



Abstract

Background: Treatment greatly prolongs life expectancy of human immunodeficiency virus (HIV)-infected people, but causes lipid abnormalities that may predispose to cardiovascular disease. We measured carotid intima media thickness (IMT) to determine whether HIV infected subjects had more subclinical vascular disease compared with population-based controls.

Methods: Cross-sectional analysis of 594 subjects: 268 Caucasian HIV-infected subjects aged 35 years and older attending five academic HIV clinics in Canada, compared with 326 Caucasian population-based community controls from the Study of Health Assessment and Risk in Ethnic groups (SHARE). We used high-resolution B-mode ultrasonography to measure 12-segment mean maximal carotid IMT. Carotid IMT was read centrally by an experienced reader using dedicated computer software. Multiple linear regression was used to model the association between HIV status and carotid IMT, adjusting for Framingham risk factors.

Results: HIV-infected adults had mean (SD) age of 46.9 (7.9) years, versus 51.3 (11.1) years for community controls ($P<0.001$), were more likely to smoke (37 vs. 16%, $P<0.001$), and had higher total:HDL cholesterol ratios (5.3 vs. 4.7, $P<0.001$). Mean (SD) carotid IMT was 0.81 (0.23) and 0.77 (0.23), respectively, among HIV-infected subjects and controls. Carotid IMT was associated with HIV in unadjusted ($\beta=0.078$, 95% CI: 0.052, 0.105, $P<0.001$) and covariate adjusted models ($\beta=0.069$, 95% CI: 0.045, 0.092, $P<0.001$). HIV status was not significant after adjusting for exposure to the HIV drug stavudine, or to the drug class of protease inhibitors ($\beta=-0.001$, 95% CI: -0.040, 0.039, $P=0.39$).

Conclusions: HIV-infected subjects had a statistically significant and clinically important increase in carotid atherosclerosis compared with community controls, even after adjusting for cardiovascular risk factors. This risk is likely attributable to HIV medications, and not to HIV infection itself.

Background

- Anti-retrovirals greatly prolong the life expectancy of human immunodeficiency virus (HIV)-infected people
- However, drug-induced hyperlipidemia may cause CV disease.
 - D:A:D study: risk increased by 17% per year of treatment
 - Protease inhibitors associated with increased risk of 16% per year
 - Non-nucleoside reverse transcriptase inhibitors not clearly associated with increased risk
- However, HIV subjects may be more prone to CV disease due to other CV risk factors such as smoking

Objective

1. To determine whether subclinical vascular disease is increased in HIV+ve subjects compared with community controls, using highly standardized ultrasound methods.
2. To determine whether any increase is associated with standard CV risk factors or anti-retroviral drug exposure

Methods

- Design: prospective multicentre cohort study
- Setting: Canadian university-affiliated HIV clinics in Hamilton, Toronto, Quebec, Montreal, Calgary and Vancouver
- We are recording CV risk factors, fasting lipids, CD4 lymphocyte counts, viral load, and anti-retroviral drugs.
- 12-segment mean maximum carotid intima media thickness (IMT) measured by B-mode ultrasound (Figure)
 - Technique standardized, reproducible (ICC 0.92-0.96)
 - Videotaped and read off-line by experienced vascular laboratory with dedicated computer workstation
- Comparison group: Population-based community controls from the Study of Health Assessment and Risk in Ethnic groups (SHARE, Lancet 2003).

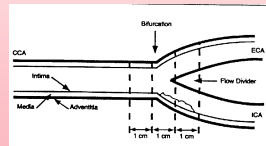


Figure. 12-segment carotid intima media Thickness by B-mode ultrasound

Results

- HIV+ve Subjects:
 - 300 recruited in 5 centres
 - 262 self-classified as White ethnicity
 - Mean (SD) age: 46.9 (7.9) years
 - Gender: 92% males
- Community controls from SHARE study:
 - 1200 population-based controls in four ethnic groups
 - 326 self-classified as White ethnicity
 - Mean age: 51.3 (11.1) years
 - Gender: 48%

•Comparisons (see Table 1):

- HIV subjects:
 - Younger: 46.9 (7.9) vs. 51.3 (11.3)
 - Males: 92% vs. 48%
 - Smokers: 37% vs. 16%
 - Total:HDL cholesterol: 5.3 vs. 4.7
 - Lower BMI: 25 vs. 27 kg/m²

•Carotid 12-segment IMT:

- HIV+ve: 0.81 (0.23) mm
- Controls: 0.77 (0.23) mm
- Beta=0.078
- 95% CI: 0.052, 0.105
- P=0.008

•Adjusted for Framingham risk factors:

- Beta=0.069
- 95% CI: 0.045, 0.092
- P<0.001

•Adjusted for PI or d4T exposure:

- Beta=-0.001
- 95% CI: 0.040, 0.039
- P=0.39

Table 1. Subject characteristics

Characteristic	HIV +ve	Controls	P-value
Number	268	326	
Age (SD), years	46.9(7.9)	51.3 (11.1)	<0.001
Males	246 (92%)	157 (48%)	<0.001
Current smoker	99 (37%)	53 (16%)	<0.001
Former smoker	86 (32%)	113 (35%)	NS
Previous CV disease	18 (7%)	21 (6%)	NS
Diabetics	12 (5%)	19 (6%)	NS
Past Hypercholesterolemia	28 (10%)	53 (16%)	NS
Past Hypertension	28 (10%)	53 (16%)	P=0.04
Blood pressure, mm Hg	121 (16) / 77 (11)	120 (17) / 73 (10)	NS
Total: HDL cholesterol	5.3 (2.5)	4.7 (1.7)	<0.001
Total cholesterol, mmol/L	5.2 (1.4)	-	-
HDL cholesterol, mmol/L	1.1 (0.3)	1.2 (0.4)	-
Triglycerides, mmol/L	2.9 (2.7)	1.7 (1.2)	<0.001
CD4 median (IQR), cells/mm ³	460 (284, 630)	-	-
CD4 nadir	155 (49, 283)	-	-
Current viral load, copies/mL	<50 (<50, 1090)	-	-
AZT, (months)	79.6% (41.9)	-	-
D4T	60.5% (37.7)	-	-
NNRTI	60.5% (25.9)	-	-
Protease inhibitors	70.4% (46.1)	-	-

Table 2. Association with log Carotid Intima Media Thickness (N=594)

Variable	Model 1 (Beta, P)	Model 2 (Beta, P)	Model 3 (Beta, P)
HIV	0.029 (P=0.001)	0.028 (P<0.001)	-0.014 (P=0.24)
Age (decade)	0.068 (P<0.001)	0.061 (P<0.001)	0.055 (P<0.001)
Male	0.041 (P<0.001)	0.028 (P=0.002)	0.028 (P<0.001)
Current smoker	0.034 (P<0.001)	0.038 (P<0.001)	0.036 (P<0.001)
Former smoker	0.015 (P=0.08)	0.015 (P=0.06)	0.017 (P=0.03)
Total: HDL cholesterol	-	0.024 (P=0.32)	0.004 (P=0.86)
Systolic BP	-	0.001 (P<0.001)	0.001 (P<0.001)
PI ever	-	-	0.038 (P=0.002)
d4T ever	-	-	0.020 (P=0.07)

Conclusions:

- HIV-infected subjects had a statistically significant and clinically important increase in carotid atherosclerosis compared with community controls, even after adjusting for cardiovascular risk factors.
- This risk is likely attributable to smoking, hypercholesterolemia and HIV medications, and not to HIV infection itself.
- This multi-centre Canadian study has successfully recruited over 300 subjects to date, and will continue to follow progression of carotid IMT

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