Should HIV-infected patients be screened for silent myocardial ischemia using gated myocardial perfusion SPECT ?

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Abstract

Purpose A higher prevalence of cardiovascular risk factors (CRFs) in HIV-infected patients, together with chronic infection and treatments, has resulted in an increased risk of silent myocardial ischemia (SMI). The objective of this study was to evaluate whether myocardial SPECT should be used for screening HIV-infected patients with no clinical symptoms of coronary artery disease (CAD). *Methods* The prevalence of SMI detected by myocardial SPECT was studied in 94 HIV-infected patients with normal clinical cardiovascular examination in relation with anthropomorphic parameters, CRFs, inflammatory and HIV-infection status, and treatment. *Results* Nine cases of silent CAD were detected (8 ischemia, 1 myocardial infarction), corresponding to 9.6% positive screening. All but two scintigraphic diagnoses of ischemia were confirmed by coronarography. Univariate analysis revealed that the overall number of CRFs and the combination of gender and age were associated with the diagnosis of SMI ($p<0.05$). According to multivariate analysis, the only independent parameter significantly associated with the scintigraphic diagnosis of SMI was the combination of gender and age ($p=0.01$). All the positive myocardial SPECT concerned men older than 52 years having at least two other CRFs. In this subpopulation of 47 patients, the prevalence of SMI detected by myocardial SPECT reached 19.2%. *Conclusion* Using myocardial SPECT, positive screening for SMI in male HIV-infected patients older than 52 and with at least two other CRFs was about fourfold greater than in the general population. This may motivate physicians to advise these patients to undergo more systematic screening for SMI using this technique.

Keywords AIDS, HIV infection, Silent myocardial ischemia, Gated SPECT, Myocardial perfusion.

Introduction

Combination antiretroviral therapy has changed the prognosis of HIV-infected patients, reducing HIV-related deaths and leading to longer survival. These patients are thus more likely to develop the complications of chronic infection, treatment side effects, and the risk factors associated with HIV infection. Within the last decade, the morbidity and mortality of HIV-infected patients has become more diversified, with the most frequent non-HIV-related causes of death being non-AIDS cancers, hepatitis C and cardiovascular diseases [1,2]. Although some published results are uncertain or negative [3], numerous epidemiological and clinical studies have highlighted the higher risk of coronary artery disease in HIV-infected patients [4-7], motivating the search for biological explanations of this increased risk [2,6-13]. Several studies have suggested that the HIV infection itself could contribute to atherosclerosis [8-11] and that antiretroviral therapies are associated with adverse effects on lipid levels and metabolism [2,6,7,12]. Moreover, both are likely to induce an autonomic sensory neuropathy, which might contribute to the development of silent myocardial ischemia (SMI) in these patients [13].

However, only a few studies have focused on the exact prevalence of silent myocardial perfusion abnormalities in this specific population. In all these studies [14-20], the tests used to detect SMI were not optimal in terms of sensitivity (rest electrocardiogram [14] or echocardiography [16], simple exercise stress [15], severe narrowing using computed tomography angiography [18]) or not specific to ischemia (plaques [19], coronary artery calcium [20] or moderate narrowing using computed tomography angiography [17]). Thus, the prevalence found by the former (approximately 11%) and the latter (30%) are likely to be under- and overestimated, respectively. Gated single-photon computed emission tomography myocardial perfusion scintigraphy (SPECT) is more sensitive than stress ECG for the detection of coronary artery disease (CAD), is useful and cost-effective for identifying patients in need of coronary angiography, and provides independent and incremental information for predicting cardiac events [21,22]. However, this modality has been used in only one study, which showed no evidence of an increased risk for SMI in young HIV-infected patients receiving highly active antiretroviral therapy and showing a

high prevalence of dyslipidemia and an alteration in circulating markers of inflammation [23].

In this study, we sought to determine whether we would reproduce this finding, which seems to conflict with the results obtained with less sensitive techniques to evaluate SMI in HIV-infected patients. We thus evaluated the utility of myocardial SPECT in the detection of silent myocardial ischemia, together with other traditional or AIDS-specific cardiovascular risk factors, in a more heterogeneous population of HIV-infected patients in order to try to optimize a screening procedure in routine clinical settings.

Materials and methods

Patient Population

All patients were prospectively recruited from the outpatient department of infectious and tropical diseases of Montpellier University Hospital between November 2009 and January 2012. All gave informed consent prior to study inclusion. During this period, all HIV-infected patients with cardiovascular risk factors but no clinical symptoms of CAD were referred to the cardiology department for cardiovascular risk stratification. Patients with no cardiac history, normal clinical cardiac examination, normal resting ECG and normal resting echocardiography were systematically considered for myocardial SPECT, according to the guidelines and indications of this imaging technique [24]. Five patients referred to the cardiology department were excluded from the study because of an abnormal electrocardiogram (3 patients had pathological Q waves and one had negative T waves) or because of history of coronary dilation for one patient. Ninety-four patients (82 male, 12 female; age 55±8 years) were prospectively included in the study. The anthropomorphic characteristics of this population are given in Table 1. The distribution of traditional cardiovascular risk factors in this population is detailed in Table 2. Table 3 summarizes the characteristics of the population that are linked to chronic HIV infection, its treatment and the presence of co-infections.

Myocardial Gated-SPECT Studies

All subjects underwent a one-day combined dipyridamole (0.75 mg/kg) exercise stress test followed by a rest myocardial perfusion SPECT study, 3 hours later. Acquisitions were performed 15 minutes after intravenous administration of ^{99m}Tc-tetrofosmin (3.7 MBq/kg) for the stress study and 45 minutes after intravenous administration of ^{99m}Tc-tetrofosmin (11 MBq/kg) for the rest study [25]. When stress data were strictly normal (normal exercise stress test, normal gated stress perfusion data without left ventricular dilation nor decreased ejection fraction), no rest acquisition was performed. Both acquisitions were performed in the prone position using a dual-headed Infinia Hawkeye I gamma-camera (GE Healthcare, Chalfont St. Giles, UK) in a 90° configuration, with low-energy high-resolution parallel-hole collimators. Gated tomographic perfusion scintigraphy was performed with the following acquisition parameters [26]: 6° per step (15 steps over 90° per head) for 180°, 40 sec. acquisition per step, 10% R-R interval acceptance window, eight gated intervals, and 64*64 matrix size (pixel size: 5.5-6.6 mm). With these acquisition parameters, the examination time was 12 minutes for patients with regular pacing. Images were reconstructed using a filtered backprojection algorithm (Butterworth filter, order 4 and cut-off frequency 0.25/cm for stress studies, order 10 and cut-off frequency 0.4/cm for rest studies), and short-axis, horizontal long-axis, and vertical long-axis sections were obtained.
Two experienced nuclear medicine physicians performed image analysis of defect number and severity. The myocardial perfusion bull's eye images were divided into 20 segmental regions. Each region was scored independently using a 5-point model depending on the mean segmental activity (MSA) expressed as a ratio of the maximal myocardial activity (0: MSA≥70%; 1: 50≤MSA<70; 2: 30≤MSA<50; 3: 10≤MSA<30; 4: MSA<10%). Inside a segment, hypoperfusion was considered significant if the mean activity in the segment was below 70% of the maximal myocardial activity. The 20 segmental scores were summed using the stress and rest studies to derive summed stress scores, summed rest scores and summed difference scores [26]. Stress gated myocardial SPECT with a summed stress score lower than 3, normal stress wall-thickening and normal left ventricular ejection

fraction on gated data were regarded as normal studies and these patients did not undergo the rest study [27].

Ischemia was defined as a reversible perfusion defect (summed difference scores ≥3) and necrosis as a fixed significant defect with corresponding abnormal wall thickening. Fixed defects with normal rest wall thickening in the same segment were regarded as artefacts.

A coronary angiography was proposed to all patients with reversible perfusion defects, except for one patient who had haemophilia. Only one patient refused to undergo both coronary angiography and stress echocardiography.

Statistical Analysis

The cardiovascular risk factors used in the statistical analysis included age and gender (male >50 years or female >60 years), smoking (except if smoking cessation >3 years ago), hypertension (multiple measures of blood pressure ≥140/90 mm Hg or antihypertensive medication), treated diabetes, dyslipidemia (LDL cholesterol >1.3 g/L and HDL cholesterol <0.6 g/L or medication) or family history of premature coronary heart disease (occurring in a male or female first-degree relative <55 or 65 years, respectively). The other clinical and biological patient characteristics in the statistical model were anthropomorphic parameters (sex, age, weight, height, body mass index, waist and hip circumferences, waist-to-hip ratio), Centers for Disease Control and Prevention (CDC) classification [28], occurrence of lipohypertrophy, lipoatrophy, or HIV-associated neuropathy, occurrence of co-infections, durations of HIV infection, antiretroviral therapy and protease inhibitor medication, viral load and CD4 count, and classes of antiretroviral therapies.

The mean ± standard deviation characterizes the distributions of the clinical data. Univariate association of these parameters with the detection of SMI by myocardial SPECT was sought using Fisher's exact test, a Chi-squared test, Student's t test or a Wilcoxon test, as appropriate. The odds ratios of all parameters characterizing the population were evaluated. Independent covariates associated with the diagnosis of SMI with a conservative p value <0.25 in univariate analysis were subsequently tested in a multivariate logistic analysis. A stepwise procedure was used to select covariates in the final model.

In order to identify a subpopulation containing all patients for whom SMI was detected, we looked for a predictive classification rule with a sensitivity of 100% for the prediction of a positive scintigraphic screening for myocardial ischemia. Among the models with perfect sensitivity, we chose the rule with optimal specificity.

Results

Of the 94 asymptomatic patients who were screened, 80 (85.1%) had normal stress tests and normal myocardial SPECT. Five patients (5.3%) had abnormal combined dipyridamole exercise stress tests but normal myocardial SPECT data. Three of them (one 53-year-old female, and two 66 and 68-year-old males, 3 CRFs) had no chest pain during exercise but significant horizontal ST segment depression appearing on the ECG during the stress test. These three patients were not treated and had no adverse cardiovascular event over the ten months, nine months and two years of follow-up, respectively. Two male patients (50 and 59-year-old with 4 and 3 CRFs respectively) had both chest pain and ECG changes during the stress test, but normal myocardial SPECT. Both underwent coronary angiography, which ruled out any significant coronary artery disease. As a consequence, the five patients with abnormal exercise stress but normal myocardial SPECT images were false positive for stress test but true negative for myocardial SPECT.

Nine patients (9.6% of the whole population, age: 59 ± 7 years) had abnormal myocardial SPECT (Table 4). Six of them had normal exercise stress tests (patients 1-6), two had ECG changes (patients 7 and 8) and one had both ECG changes and chest pain during the exercise stress test (patient 9). One of these nine patients had a scintigraphic pattern of unknown inferior myocardial infarction. The myocardial SPECT data showed significant reversible stress myocardial defects for eight patients. Coronary angiography could not be performed for two of these patients (1 patient refused further investigations, and coronary angiography was denied for the second patient because of an increased iatrogenic risk due to haemophilia). These two patients were treated medically and underwent no cardiovascular event during 21 and 28 months of follow-up. Six patients underwent coronary angiography. Severe coronary lesions in territories consistent with the SPECT

findings were found in three patients and intermediate lesions (50% reduction in coronary diameter) were found in the three other patients. All patients with coronary diameter reduction greater than 80% had changes in ECG and/or chest pain during the stress test.

Using univariate analysis (Tables 5 and 6), we found that the overall number of cardiovascular risk factors and the combination of gender and age (male >50 or female >60 years) were associated with the diagnosis of SMI ($p<0.05$). Body mass index and related parameters, high systolic blood pressure, the triglyceride levels in patients with high LDL and low HDL cholesterol levels, family history of premature coronary heart disease, and medications including non-nucleotide reverse transcriptase inhibitors or protease inhibitors were also associated with the diagnosis of SMI ($p<0.25$) and tested in a multivariate analysis.

Using this multivariate analysis, the only significant independent parameter associated with the scintigraphic diagnosis of SMI was the combination of gender and age ($p=0.01$ for male >50 or female >60 years). A simple tendency was found with the overall number of other cardiovascular risk factors ($p=0.07$). The best multivariate model that predicted all the detected SMI included male gender, age and the number of cardiovascular risk factors as a priori predictive factors. All the positive myocardial SPECT concerned men older than 52 years having at least two other cardiovascular risk factors (i.e., 2 factors among smoking, hypertension, diabetes, dyslipidemia or family history of premature CAD). This subpopulation of 47 patients (i.e., 50% of the entire study population) was characterized by an age of 59 ± 5 years. Besides age and gender, the number of cardiovascular risk factors in these 47 patients was two for 37 patients, three for nine patients and four for one patient. The prevalence of SMI detected in this subpopulation by myocardial SPECT reached 19.15%. The sensitivity and negative predictive value of being a man older than 52 years with two other cardiovascular risk factors for the scintigraphic detection of SMI with myocardial SPECT was 100% (Table 7).

Discussion

Highly active antiretroviral therapy has greatly reduced mortality and morbidity in HIV-infected patients but is known to have metabolic side effects, including lipodystrophy, dyslipidemia and diabetes. In a review of 15 studies, Graham found the prevalence of lipodystrophy to be greater than 60% after one year of protease inhibitor (PI) treatment and hypothesized that PI causes this syndrome by impairing the conversion of retinoic acid to cis-9-retinoic acid and inhibiting low-density lipoprotein receptor-related protein [29]. This prevalence is similar to that observed in the present study (55%), in which more than two thirds of the patients were treated with PI. Hyperlipidemia is also more frequent in these patients than in matched control subjects, with a prevalence of about one third in published studies, as is diabetes, with a prevalence of about 7% in HIV-infected patients under highly active antiretroviral therapy [30]. The population of the present study, which was recruited from a University Hospital, presents a higher proportion of patients with diabetes (13%) and hypercholesterolemia (76%) in comparison with general HIV-infected patients. These glucose and lipid metabolic anomalies are known to be causal factors in the development and acceleration of atherogenesis. Last, chronic inflammation (due to HIV or co-infections), together with the adverse effects of nucleoside analog treatment, is known to induce an autonomic sensory neuropathy that might contribute to the development of SMI in HIV-infected patients [13].

The prevalence of SMI has been the focus of many studies in healthy subjects and is less than 5% of the total population [31,32]. Systematic screening of the whole population is thus not justified from an economic point of view. However, as over a quarter of myocardial infarctions go unrecognized and half of them cause no symptoms at all [33], it is important to determine the measurable factors associated with an increased prevalence of SMI. Classical cardiovascular risk factors such as age, gender, smoking, hypertension, and family history of CAD are known to be strong predictors of SMI [34]. Among them, aging appears to be more particularly important. The prevalence of exercise-induced silent ischemia was found to increase more than sevenfold from 2% in the fifth and sixth decades to more than 15% in the ninth decade [34,35]. Similarly, in a prospective, population-based

cohort study, Sigurdsson et al. reported that the prevalence of unrecognized myocardial infarction increased from nearly undetectable before 40 years old to more than 5% in patients in the seventh decade [36]. Aging and the higher frequency of certain cardiovascular risk factors in HIV-infected patients, such as smoking [12], metabolic anomalies, and the autonomic sensory neuropathy induced by both chronic infection and the adverse effects of highly active antiretroviral therapy, are likely to increase the prevalence of SMI in this population.

The mechanisms underlying the potentially increased cardiovascular risk in HIV-treated patients are beginning to be understood [2,37], but very few studies have been dedicated to the clinical measurement of SMI prevalence. Using electrocardiograms at rest in a large cohort of asymptomatic HIV-infected patients, Carr et al. found ECG evidence of ischemic heart disease in 11%, the predominant determinants of risk being older age and current hypertensive therapy [14]. The same prevalence was reported by Duong et al., using exercise stress testing on a smaller cohort of HIV-infected patients who had been receiving highly active antiretroviral therapy for at least one year [15]. In this study, age, central fat accumulation and cholesterol level were the independent variables associated with the detection of SMI. Last, using echocardiography at rest and exercise testing, Schuster et al. found more frequent left ventricular systolic or diastolic dysfunctions and a higher pulmonary artery pressure in HIV-infected patients compared with age-matched healthy subjects, but no case of SMI [16]. Using coronary computed tomography angiography, d'Ettore et al. found luminal coronary narrowing exceeding 50% in 29% of a small cohort of asymptomatic HIV-infected subjects whose age was the only independent variable associated with the narrowing [17]. With the same imaging modality, Lo et al. found a 6.5% prevalence of luminal coronary narrowing greater than 70% in young HIV-infected men with longstanding HIV disease [18]. Similarly, in HIV-infected cardiovascularly asymptomatic African Americans with long-term antiretroviral therapy, Lai et al. found an overall 30% prevalence rate of coronary plaques [19]. On the other hand, Talwani et al. quantified coronary artery calcium using electron beam computed tomography but found no difference between HIV-infected patients and controls [20]. The tests in these studies [14-20] to detect SMI were not optimal in terms of sensitivity (rest electrocardiogram or

echocardiography, simple exercise stress, severe narrowing using computed tomography angiography) or not specific to ischemia (plaques or moderate narrowing using computed tomography angiography). In similar situations, such as screening diabetic patients for SMI, SPECT has proven to be more sensitive than stress ECG for detecting coronary artery disease and cost-effective for identifying patients who need coronary angiography. Moreover, it provides independent and incremental information for predicting cardiac events [21,22]. To our knowledge, all but one of the myocardial scintigraphic studies in HIV-infected patients have been used to study only endothelial or vasomotor function [37,38] or described a single clinical case [39]. The only clinical study of myocardial perfusion using gated SPECT in HIV-infected patients under highly active antiretroviral therapy was performed by Catzin-Kuhlmann et al. and the finding was negative [23]: the author found no difference in SMI prevalence in HIV-infected patients compared with an age- and gender-matched group of infection-free subjects, with the prevalence in HIV-infected patients (4.8%) being similar to that generally found in studies involving healthy subjects. This result in a significant number of patients (105 subjects in each group) is interesting and surprising regarding the growing importance of cardiac death in the outcome of HIV-infected patients under antiretroviral therapy [1,2]. In contrast, we found a more elevated prevalence of SMI in the population of the present study, but the positive screenings concerned only men older than 52 years having at least two other cardiovascular risk factors (19.2% of SMI in this subpopulation). This important point explains the apparent discordance between our results and Catzin-Kuhlmann's because in his study, the ages of all HIV-infected patients and controls were below 47 years. In fact, our results together with those of previously published papers [14,15,17,23] emphasize that the aging of HIV-infected patients because of the efficiency of highly active antiretroviral therapy may be more relevant to explain the increased incidence of SMI than the possible side effects of these medications.

Moreover, in the older population of the present study, certain cardiovascular risk factors such as hypertension or current smoking were more frequent (39% versus 18% and 64% versus 34%, respectively). Thus the comparison between Catzin-Kuhlmann's study and the

present paper emphasizes the key role of age and gender in the prevalence of SMI in HIV-infected patients.

The present study was designed to evaluate the utility of myocardial SPECT in the detection of silent myocardial ischemia among HIV-infected patients. As we did not aim at testing whether HIV-infection has to be considered as a cardiovascular risk factor per se, we did not perform myocardial SPECT on a control population of HIV-uninfected patients matched for age and other cardiovascular risk factors. However, the comparison between our results and the data collected by J. Fleg and al from the Baltimore Longitudinal Study of Aging (BLSA) [35] may give an insight into this question. More smokers were found in the population of the present study compared with Fleg's (64% versus 14%), but the frequency of hypertensive patients, serum cholesterol and fasting plasma glucose levels as well as body mass indexes were similar. In a population of HIV-uninfected patients, Fleg found that the prevalence of exercise-induced silent ischemia increased with age, from 2% in the fifth and sixth decade to 15% in the ninth decade. In our population of HIV-infected patients, all patients but one with positive myocardial SPECT were in the fifth and sixth decade and the prevalence of SMI was 7.5% during the fifth decade and 11.5% during the sixth decade. In comparison with the increase of SMI prevalence with age described by Fleg (Figure 1 in [35]), SMI appears a decade earlier in our population of HIV-infected patients. As the relative risk of smoking for predicting coronary events can be evaluated between 1.7 and 2.3 depending on the model chosen [35], it is likely that the difference in smoking habits between Fleg's population and our HIV-infected patients can not explain alone the precocity of SMI detection in the later population. These results support the hypothesis of regarding HIV infection as a possible cardiovascular risk factor per se or, at least, as a situation that is likely to bring forward the adverse effects of traditional cardiovascular risk factors. This hypothesis needs to be confirmed by a larger case-control study. In any case, together with Fleg's results [35], our study shows that before the fifth decade, the prevalence of SMI is very low for HIV-infected patients. On a very practical point of view, this result is important because it means that a systematic screening of HIV-infected patients is not justified before the fifth decade, even if further studies confirm that HIV infection can be regarded as a cardiovascular risk factor per.

Another limitation of our study is the origin of the population, which was recruited from the outpatient department of infectious and tropical diseases of a University Hospital. In comparison with the DAD (Data Collection on Adverse Events of Anti-HIV Drugs) study [40], our study presents a higher proportion of patients with cardiovascular risk factors, with more smokers (64% versus 51.5%), more patients with hypertension (39% versus 8.5%), more diabetic patients (13% versus 2.5%) or patients with BMI >30 kg/m^2 (5.3% versus 3.5%), more patients with hypercholesterolemia (76% versus 22.2%), and more patients with a family history of CAD (24% versus 11.4%). As a consequence, the relatively high prevalence of SMI found in patients older than 52 with at least two other cardiovascular risk factors may partially reflect the characteristics of this subpopulation of HIV-infected patients. However, this result is very similar to the 18% prevalence of concordant exercise-induced asymptomatic ST-segment depression on electrocardiography and perfusion defects on myocardial SPECT found by Katzel et al. in men aged 55 to 70 years with no previously known CAD [34]. Thus, the observed increasing prevalence of SMI among HIV-infected patients is more likely to be the consequence of an ageing of these patients than an effect of chronic infection, HIV-related metabolism changes or highly active antiretroviral therapy. In all cases, myocardial SPECT should not be used systematically to screen asymptomatic HIV-infected patients before the fifth decade. In fact, for all subjects, but even more so for HIV-infected patients, a very simple cardiovascular risk factor like the combination of age and male gender appeared essential to discriminate the patients who are likely to have a positive SPECT screening for SMI. The results of the present study should motivate further studies (i) to confirm our preliminary finding on the prevalence of SMI in HIV-infected men older than 50 years and (ii) to evaluate the benefit of scintigraphic screening in terms of morbidity and mortality.

Conclusion

In the asymptomatic population of this study, only male HIV-infected patients older than 52 with at least two other cardiovascular risk factors had positive screenings for SMI using myocardial SPECT. In this subpopulation, the prevalence of SMI was evaluated to 19%,

about fourfold greater than the upper limit for SMI prevalence in non-infected subjects. On the other hand, all myocardial SPECT findings were normal for HIV-infected patients without these characteristics.

As combination antiretroviral therapy has led to the longer survival of HIV-infected patients, this result may prompt physicians to advise this subpopulation of aging male patients to undergo more systematic screening for SMI using myocardial SPECT.

Conflicts of interest: The authors declare that they have no conflict of interest.

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TABLES

Anthropomorphic characteristics	
Age	55 ± 8 years
Male	82 patients (87 %)
Female	12 patients (13 %)
Weight	73 ± 13 kg
Height	174 ± 7 cm
Body mass index	24 ± 4 kg/cm²
Waist circumference	96 ± 15 cm
Hip measurement	95 ± 10 cm
Waist-to-hip ratio	1.00 ± 0.08

TABLE 1: Anthropomorphic characteristics of the population (mean ± standard deviation).

Cardiovascular risk factors	
Male older than 50 years	63 patients (67%)
Female older than 60 years	5 patients (5%)
Cigarette smoking	60 patients (64%)
Hypertension (≥140/90 mm Hg or antihypertensive medication)	37 patients (39%)
Treated type 2 diabetes	12 patients (13%)
Glycated haemoglobin in patients with diabetes	6.3 ± 1.7%
Dyslipidemia (medication or LDL >1.3 g/L and HDL <0.6 g/L)	72 patients (76%)
Mean HDL cholesterol in patients with dyslipidemia	0.45 ± 0.19 g/L
Mean LDL cholesterol in patients with dyslipidemia	1.30 ± 0.47 g/L
Mean triglycerides in patients with dyslipidemia	1.55 ± 0.87 g/L
Family history of premature coronary heart disease	23 patients (24 %)
Number of cardiovascular risk factors:	
1 cardiovascular risk factor	3 patients (3%)
2 cardiovascular risk factors	22 patients (23%)
3 cardiovascular risk factors	53 patients (56%)
4 cardiovascular risk factors	15 patients (16%)
5 cardiovascular risk factors	1 patient (1%)

TABLE 2: Cardiovascular risk factors of the population (mean ± standard deviation).

Population characteristics in relation to HIV infection	
Lipoatrophy	35 patients (37%)
Lipohypertrophy	23 patients (24%)
Neuropathy	9 patients (10%)
Cytomegalovirus co-infection	4 patients (4%)
Hepatitis C virus co-infection	16 patients (17%)
CRP >5 mg/L	14 patients (15%)
Known duration of HIV infection	16 ± 7 years
Duration of antiretroviral treatment	12 ± 6 years
CD4 count	555 ± 261 cells/mm^3
Viral load: more than 20 copies/mL	18 patients (19%)
CDC classification:	
Stage A	44 patients (47%)
Stage B	17 patients (18%)
Stage C	33 patients (35%)
Antiretroviral treatment:	
Nucleotide reverse transcriptase inhibitor	84 patients (89%)
Non-nucleotide reverse transcriptase inhibitor	31 patients (33%)
Entry inhibitor	1 patient (1%)
Integrase inhibitor	13 patients (14%)
Protease inhibitor	63 patients (67%)
Duration of protease inhibitor treatment	7 ± 5 years

TABLE 3: HIV-infection related characteristics of the population (mean ± standard deviation; CDC: Centers for Disease Control and Prevention).

Patient	SSS	SDS	Myocardial SPECT diagnosis	Coronary angiography
1	16	7	Septal ischemia and inferior necrosis	Impossible (haemophilia)
2	6	5	Inferior ischemia	Patient refusal
3	3	0	Inferior necrosis	Not necessary (no ischemia)
4	4	3	Inferior lateral ischemia	Cx 50%
5	7	3	Inferior lateral ischemia	LAD 50%
6	5	5	Anterior ischemia	D1 50%
7	24	23	Antero-septal ischemia	LAD 100%
8	10	5	Apical and inferior ischemia	LAD & RCA 100%, Cx 80%
9	3	3	Apical ischemia	LAD & M1: 90%

TABLE 4: Characteristics of the patients for whom silent coronary artery disease was detected using myocardial SPECT. SSS: summed stress score; SDS: summed difference score; LAD: left anterior descending artery; D1: first diagonal branch; Cx: circumflex artery; M1: first marginal branch; RCA: right coronary artery.

Anthropomorphic characteristics and CRFs	Odds ratio	p-value
Weight	1.04 (0.99-1.10)	0.10†
Height	0.99 (0.89-1.10)	0.86
Body mass index	1.17 (0.99-1.39)	0.06†
Waist circumference	1.04 (1.00-1.10)	0.08†
Hip measurement	1.07 (0.97-1.17)	0.16†
Male older than 50 or female older than 60	1.44 (1.16-1.78)	0.001†
Cigarette smoking	1.15 (0.27-4.92)	0.85
Pack years	1.05 (0.95-1.16)	0.36
Hypertension (≥140/90 mm Hg or medication)	3.48 (0.81-14.92)	0.09†
Systolic pressure	1.03 (0.99-1.08)	0.13†
Diastolic pressure	1.02 (0.96-1.08)	0.50
Fasting blood sugar level	1.01 (0.59-1.74)	0.97
Treated type 2 diabetes	2.14 (0.39-11.78)	0.38
Glycated haemoglobin in patients with diabetes	0.23 (0.01-3.92)	0.31
Dyslipidemia (medication or LDL >1.3 and HDL <0.6 g/L)	2.63 (0.31-22.23)	0.38
HDL cholesterol level (dyslipidemic patients)	0.83 (0.02-39.54)	0.92
LDL cholesterol level (dyslipidemic patients)	0.39 (0.05-3.20)	0.38
Triglyceride level (dyslipidemic patients)	0.41 (0.12-1.39)	0.15†
Family history of premature coronary heart disease	0.14 (0.00-1.50)	0.11†
Number of cardiovascular risk factors	3.67 (1.24-10.85)	0.02†
Number of CRFs except gender and age	1.95 (0.71-5.42)	0.21†

TABLE 5: Results of the univariate analysis. Odds ratios are given with a 95% confidence interval. Parameters associated with an abnormal myocardial SPECT (†) were included in the multivariate analysis (CRFs : Cardiovascular risk factors).

Population characteristics in relation to HIV infection	**Odds ratio**	**p-value**
Lipoatrophy	1.39 (0.35-5.58)	0.64
Lipohypertrophy	2.30 (0.46-11.44)	0.31
Neuropathy	0.43 (0.00-5.16)	0.59
Cytomegalovirus co-infection	0.95 (0-15.5)	1.00
Hepatitis C virus co-infection	0.58 (0.07-5.02)	0.62
CRP	0.89 (0.67-1.19)	0.43
Known duration of HIV infection	0.99 (0.89-1.10)	0.83
Duration of anti-retroviral treatment	1.00 (0.88-1.13)	0.96
CD4 count	1.00 (0.99-1.00)	0.33
Viral load: more than 20 copies/mL	0.99 (0.97-1.02)	0.59
Stage C (CDC classification)	0.50 (0.10-2.53)	0.40
Nucleotide reverse transcriptase inhibitor	0.95 (0.11-8.47)	0.96
Non-nucleotide reverse transcriptase inhibitor	0.23 (0.03-1.92)	0.17†
Entry inhibitor	2.96 (0.00-366.20)	1.00
Integrase Inhibitor	1.92 (0.35-10.46)	0.45
Protease inhibitor	0.35 (0.09-1.42)	0.14†
Duration of protease inhibitor treatment	1.10 (0.88-1.38)	0.38

TABLE 6: Results of the univariate analysis. Odds ratios are given with a 95% confidence interval. Parameters associated with an abnormal myocardial SPECT (†) were included in the multivariate analysis (CDC: Centers for Disease Control and Prevention).

	Positive SPECT	Negative SPECT	
Men >52 years and 2 CRFs	9	38	PPV = 19.15%
other	0	47	PPN = 100%
	Se = 100%	Sp = 55.3%	

TABLE 7: Diagram illustrating the sensitivity (Se), specificity (Sp), and negative (NPV) and positive (PPV) predictive values of being a man older than 52 years with two other cardiovascular risk factors (CRFs) for the scintigraphic detection of silent myocardial ischemia.