

# Lack of Evidence of Abnormal Myocardial Perfusion in HAART-treated, HIV-infected Mexican Patients

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## ABSTRACT

**Background:** Premature coronary heart disease (CHD), secondary to endothelial dysfunction, thrombophilia, and metabolic abnormalities associated with HIV or its treatment, has been postulated. Our objective was to test the hypothesis that HIV-infected Mexican patients were more likely to have abnormal myocardial perfusion than age- and gender-matched HIV-negative individuals.

**Methods:** Using radionuclide imaging, we compared 2 groups: a sample of 105 HIV+ patients randomly selected from those attending an HIV clinic in Mexico City, and a community sample of 105 HIV- subjects. All individuals were assessed for myocardial perfusion (blinded interpretation of a Tc99m sestamibi SPECT), smoking, alcohol consumption, physical activity, and dietary habits; blood pressure, body composition, and fasting plasma glucose, lipid profile including apolipoproteins, C-reactive protein (hs-CRP), homocysteine, and fibrinogen. Time of exposure to combination ART and CD4 count and HIV viremia history were reviewed in the HIV+ patients. We calculated 95% confidence intervals (95% CI) of proportions (binomial distribution), and confounders-adjusted odds ratio (OR) and its 95% CI estimated with logistic regression analysis.

**Results:** An abnormal SPECT was found in 4.8% (95% CI = 1.5 to 10.8) of HIV+ patients and in 7.6% (95% CI = 3.3 to 14.5) of HIV- subjects; OR = 0.61 (95% CI = 0.19 to 1.92). Severity of SPECT abnormalities was similar between both groups. Median time since HIV diagnosis was 55.8 months. In the HIV+ group 91% had received combination ART (100% a nucleoside reverse transcriptase inhibitor, 72% a protease inhibitor, and 70% a non-nucleoside reverse transcriptase inhibitor). Median time (months) of exposure to them was 41.7, 36.5, and 19.3, respectively. In the HIV+ group 32% were current smokers, 22% had abnormal fasting plasma glucose or diabetes, 17% hypertension, 73% HDL cholesterol <40 mg/dl, 76% triglycerides ≥150 mg/dl, 39% apolipoprotein B >90th percentile for Mexican adults; 10% abdominal obesity, and 66% hsCRP >1.5 mg/l.

**Conclusions:** In these Mexican HIV+ patients, despite a long time of infection and of exposure to diverse combined ART regimens and other known risk factors for CHD, no evidence of increased risk for severe abnormal coronary blood flow was found.

## RATIONALE AND AIM

Data from some large cohorts suggest an increased rate of acute coronary events with longer exposure to combination antiretroviral therapy or to protease inhibitor-containing HAART.

Few studies have addressed the question of the actual magnitude of risk increment for coronary heart disease in HIV patients as compared to the non-infected population with similar known risk determinants for cardiovascular illness.

Surveys that have included HIV-free subjects as a control group yield contradictory results and their conclusions could be distorted due to a lack of control of confounders or to diagnostic ascertainment biases.

There is no published study assessing the coronary blood flow in asymptomatic HAART-treated HIV-infected patients.

The Mexican population has a particularly high prevalence of the metabolic syndrome and its characteristic dyslipidemias: low HDL cholesterol and hypertriglyceridemia.

This cross-sectional study was designed to test the hypothesis that HIV(+) Mexican patients were more likely to have abnormal myocardial perfusion (by single photon emission computed tomography or SPECT) than age- and gender-matched non-infected individuals.

## CONCLUSIONS

In these Mexican, HAART-treated, HIV(+) patients, with a high prevalence of atherogenic dyslipidemia and of increased circulating C-reactive protein, no evidence of higher risk for abnormal coronary blood flow was found.

Possible explanations for this negative result are:

Insufficient time with HIV infection or with antiretroviral therapy. Worth considering is the fact that our patients had a similar median time of exposure to the virus, and to PI-containing HAART, than patients from previous studies claiming an association between these factors and cardiovascular diseases.

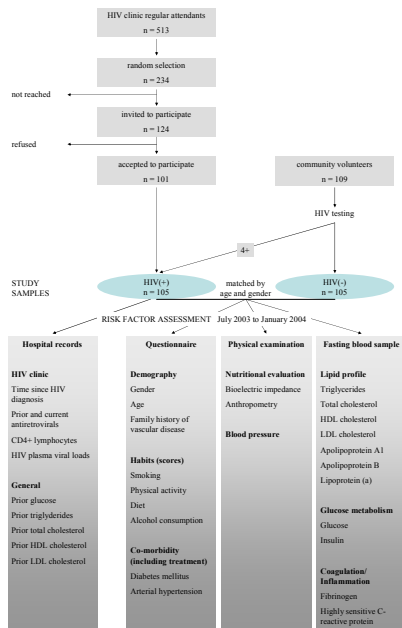
Our infected patients could have had a lower exposure to traditional cardiovascular risk factors, such as cigarette smoking, as compared to other studied populations.

Our finding supports the concept of a much more complex interaction between HIV, HAART and known risk factors, as potential determinants of premature coronary heart disease. It is likely that different hazard magnitudes may occur in diverse populations with different frequencies of traditional predisposing factors of cardiovascular illness.

## METHODS

### STUDY DESIGN

Cross-sectional survey with sampling by exposure



Myocardial perfusion radionuclide imaging:  
Single photon emission computed tomography

## SPECT

### Sample size estimation

We computed the sample size needed to compare a hypothetical 15% proportion of coronary artery disease in HIV-infected patients with the reported 5% prevalence of the disease in the adult general population, using a one-sided alpha value of 0.05 and 80% power.

With the arc/sinus method we obtained that 105 subjects were required in each group.

## RESULTS

### Comparison of HIV-infected with non-infected subjects

	HIV(-) n = 105	HIV(+) n = 105	P value
<b>Male gender</b>	85 (81%)	85 (81%)	NS*
<b>Age (years): median (IQR)†</b>	38 (31-47)	37 (32-44)	NS
<b>Family history of early vascular disease</b>	15 (14%)	22 (21%)	NS
<b>Current smoking</b>	45 (43%)	34 (32%)	NS
<b>Physical activity (index): median (IQR)</b>	24 (13-31)	17 (10-27)	0.03
<b>Diet (index): median (IQR)</b>	77 (70-84)	77 (70-84)	NS
<b>Alcohol (&lt;3 standard drinks/week)</b>	85 (81%)	98 (93%)	0.007
<b>Triglycerides (mg/dl): median (IQR)</b>	155 (99-255)	230 (156-345)	<0.0001
<b>Total cholesterol (mg/dl): median (IQR)</b>	186 (163-219)	173 (148-210)	0.065
<b>HDL cholesterol (mg/dl): median (IQR)</b>	36 (22-42)	33 (29-40)	0.018
<b>Apolipoprotein A1 (mg/dl): median (IQR)</b>	98 (88-106)	93 (86-105)	0.061
<b>Apolipoprotein B (mg/dl): median (IQR)</b>	100 (88-118)	98 (81-116)	NS
<b>Lipoprotein (a) (mg/dl): median (IQR)</b>	6.7 (3.3-20.1)	7.3 (3.5-15.1)	NS
<b>Isolated hypertriglyceridemia</b>	15 (14%)	28 (27%)	0.026
<b>Triglycerides ≥2.26 mmol/l + total cholesterol &lt;5.2 mmol/l</b>			
<b>Isolated hypercholesterolemia</b>	13 (12%)	2 (2%)	0.003
<b>Triglycerides &lt;2.26 mmol/l + total cholesterol ≥5.2 mmol/l</b>			
<b>Severe hyperlipidemia</b>	5 (5%)	10 (10%)	NS
<b>Triglycerides ≥5.6 mmol/l + total cholesterol ≥7.8 mmol/l</b>			
<b>Combined hyperlipidemia</b>	24 (23%)	29 (28%)	NS
<b>Triglycerides ≥2.26 mmol/l + total cholesterol ≥5.2 mmol/l</b>			
<b>Normotriglyceridemic hypoalphalipoproteinemia</b>	20 (19%)	26 (25%)	NS
<b>HDL cholesterol &lt;0.9 mmol/l + triglycerides &lt;2.26 mmol/l</b>			
<b>Hypertriglyceridemic hypoalphalipoproteinemia</b>	20 (19%)	32 (31%)	0.055
<b>HDL cholesterol &lt;0.9 mmol/l + triglycerides ≥2.26 mmol/l</b>			
<b>Glucose (mg/dl): median (IQR)</b>	92 (85-101)	89 (84-96)	0.056
<b>Diabetes mellitus</b>	9 (9%)	11 (11%)	NS
<b>Abnormal fasting glucose</b>	18 (17%)	11 (11%)	NS
<b>Insulin (µU/ml): median (IQR)</b>	10.6 (7.3-16.7)	10.2 (6.8-16.4)	NS
<b>Insulin resistance (HOMA-IR): median (IQR)</b>	2.56 (1.68-3.92)	2.44 (1.57-3.77)	NS
<b>Fibrinogen (centesimal index): median (IQR)</b>	1.16 (0.97-1.35)	1.09 (0.88-1.47)	NS
<b>Highly sensitive C-reactive protein (mg/l): median (IQR)</b>	1.7 (0.9-4.1)	2.4 (1.6-3.3)	0.029
<b>Body fat mass (%): median (IQR)</b>	28 (24-31)	24 (20-27)	<0.0001
<b>Body mass index (kg/m²): median (IQR)</b>	28.8 (26-33.2)	25.5 (23-27.9)	<0.0001
<b>Waist circumference (cm): median (IQR)</b>	94 (88-100)	87 (82-91)	<0.0001
<b>Skin folds' ratio (limb/trunk): median (IQR)</b>	0.73 (0.56-0.87)	0.59 (0.48-0.73)	<0.0001
<b>Systemic blood pressure (mmHg): median (IQR)</b>	120 (110-130)	118 (110-130)	0.008
<b>Diastolic blood pressure (mmHg): median (IQR)</b>	89 (79-89)	78 (70-80)	0.002
<b>Arterial hypertension‡</b>	33 (31%)	18 (17%)	0.016
<b>Metabolic syndrome¶</b>	36 (34%)	25 (24%)	0.095
<b>10-year CHD risk (Framingham) †† median (IQR)</b>	2 (1-6)	1 (1-3)	0.064
<b>10-year risk &lt;10%</b>	85 (81%)	92 (88%)	NS
<b>10-year risk 10-20%</b>	17 (16%)	13 (12%)	NS
<b>10-year risk &gt;20%</b>	3 (2.9%)	0	NS

\* NS denotes non-significant  
† IQR denotes interquartile range  
‡ HDL denotes high density lipoprotein  
§ HOMA denotes Homeostasis Model Analysis  
¶ according to the Adult Treatment Panel III  
†† CHD denotes coronary heart disease

### Time of exposure to the HIV and to antiretroviral agents

	Months	Proportion of patients
<b>HIV: median (IQR)*</b>	55.8 (32.6-80.3)	100%
<b>Nucleoside reverse transcriptase inhibitors</b>	39.7 (20.7-71.2)	90%
<b>Protease inhibitors</b>	20.1 (0-49.9)	69%
<b>Non-nucleoside reverse transcriptase inhibitors</b>	9.7 (0-24.5)	67%

\* IQR denotes interquartile range

### Comparison of subjects with and without abnormal SPECT

	Normal SPECT n = 197	Abnormal SPECT n = 12	P value
<b>Age (years): median (IQR)*</b>	37 (31-45)	41 (36-50)	0.085
<b>Waist circumference (cm): median (IQR)</b>	90 (84-96)	95 (90-99)	0.03
<b>Arterial hypertension</b>	45 (23%)	6 (46%)	0.083
<b>10-year CHD risk (Framingham)† median (IQR)</b>	2 (1-6)	4 (2-10)	0.048
<b>10-year risk &gt;20%</b>	26 (13%)	4 (31%)	0.096

\* IQR denotes interquartile range  
† CHD denotes coronary heart disease

### Comparison of type of SPECT abnormalities between infected and non-infected subjects

#	HIV(-)			HIV(+)		
	reverse reversibility† territories (severity)	ischemia† territories (severity)	necrosis† territories (severity)	reverse reversibility† territories (severity)	ischemia† territories (severity)	necrosis† territories (severity)
2	8 (2)	4 (1)	0	2	17 (1)	0
2	3 (3)	3 (3)	0	1	4 (2)	0
2	17 (1)	0	0	1	0	4 (2)
1	0	6 (3)	4 (2)	1	5 (2)	0
1	0	4 (2)	0	1	3 (2)	0
1	2 (3)	0	0			
1	2 (2)	0	0			
1	2 (2)	0	0			
>1:				>1:		
3/8	6/8	4/8	1/8	1/7	4/5	2/5
37%	75%	50%	12%	20%	80%	40%

\* Reverse reversibility means resting hypoperfusion that improves during stress, it mandates abnormal vasodilation which can still be reversed by stress-induced hyperemia, and implies an impaired coronary reserve.  
† Ischemia denotes hyperperfusion during stress reversible with rest.  
‡ Necrosis defines lack of perfusion both at rest and during stress.  
§ The 1 main coronary artery (left anterior descending, right and circumflex).  
¶ A total of 20.  
†† Scored as follows: during stress 0 was normal and 1, 2 and 3 mild, moderate and severe hyperperfusion, respectively; during rest 0 was attributed to no perfusion defect, 1 and 2 mean completely and partially reversible, respectively, and 3 was irreversible.

The perfusion abnormalities were similar in both HIV(-) and HIV(+) groups.

### Association between HIV-infection and abnormal myocardial perfusion assessed by SPECT

#### Conditional logistic regression analysis

	HIV(-)	HIV(+)	P value
<b>Abnormal SPECT</b>	8/105 (7.6%)	5/105 (4.8%)	NS*
<b>Cross-odds ratio (95% confidence interval)</b>	reference	0.62 (0.20-1.91)	NS
<b>Odds ratio (95% confidence interval) adjusted for: waist circumference 10-year CHD risk (Framingham)†</b>	reference	0.54 (0.13-2.25)	NS

\* NS denotes non-significant  
† CHD denotes coronary heart disease

We detected a 4.8% prevalence of abnormal myocardial perfusion in HIV(+) patients vs. 7.6% in HIV(-) subjects. The crude odds ratio (OR) relating HIV-infection to SPECT was 0.62 with a 95% confidence interval of 0.2 to 1.91. After controlling for the potentially confounding variables: waist circumference and 10-year coronary heart disease (Framingham) risk, the OR was 0.54 (0.13-2.25). Thus, no significant relationship between HIV-infection and abnormal myocardial perfusion was found.