management. Participants were eligible for this study if they were 18 years or older, had a documented diagnosis of HIV and had a carotid ultrasound performed between January 1, 2002 and June 30, 2012.

Data sources

Clinical data for traditional risk factors were collected from the clinic consultation, laboratory and imaging reports. HIV-related risk factors were obtained from the HIV/AIDS Drug Treatment Program. This centralized program is managed under the BC-CfE and coordinates the distribution of HAART in BC to all eligible residents living with HIV and free-of-charge according to specific guidelines generated by the BC-CfE's Therapeutic Guidelines Committee. These guidelines have remained consistent with those put forward by the International AIDS Society-USA since 1996 [16]. The BC-CfE maintains records of drugs dispensed and HIV serology profiles for all its patients.

Documentation of the following risk factors at the date of the carotid ultrasound were recorded: history of smoking (yes, no), intravenous drug use (yes, no, unknown), alcohol use (current, former, never), history of diabetes mellitus (yes, no), history of hypertension (yes, no), history of dyslipidemia (yes, no), history of renal insufficiency (yes, no) and age at the carotid ultrasound date (years). Anthropometric and laboratory values nearest to the date of the carotid ultrasound, within +/-6 months were recorded. These included systolic and diastolic blood pressure (mmHg), total cholesterol (mmol/L), high-density lipoproteins (HDL) (mmol/L), low-density lipoproteins (LDL) (mmol/L), triglycerides (mmol/L), apolipoprotein B (apoB) (g/L) body mass index (kg/m²), estimated glomerular filtration rate (e-GFR) (mL/min/1.73 m²), serum creatinine (μmol/L), urine albumin-creatinine ratio (ACR) (mg/mmol), C-reactive protein (CRP) (mg/L) and fasting blood glucose (mmol/L). Concomitant medications at the time of the carotid ultrasound were also obtained. These included lipid-lowering, anti-hypertensive and anti-diabetic medications.

The following HIV-related risk factors were recorded up to the date of the carotid ultrasound: nadir and CD4 cell count nearest to the date of the carotid ultrasound (cells/mm³), peak and plasma viral load nearest to the date of the carotid ultrasound (copies/mL), previous history of AIDS at the start of antiretroviral therapy (yes, no), duration of antiretroviral therapy prior to the ultrasound date (years). Other HIV-related risk factors included first antiretroviral treatment class

(non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PIs), boosted protease inhibitors (PIb), and other regimens) and baseline (i.e. prior to starting antiretroviral treatment) CD4 cell count (cells/mm³) and plasma viral load (copies/mL).

Carotid ultrasound

All standard B-mode carotid ultrasounds were performed at St Paul's Hospital Radiology Department. Both carotid arteries were imaged at the level of the carotid bifurcation for carotid plaque and CIMT estimated. The carotid ultrasound report was the primary outcome variable for this study and it was recorded as either a normal or abnormal carotid ultrasound. The detection of one or more carotid plaques on ultrasound was considered abnormal, and the failure to detect carotid plaques was considered normal. Two technicians were responsible for reporting the results of the ultrasounds and the final report generated by a staff radiologist.

Statistical analysis

Categorical variables were compared using the Chi-square or the Fisher's exact test (for small counts and non-two-by-two associations), and continuous variables were compared using the Wilcoxon rank sum test. Because the extensive list of explanatory variables, we selected the significant variables associated with the carotid ultrasound result (abnormal/normal) in bivariable analyses to be potentially included as covariates in our logistic regression models. The selection of the variables for multivariable model was based on two criteria: Akaike Information Criterion (AIC) and Type III p-values [17]. These two criteria balance the model choice on finding the best explanatory model (Type III p-values – lower p-values indicate more significance) and at the same time a model with the best goodness-of-fit statistic (AIC – lower values indicate better fit). At each step of this process, the AIC value and the Type III p-values of each variable are recorded, and the variable with the highest Type III p-value is dropped, until there are no more variables left in the model. The final model has the lowest AIC. All reported p-values are two-sided. All analyses were performed using SAS software (version 9.3).

Results

A total of 246 patients from the HIV Metabolic Clinic had a carotid ultrasound performed between January 1, 2002 and June 30, 2012. Of the 246 patients, 232 were males (94%) and 14 (6%) were females. Because of the low number of females, our analyses excluded these patients. To analyze the duration of protease inhibitor exposure, we focused our study on patients who had received their first antiretroviral drugs after January 1, 1996, which yielded 175 patients. Of these remaining 175 patients, 93 (53%) had a normal carotid ultrasound (median age at ultrasound date: 47 years) and 82 (47%) had an abnormal carotid ultrasound (median age at ultrasound date: 54 years).

As shown in the bivariable associations in Tables 1a and 1b, several traditional and HIV-related risk factors were associated with a carotid ultrasound abnormality. These included the following: age at first antiretroviral initiation; age at the time that the carotid ultrasound was performed; <95% adherence in the first year of antiretroviral treatment; antiretroviral therapy initiation before the year 2000; history of intravenous drug use; having a protease inhibitor-based regimen and unconventional regimens as the first antiretroviral regimen; history of high blood pressure prior to the carotid ultrasound exam; being on antiretroviral treatment for a longer period of time prior to the carotid ultrasound date; and higher exposure to NNRTIs prior to the carotid ultrasound date (p<0.05). We categorized age at carotid ultrasound

Characteristics	Carotid ultrasound normal N=93		Carotid ultrasound abnormal N=82		p-value
	N	(%)	N	(%)	
Age at the carotid ultrasound date (years)					
≤45	38	(75)	13	(25)	<0.001
46-55	36	(51)	34	(49)	
≥56	19	(35)	35	(65)	
Age at the carotid ultrasound date (years)	47	(42-53)	54	(49-59)	<0.001
Age at antiretroviral therapy initiation date	43	(36-47)	47	(40-52)	0.005
Adherence in the first year of antiretroviral therapy					
<95%	9	(31)	20	(69)	0.007
≥95%	81	(59)	57	(41)	
Year of first antiretroviral therapy					
1996-1999	21	(36)	37	(64)	0.005
2000-2005	36	(65)	19	(35)	
After 2006	36	(58)	26	(42)	
History of injection drug use					
No	82	(57)	63	(43)	0.046
Yes	5	(26)	14	(74)	
Unknown	6	(55)	5	(45)	
First antiretroviral therapy regimen					
NNRTI	23	(55)	19	(45)	0.005
PI Single	11	(39)	17	(61)	
Boosted PI	48	(67)	24	(33)	
Other	11	(33)	22	(67)	
Any AIDS defining illnesses prior to ultrasound date					
No	69	(53)	60	(47)	0.878
Yes	24	(52)	22	(48)	
Years on antiretroviral therapy before carotid ultrasound date	5	(2-7)	7	(3-12)	0.008
Duration (years) of NNRTI exposure prior to ultrasound date	1.30	(0.21-2.94)	2.27	(1.12-5.22)	0.034
Duration (years) of PI exposure prior to ultrasound date	3.62	(1.96-5.18)	4.09	(1.43-5.73)	0.582
Nadir CD4 cell count (prior to ultrasound date) (cells/mm³)	140	(40-250)	140	(50-190)	0.795
CD4 value nearest to time of ultrasound (cells/mm³)	500	(410-620)	480	(380-600)	0.268
Peak plasma viral load (prior to ultrasound date) (copies/mL)	100010	(73900-100010)	100010	(76378-100010)	0.987
Plasma viral load nearest to time of ultrasound (copies/mL)	499	(499-499)	499	(499-499)	0.337

Note: For continuous variables, we presented the median and the 25th-75th percentiles.

Table 1a: Baseline characteristics of 175 male patients with human immunodeficiency virus who started antiretroviral therapy after 1996.

Characteristics	Carotid ultrasound normal N=93		Carotid ultrasound abnormal N=82		p-value
	N	(%)	N	(%)	
Diabetes (at the time of ultrasound)					
No	87	(55)	70	(45)	0.171
Yes	6	(38)	10	(63)	
History of high blood pressure (at the time of ultrasound)					
No	79	(59)	56	(41)	0.013
Yes	14	(36)	25	(64)	
Any concurrent statin use (at the time of ultrasound)					
No	86	(54)	74	(46)	0.599
Yes	7	(47)	8	(53)	
History of smoking (at the time of ultrasound)					

No	31	(63)	18	(37)	0.168
Yes	46	(51)	44	(49)	
History of alcohol consumption (at the time of ultrasound)					
Never	26	(55)	21	(45)	0.477
Former	4	(40)	6	(60)	
Current	44	(60)	29	(40)	
History of renal failure (at the time of ultrasound)					
No	86	(54)	72	(46)	0.994
Yes	6	(55)	5	(45)	
BMI measurement (at the time of ultrasound) (kg/m²)	27	(24-29)	26	(24-28)	0.767
Framingham score (at time of ultrasound)	7	(4-8)	8	(5-8)	0.415
CRP value nearest to time of ultrasound (mg/L)	1	(1-3)	2	(1-4)	0.475
Total cholesterol value nearest to time of ultrasound (mmol/L)	5.44	(4.86-6.30)	5.46	(4.94-6.02)	0.530
HDL value nearest to time of ultrasound (mmol/L)	1.09	(0.93-1.37)	1.08	(0.94-1.22)	0.766
LDL value nearest to time of ultrasound (mmol/L)	3.22	(2.73-4.07)	3.25	(2.80-3.80)	0.815
Triglyceride value nearest to time of ultrasound (mmol/L)	2.13	(1.56-3.56)	2.25	(1.41-3.18)	0.625
apoB value nearest to time of ultrasound (g/L)	1.11	(0.95-1.28)	1.15	(0.97-1.28)	0.439
Glucose value nearest to time of ultrasound (mmol/L)	5.50	(5.10-5.90)	5.70	(5.30-6.00)	0.055

Note: * For continuous variables, we presented the median and the 25th-75th percentiles.

Table 1b: Baseline traditional cardiovascular risk factors of 175 male patients with human immunodeficiency virus.

date into three groups: ≥ 45 years, 46 to 55 years, and ≥ 56 years. The proportion of abnormal carotid ultrasounds was higher in patients in the older age categories as compared to patients in the younger age categories (Table 1a). There were no significant differences in laboratory results, including lipid profile, apoB, CRP, fasting blood glucose (Table 1b), and ACR, serum creatinine and e-GFR (data not-shown).

Table 2 shows the results of the univariable and multivariable logistic regression models. Of the variables associated with carotid ultrasound abnormality in Tables 1a and 1b, duration of NNRTI exposure was omitted from the models because we had data on only 77 (44%) patients. In the multivariable model, the odds ratio of having an abnormal carotid ultrasound for patients with a history of high blood pressure was 2.68 (95% confidence interval: 1.17, 6.13) times higher than the odds ratio for patients without a history of high blood pressure. The odds ratio of having an abnormal carotid ultrasound for patients in the 46-55 years and ≥ 56 years age categories was 2.57 (95% CI: 1.08, 6.14) and 5.16 (95% CI: 2.02, 13.19) times higher than the odds ratio of patients in the ≤ 45 years category. The odds ratio of having an abnormal carotid ultrasound for patients with a history of intravenous drug use was 4.55 (95% CI: 1.40, 14.79) times higher than the odds ratio for patients without a history of intravenous drug use. Finally, the odds ratio of having an abnormal carotid ultrasound was 1.10 (95% CI: 1.01, 1.19) higher for every additional year patients were exposed to antiretroviral therapy before the carotid ultrasound date.

Discussion

We carried out a cross-sectional study on male HIV-positive patients with low to moderate cardiovascular risk. The goal was to characterize the relationship between carotid ultrasound abnormality and traditional and HIV-related risk factors in patients receiving HAART. The data for this study was obtained from January 1st 2002 to June 30th 2012. It is important to note that during this period of time there were changes to the antiretroviral therapy received by most patients which were accounted for in the analysis, but the US imaging techniques remained consistent throughout the study. Our results showed that the overall prevalence of carotid ultrasound abnormality in this study group was 47%, at a median age of 54 years. These findings are higher than those

found in the non-HIV infected population (38.9% prevalence with a mean age of 55.4 years) [18]. Depairon et al. reported comparable rates in a similar cross-sectional study using carotid plaques as a surrogate marker of vascular disease in HIV and non-HIV participants [19]. Their results showed that the prevalence of carotid plaque in HIV and non-HIV controls was 55% and 38% respectively. Our analysis is consistent with this study, which suggests that the prevalence of atherosclerotic

Characteristic	Bivariable	Multivariable
	Odds Ratio (95% Confidence Interval)	Odds Ratio (95% Confidence Interval)
First antiretroviral therapy regimen		
NNRTI	1.00 (-)	
PI Single	1.55 (0.69, 3.46)	
Boosted PI	2.85 (1.13, 7.22)	
Other	4.60 (1.86, 11.35)	
History of high blood pressure (at the time of ultrasound)		
No	1.00 (-)	1.00 (-)
Yes	2.51 (1.19, 5.29)	2.68 (1.17, 6.13)
Age at carotid ultrasound date		
≤ 45	1.00 (-)	1.00 (-)
46-55	2.60 (1.18, 5.75)	2.57 (1.08, 6.14)
≥ 56	4.90 (2.08, 11.56)	5.16 (2.02, 13.19)
Adherence in the first year of antiretroviral therapy		
<95%	1.00 (-)	1.00 (-)
$\geq 95\%$	0.31 (0.13, 0.73)	0.45 (0.17, 1.20)
History of injection drug use		
No	1.00 (-)	1.00 (-)
Yes	3.81 (1.3, 11.18)	4.55 (1.40, 14.79)
Unknown	0.91 (0.25, 3.36)	1.43 (0.35, 5.79)
Years on antiretroviral therapy before carotid ultrasound date		
	1.12 (1.04, 1.20)	1.10 (1.01, 1.19)

Table 2: Results of the logistic regression models modeling the probability of carotid ultrasound abnormality.

disease in the HIV population is higher than the general population.

In this study, we demonstrated that carotid ultrasound abnormality was associated with age at carotid ultrasound date, history of high blood pressure, history of injection drug use and years on antiretroviral therapy before carotid ultrasound date. Age and hypertension are traditional risk factors that are well established in predicting cardiovascular morbidity and mortality in HIV-infected and uninfected individuals [20,21]. In an Italian study up to 30% of HIV-positive patients had a diagnosis of hypertension, and over one third of the cohort were not aware of their condition [22]. Our results are consistent with the literature and they support the notion that certain traditional risk factors for HIV disease progression are important contributors to atherosclerotic disease in the HIV population. Previous observational studies that investigated the relationship between traditional risk factors and carotid ultrasound surrogate markers in HIV patients have found similar results [23-26]. However, our analysis failed to demonstrate a significant association between carotid ultrasound abnormality and other traditional risk factors such as dyslipidemia, diabetes mellitus, hypertension and smoking. This can be explained by our relatively young population, the fact that we included patients with low to moderate cardiovascular risk, and the small sample size in this study. There may also be additional factors unrelated to the traditional risk factors, which may explain these findings, including inflammation related to HIV infection and use of certain antiretrovirals.

It is hypothesized that certain protease inhibitors induce unfavorable lipid profiles that contribute to atherosclerotic disease [27]. In the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, the rate of myocardial infarctions for HIV patients who were exposed to protease inhibitors for one year was 1.16 times the rate of HIV patients who were not exposed to protease inhibitors [28]. After adjusting for serum lipid levels, the relative risk remained significant at 1.10, suggesting that protease inhibitors contribute to cardiovascular disease through different mechanisms. Previous observational studies that investigated the relationship between protease inhibitor and carotid plaques produced conflicting results [19,23,29-31]. Maggi demonstrated that protease inhibitor exposure was associated with carotid plaques [29,30] while other observational studies failed to show this association [19,23,31]. Although protease inhibitor exposure was not significantly associated with abnormal carotid ultrasound in our analysis, we found that longer duration of antiretroviral therapy was associated with an abnormal result. This finding was also found in an observational study by Jericho [25]. One possible explanation for why we were unable to detect a significant association with protease inhibitors exposure could be related to the short follow-up time in our study. The median years of protease inhibitor exposure prior to the ultrasound date for patients with normal and abnormal carotid ultrasound was 3.62 (1.96, 5.18) and 4.09 (1.43, 5.73) years respectively.

Inflammation plays a major role in the pathogenesis of atherosclerotic cardiovascular disease [32]. CRP is an inflammatory marker that is associated with cardiovascular events in the general population [33]. The Jupiter trial selected individuals with a CRP > 2.0 mg/L and an LDL < 3.5 mmol/L in the absence of vascular disease. This trial showed that rosuvastatin was effective in reducing cardiovascular events in this group of patients. The reduction in cardiovascular events may be related to a decrease in CRP [34]. Due to their state of chronic inflammation, CRP was elevated in the HIV-positive population and it was an independent risk factor for acute myocardial infarctions [35,36]. Elevated CRP in the HIV-positive population was found to be associated with abnormal carotid surrogate markers in several

observational studies [37,38]. Our analysis failed to detect a significant association between CRP and carotid ultrasound abnormality. As previously stated, the HIV Metabolic Clinic is an outpatient medical service that actively treats metabolic disorders in healthy and virally-suppressed HIV-positive patients. The effect of antiretroviral therapy on viral suppression may have decreased serum CRP and obscured our ability to detect an association of CRP and an abnormal carotid ultrasound [34,39,40].

The strength of our study was to confirm the high prevalence of carotid US abnormalities in a group representative of HIV-positive patients in British Columbia, Canada, with low to moderate risk for CVD receiving HAART. Our findings highlight the importance of early intervention and risk factor modifications in this population. Second, this study was based on patients with free access to medical care, antiretroviral therapy, and laboratory monitoring. Some limitations were identified in this investigation. First, the cross-sectional nature of this study made it difficult to establish the temporal relationship between the exposure of risk factors and the development of carotid plaque. However, the presence of a dose-response relationship between duration of antiretroviral therapy exposure and prevalence of carotid plaques increased our confidence in a temporal relationship. Second, this study used a surrogate marker instead of a defined end point such as the incidence of myocardial infarction. Carotid plaque and CIMT are validated surrogate markers of cardiovascular disease [10,11]; they are frequently used as clinical endpoints in research and used for risk stratification in patient care [41,42]. Third, it is important to mention that carotid ultrasounds were more frequently performed in recent years due to changes in the standard of care in our clinic. Finally, although we adjusted our analyses for several demographical and clinical characteristics, as in all observational studies unmeasured differences may exist among study populations, and for this reason, our findings should be interpreted with caution.

In conclusion, this study suggests that in this group of HIV-positive patients there is a high prevalence of atherosclerotic disease. Unlike previous studies, carotid plaque was identified using conventional carotid ultrasound techniques available at our center. This suggests that conventional carotid ultrasound imaging is a useful technique to screen HIV patients for plaque and this information can be used to determine their overall vascular risk. This is consistent with vascular risk assessment guidelines that suggest that HIV is an inflammatory condition that increases vascular risk [14]. Our study showed that duration of antiretroviral therapy, age, hypertension and history of intravenous drug use were associated with the risk of having an abnormal carotid ultrasound result. Consequently a strong emphasis should be placed on modifying traditional risk factors when optimizing cardiovascular care for HIV-positive patients. Further research is required to validate our findings in a more representative study population of HIV-positive patients on antiretroviral treatment.

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